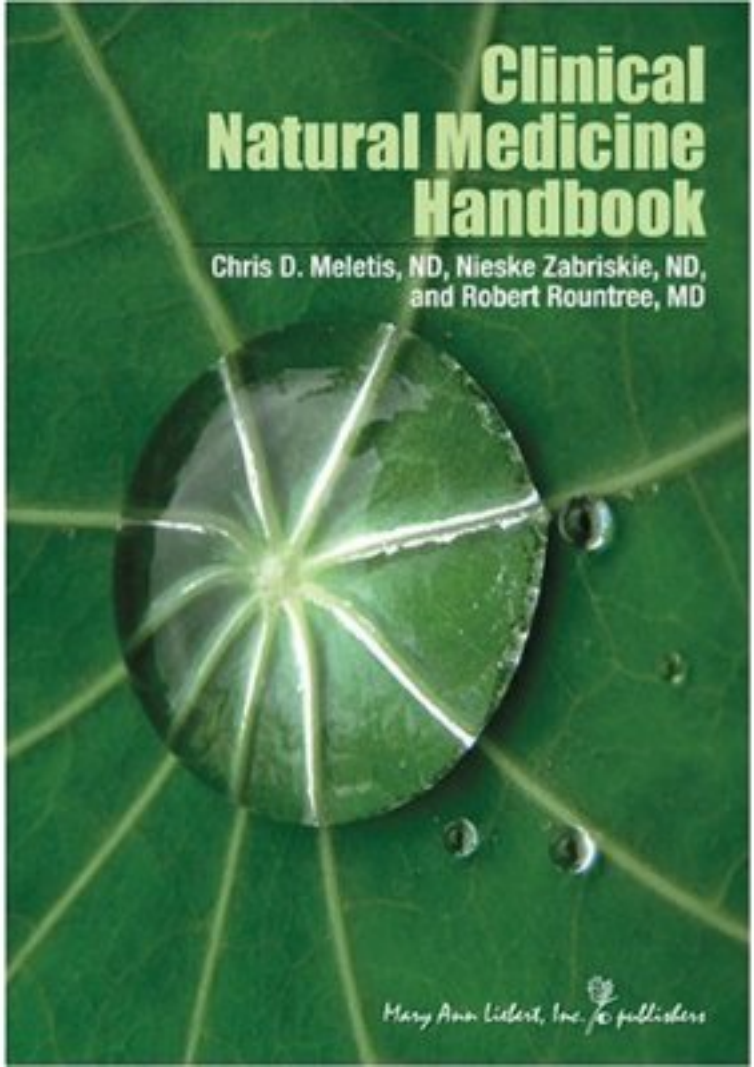
Clinical
Natural Medicine
Handbook
Chris D. Meletis, ND, Nieske Zabriskie, ND,
and Robert Rountree, MD
Mary Ann Liebert, Inc. publishers

Preface

Developed to fill a critical void in the current literature, the Clinical Natural Medicine Handbook provides guidelines, protocols, and practice-oriented literature review to help integrative clinicians optimize their use of nutrition, nutracauticals, and botanicals. Up-to-date, authoritative, and scientifically referenced, the Handbook was written by practicing clinicians for practicing clinicians and, as such, provides a solid foundation on which to base individualized patient treatment regimens and approaches.

The Handbook contains nearly three dozen disease- or condition-specific chapters featuring in-depth information and insight on natural, nutritional, and botanical approaches to treatment and management. A practice-oriented compendium, it focuses on the diseases and conditions that today's practitioners are most likely to encounter, and provides a wealth of clinical insight based on the very latest medical and scientific research and evidence:

Detailed diagnostic information including prevalence, pathophysiology, risk factors, symptoms, and associated conditions.
Integrative treatment guidelines and protocols comprising conventional approaches (medical and surgical), nutracauticals, botanicals, lifestyle modifications, and other naturopathic approaches.
Specific prescribing and dosage recommendations featuring nutrient-drug interactions, hormone and food allergy considerations, and possible affects on laboratory test results.
Quick-reference charts to speed diagnostics and prescribing.

In sum, the Clinical Natural Medicine Handbook provides an evidence-based foundation on which integrative clinicians can build, expand, and enhance their practices as they improve patient outcomes and establish a formal standard of care.

Acknowledgments

We would like to thank Vicki Cohn and the entire Mary Ann Liebert team for allowing this important clinical resource to reach the tens of thousands of health care providers that practice solid, evidence-based, integrated medicine.

Special acknowledgment to the physicians that made this book possible with their contributions: Dr. Jason Barker, Dr. Ben Bramwell, Dr. Wayne, and Dr. Elizabeth Wagner.

The clinical wisdom, amazing breadth of knowledge, and commitment to excellence offered by Dr. Robert Rountree cannot be emphasized enough. Without him, this work would still be a work in progress.

Lastly, a personal thanks to all the clinicians and researchers that continue to drive the fields of natural medicine, appreciation of human physiology, and the exploration of supporting enhanced biochemical performance of the 75 trillion cells of the human body.

1

STRESS AND ADRENAL FATIGUE

Enhancing Quality of Life for Patients with a Functional Disorder

The human organism is bombarded with an incredible variety of stressors at any given time. Stress can be categorized in an equally dizzying number of ways. There are both chronic and acute stressors. There are somatic stressors that push the body away from homeostasis. There are psychogenic stressors that seem to be triggered at the slightest provocation. In fact, according to a national survey, it is estimated that 50%–80% of physical disorders are stress related.[1] An elaborate system of hormones and neurotransmitters (coupled with the human penchant for becoming upset about nonphysical stressors) engenders psychogenic stress in human beings more than in any other species of animal.[2] There are two basic kinds of psychogenic stress (1) rational (fear) and (2) irrational (anxiety). Regardless of the nature of the stress—mental or physical, rational or irrational—the body responds to all stress in a fairly predictable manner. In the early 1930s, Selye[3] termed this predictable pattern of response the general adaptation syndrome. Both conventional and nutritionally oriented health care providers principally utilize and share the same biomedical model of stress and its physiologic effects. However, the two schools of practice diverge when it comes to diagnostic methodologies that are used to identify subclinical cases of adrenal dysfunction and the modalities used to treat these patients.

HOW THE ADRENAL GLANDS RESPOND TO STRESS

At the center of the stress response are the adrenal glands. The adrenals produce epinephrine and norepinephrine, along with other hormones such as cortisol that enable the body to adapt to and survive a stressor. The acute alarm, or immediate reaction to a stressor, is a physiologic phenomenon in which the sympathetic nervous system responds to exogenous or endogenous stressors that put the body into what is popularly called the ''fight, fright, or flight'' mode. When the body is in this state, such as in potentially life-threatening situations, adrenal hormones are released to increase heart rate and blood pressure and divert blood to the brain, heart, and skeletal muscles. This physiologic compensation is a key mechanism in stress and the clinical phenomenon of adrenal fatigue. The adrenal cortex produces steroid hormones, which include cortisol, corticosterone, testosterone, estrogen, 17-hydroxyketosteroids, dehydroepiandrosterone (DHEA), DHEA sulfate, pregnenolone, aldosterone, androstenedione, progesterone, and other intermediates to hormone production. These are the most widely studied of the stress-related hormones. Although most of these hormones are created in different parts of the body, aldosterone, cortisone, and hydrocortisone are produced only in the adrenal glands. Aldosterone, working in cooperation with the renal system, helps to regulate the balance of sodium and potassium in the body. This regulation is critical to many physiologic functions, including the ability to react to stress and to maintain fluid balance. This hormone also contributes to the maintenance of blood pressure. In ''adrenal fatigue'' states, patients may have alterations in the

fluid-balancing mechanism, with the most commonly described symptom being ''puffy hands and feet.'' Recent conventional medical research has shown that subclinical adrenocortical disease can exist without adrenal function failure.[4] The etiology of this subclinical disease process has not been elucidated fully in conservative research. Authors who write for alternative medical periodicals and texts have historically expressed a belief that severe, long-term stress can lead to a clinical phenomenon known as ''adrenal burnout.''[5,6] Most individuals adapt to the stresses of life and, when these stressors are reduced, these patients experience favorable psychophysiologic responses, demonstrating the correlation between stress and physiologic functioning.[7] Being unable to adapt to stressors can manifest as ''staleness syndrome'' or adrenal dysfunction.[5,6,8] Individuals who experience this disorder are unable to perform at their customary levels of activity at the office or home. They seem to suffer from persistent deterioration in their everyday functioning and activities. Indeed, depression and a marked decrease in performance seem to be the hallmark of this maladaptation syndrome.[9,10]

BIOCHEMICAL REACTIONS TO STRESSORS

The fight, fright, or flight response to stressors involves the catecholamines, substances that prepare the body for a call to immediate action and response, by causing short-term hyperglycemia. This rapid catabolism of blood glucose is the result of liver-glycogen storage breakdown and an increased rate of gluconeogenesis. Catecholamines can also liberate rapid stores of energy by catabolizing fat from adipose tissue stores. The stress adaptation phase primarily involves glucocorticoids, released by the adrenal cortex, that have a profound effect on energy metabolism and biologic functions. These substances raise blood-sugar levels, increase muscle-protein breakdown and hepatic gluconeogenesis, and mobilize fatty acids.[11]

Following normal diurnal patterns for the release of serum cortisol, glucocorticoid levels are at their lowest point at approximately midnight to 1 am. Peak levels occur between 6 am and 8 am. Research has shown that elevation or suppression of daily cortisol levels indicates imbalanced hypothalamus-pituitary-axis (HPA) activity.[12] This may be interpreted as hyperfunction or hypofunction, depending on a patient's levels of cortisol and his or her clinical presentation. Sustained activation of the sympathetic nervous system marks the compensation stage, also known as the adrenal hyperfunction stage, with a secondary influence on the HPA axis. The pituitary gland responds to the influence of sympathetic nervous system activity by releasing adrenocorticotropic hormone (ACTH). In turn, the adrenal glands respond to the pituitary release of ACTH by producing excess cortisol and androgen hormones. In an attempt to compensate for this faulty hyperfunction, the HPA becomes less sensitive to the influence of cortisol's feedback inhibition. As serum cortisol levels rise, glucose utilization declines and insulin resistance increases, gluconeogenesis in the liver increases, and blood glucose levels increase rapidly. In addition, the body responds to increased cortisol by increasing the degradation of protein stores to supply amino acids for gluconeogenesis in an attempt to mobilize energy rapidly. Adrenal hyperfunction can be marked by a tendency toward insulin resistance, hypertension, mild obesity, and elevated serum lipid and triglyceride levels. What is more, high cortisol and lowered DHEA have been shown to suppress the immune system.[13] Histologic studies have revealed lowered production of secretory immunoglobulin A (sIgA) in the mucus membranes of competition swimmers under the influence of chronic levels of physiologic and psychologic stressors. At this phase of the stress response, athletes and other individuals will often complain of a decrease in performance or work production and a generalized feeling of lassitude. The final stage of the stress response is the adrenal hypofunction stage or the fatigue

stage. The body's ability to synthesize cortisol and other corticosteroid hormones is greatly diminished. The resulting excessive fatigue, changes in a person's ability to concentrate, inability to tolerate alcohol, intractable headaches, lowered blood pressure, menstrual irregularities, reactive hypoglycemia, and carbohydrate sensitivity may follow.[14] With this compromised ability to control inflammation, the body goes into a pro-inflammatory state. The absence of cortisol leads to an increase in endogenous inflammatory eicosanoids and cytokines and leads to eventual tissue damage and degenerative disease.[15]

EFFECTS OF STRESS ON THE BODY

We often hear of 30-year-old marathon runners who are forced into early retirement because of recalcitrant tendonitis. Are these simply cases of poor biomechanics and faulty training plans? Or are these athletes suffering from a maladaptation syndrome in which their bodies can no longer compensate for massive levels of exogenous and endogenous stress (work, family responsibilities, exercise, etc.)? Uncontrolled stress strains the entire organism. Stress increases the metabolic rate, resulting in the mobilization of stored energy sources and the eventual breakdown of muscle protein to make up for energy shortfalls.[16] In short, the body attempts to maintain homeostasis at all costs. Extended bouts of stress, such as high-volume exercise, psychologic stress, or other lifestyle challenges, lead to abnormal increases in serum cortisol levels and irregular circadian rhythm variations in cortisol secretion.[17] Sustained elevated levels of cortisol may lead to reduced adrenal responsiveness to ACTH.[18] This is compensated for by increases in pituitary releases of ACTH in the initial stages of overtraining. However, protracted stress causes pituitary release of ACTH to decrease and, thus, the pituitary gland becomes underresponsive to stimulation. The ultimate effects of prolonged elevated levels of cortisol are suppression of corticotropin-releasing hormone and ACTH release and atrophy of the zonae fasciculata and reticularis as a consequence of ACTH deficiency.[19] Finally, the HPA axis fails to respond to stress and stimulation.[20] This clinical measurement of suppressed endocrine function may be the defining element in the accurate identification and appropriate treatment of chronic "overstress syndrome."[21]

The stress response affects many hormones. Prolactin is secreted from the pituitary, which may suppress reproduction. The pancreas is stimulated to release the hormone glucagon, which raises blood sugar levels. Antidiuretic hormone, or vasopressin, is secreted from the pituitary, which maintains fluid levels. Additional hormones, such as growth hormone, luteinizing hormone, testosterone, thyroid releasing hormone (TRH), thyroid stimulating hormone (TSH), and insulin, are suppressed.[22,23]

Stress and the Cardiovascular System

Stress has been shown to impact cardiovascular health and related morbidity and mortality. Conditions such as atherosclerosis, hypertension, stroke, and hyperlipidemia have been linked to chronic and repetitive acute stress. Stress has been shown to increase inflammation primarily through the cytokine interleukin-6 and C-reactive protein (CRP).[24] Research suggests that the inflammation caused by the stress response is responsible for 40% of the atherosclerosis that occurs in patients with no other known risk factors.[25] Also, epinephrine has been shown to increase coagulation. Research suggests that stimulation of adrenergic receptors is responsible for platelet activation implying that the catecholamine surge may lead to increased risk of thrombosis in individuals with atherosclerosis.[26] Additional studies indicate that physiological

levels of norepinephrine as seen with aerobic exercise may increase platelet reactivity and hypercoagulability as well.[27] Hypertension is also associated with increased physiological reactivity in the sympathetic and HPA axis. Studies indicate that individuals at higher risk for hypertension show increased cortisol, blood pressure, and heart rate in response to a psychological stressor.[28] A study with nondiabetic individuals with acute myocardial infarction has also correlated increased cortisol and glucagon with insulin resistance.[29]

Stress and the Digestive System

Stress is associated with irritable bowel syndrome (IBS), peptic ulcer disease, and changes in appetite. IBS is a condition characterized by abdominal discomfort and diarrhea and=or constipation. Studies indicate that individuals with IBS have elevated cortisol as well as increased pro-inflammatory cytokines interleukin-6 and interleukin-8. Also, these patients show an exaggerated cortisol and ACTH response to infused CRH.[30] A study on women with IBS demonstrated that these individuals exhibit a greater postprandial increase in systolic blood pressure and plasma norepinephrine levels. This study also showed a greater increase in postprandial granulocytes and leukocytes and decreased natural killer cells and monocytes in these women compared to controls demonstrating altered cellular immune responses to food intake, which may at least, in part, be mediated by adrenergic mechanisms.[31] Additional studies correlate IBS with increased urinary norepinephrine, epinephrine, and cortisol levels.[32] Studies also show that physical and psychological stressors can induce gastric and duodenal ulcers.[33] Epidemiological studies have shown that an increase in self-perceived stress also increases the risk of developing peptic ulcers.[34] Researchers demonstrated that young individuals with duodenal ulcers have parietal cells and sympathetic-adrenal systems that exhibit increased sensitivity to environmental stressors.[35]

Stress and the Nervous System

Stress affects normal brain function as well as multiple psychological conditions. Studies indicate that cortisol and psychological stress impair memory retrieval, and particularly emotionally arousing words were most affected by this effect.[36] Research also has demonstrated that stress-induced cortisol effects long-term consolidation of declarative memories.[37] Stress and increased glucocorticoids have been shown to impact the size and function of the hippocampus. Hippocampal atrophy, decreased hippocampal activation with memory task, and memory deficits are associated with increased stress and particularly with posttraumatic stress disorder.[38] Cognitive function is also impacted as studies indicate that higher levels of cortisol are associated with decreased cognitive performance including processing speed, eye-hand coordination, executive functioning, verbal memory and learning, and visual memory.[39]

Additionally, the HPA axis is hyperactive in individuals with depression, and increased vasopressin levels are associated with increased suicide risk.[40] ACTH autoantibodies are correlated with conditions such as chronic fatigue syndrome, anorexia nervosa, and major depression. These autoantibodies cause a decrease in cortisol by disrupting the HPA axis.[41] Studies have shown that late-in-life depression is associated with both below and above normal levels of cortisol, suggesting a sensitivity to any variation in the HPA axis.[42] In addition to depression, dysregulation of the HPA axis is also found in anxiety and panic disorder.[43]

Stress and the Immune System

The release of cortisol that occurs in response to stress suppresses the immune system. Studies suggest that an elevated cortisol: DHEA ratio is a contributing factor to this reduced immunity, particularly in elderly patients.[44] A study correlating perceived life stress and risk of upper respiratory infections (URI) found that those individuals with high levels of negative life events and who showed high cortisol reactivity had increased numbers of URIs. Also this study showed that during times of increased perceived stress, lower reactivity of natural killer cells and CD8 cells were also correlated with increased URIs.[45]

Autoimmune disease is also correlated with dysregulation of the stress response. Individuals with rheumatoid arthritis have been shown to have a decreased cortisol response to an acute stressor and elevated pro-inflammatory interleukin-6.[46] Decreased HPA activity has also been demonstrated in individuals with Sjogrens syndrome showing a decrease in ACTH, cortisol, and a blunted adrenal-pituitary response to CRH.[47]

Stress and the Genitourinary System

Endometriosis is a disease affecting reproductive age women and is characterized by ectopic endometrial tissue outside the uterus, dysmenorrhea, and infertility. Recent research indicates that the severity of endometriosis is directly correlated to elevated serum cortisol and prolactin levels.[48] Infertile women undergoing in-vitro fertilization have been shown to exhibit increased cortisol and prolactin levels compared to fertile women, and elevated anxiety levels were correlated with decreased success of the procedure.[49] Gonadal hormones are also affected by stress. Studies show that stress significantly decreases testosterone levels. Also, estrogen has been shown to blunt the HPA axis stress response stimulated by psychological stress. Estrogen supplementation in perimenopausal women decreases cortisol, ACTH, epinephrine, norepinephrine, and blood pressure.[50]

Relationship between Stress and Weight Management

Cortisol also plays a role in weight management. Increased abdominal obesity and binge eating is associated with increased levels of cortisol.[51] Studies show that glucocorticoids increases appetite and levels of leptin, a polypeptide hormone that modulates appetite.[52] Also, studies show that increased perceived stress is associated with increased serum leptin concentrations.[53] Leptin is an intricate factor in the HPA axis, as research shows that it is involved in the expression of CRH in the hypothalamus, the adrenal level with ACTH, and is regulated by glucocorticoids. In addition, leptin and cortisol show an inverse circadian rhythm suggestive of regulatory feedback loop.[54] Furthermore, the hormone ghrelin, which stimulates increased food intake and fat mass, is increased by a stress-induced rise in cortisol.[55]

COPING MECHANISMS FOR STRESS AND DISEASE

Personality and temperament play a role in modulating the stress response and help explain why individuals with certain personality traits are more prone to acquiring stress-related diseases. Individuals with the Type A personality are described as competitive, impatient, and exhibit time urgency and intense achievement drive. Numerous studies have confirmed that this personality type is an independent risk factor for developing cardiovascular disease and have increased related morbidity and mortality.[56]

More recent studies indicate that hostility is more predictive than the Type A personality profile for acquiring stress-related disease. Researchers have demonstrated a 35% increase risk of cardiovascular events in women with higher scores on hostility inventories when adjusting for other risk factors.[57] Increased mortality in younger individuals with diagnosed coronary artery disease is also associated with hostility.[58] Studies indicate that hostile individuals exhibit increased levels of total serum cholesterol, homocysteine, and inflammatory markers such as CRP.[59–61]

Inflammatory cytokines, such as interleukin-1, interleukin-8, and TNF-alpha, are also elevated in hostile and depressed individuals.[62] Additionally, suppressed anger is associated with increased carotid artery intima-media thickness and stiffness.[63] Socioeconomic and psychosocial stressors are also associated with decreased post-stress recovery of systolic blood pressure to baseline.[64] Studies have also shown that individuals with metabolic syndrome and high levels of hostility demonstrate a fourfold increase in the risk of having a myocardial infarction.[65] Hostility, anger, and depression are correlated with increased insulin resistance and elevated fasting insulin and glucose in women.[66] Researches also propose a correlation between perceived loss of control over one's environment as a risk factor for increased hypertension and cardiovascular disease.[67]

Other stress-related diseases are also correlated with personality. A study was performed with individuals with chronic constipation with and without IBS. This study demonstrated a significant correlation with chronic constipation in all groups with increased hostility.[68] Additionally, studies with inflammatory bowel disease show a decrease in relapse and surgical interventions in those individuals with more mature psychological defense mechanisms.[69]

OVERUSE OF CORTICOSTEROIDS

Cortisone and hydrocortisone help to regulate the body's glucose. Since the late 1940s, corticosteroids have been used medically to alter and suppress immune function. With a phenomenal range of applications, corticosteroids were quickly adopted as "miracle cures" for the full range of autoimmune diseases, including the difficult-to-manage rheumatoid arthritis. However, it did not take long for clinicians and researchers to discover that there was a severe cost for chronic corticosteroid use. Countless patients developed physical conditions that, prior to such widespread use of these agents, were rarely seen by practitioners of Western medicine such as osteoporosis, poor wound healing, abdominal obesity, hypertension, hyperglycemia, and fluid retention. Poorly monitored corticosteroid administration can result in a condition similar to Cushing's syndrome, an endogenous hypercortisolemia disease. A temporary treatment with very low doses of cortisone may be beneficial, however, in patients with severe adrenal exhaustion.

DIAGNOSING ADRENAL DYSFUNCTION

The fine homeostatic balance between health and disease can be disturbed if the clinical cause of a patient's original imbalance is not fully explored and treated. Indeed, replacement or augmentation of hormones from exogenous sources, all too often, merely suppresses symptoms while leaving the underlying disease process to advance without the diagnostically helpful symptoms. When addressing adrenal imbalance, it is essential to look beyond laboratory tests and symptoms alone and to integrate the clinical presentation as a whole. Just as overt signs and symptoms of thyroid dysfunction may or may not always manifest with abnormal laboratory

tests, a functional adrenal condition may be present in the absence of abnormal laboratory findings. In fact, a recent plethora of medical literature points to the seemingly error-prone assessment that results from measuring thyroid function solely via laboratory tests. The main cause of adrenal fatigue is continual low-level stress, which taxes the adrenal glands, limiting their ability to adapt to acute stressors. This low-level stress may be caused by emotional or physical upsets or loss of sleep. Clinically, this manifests in the development of exhaustion that does not become resolved with standard rest and relaxation.

A large number of symptoms associated with adrenal dysfunction have been reported in the literature. These symptoms are often categorized according to physiologic performance, psychologic=information processing, and immunologic and biochemical parameters.[70] To date, however, there is no universally agreed-on group of symptoms that describes accurately the condition or the physiologic=psychologic=emotional distresses that some people experience. Rather, multiple symptoms may present in no particular combination under the general categories of adrenal exhaustion, hypoadrenocorticalism, and hyperadrenocorticalism. Perhaps the most confusing and controversial clinical component of diagnosing and treating adrenal imbalance is codifying the testing parameters to determine conclusively the presence of adrenal exhaustion and dysfunction. To advance alternative medicine in evidence-based clinical practice, tools must be developed that can give practitioners a comprehensive approach to diagnosing adrenal burnout syndrome. By combining biochemical studies, endocrine assays, and physiologic functioning tests, these assessment methods would allow a clinician to gain a greater understanding of a patient's stress response. Numerous assessment methods have been proposed and are utilized to measure and track adrenal dysfunction. Some of these testing models are listed below.

The 24-Hour Salivary Cortisol Pattern

This pattern consists of four points—7 am–8 am, noon, 4 pm–5 pm, and 11 pm–midnight. Research suggests that measuring salivary, as opposed to serum, cortisol and DHEA levels may be the best indication of adrenal function.[71–74] Yet controversy exists concerning the complete validity of such testing methods because of potentially confounding variables, such as dietary interference, diurnal variations in salivary production and viscosity, oral contaminants, and the potential presence of gingival disease or problems regarding the mouth ecology. A 24-hour urine test may provide a better overall picture of glandular function in contrast to a spot urine or blood test, which provides merely a ''snapshot'' of physiological functioning. In addition, the

> To compensate for increased stressors, many individuals have turned to ergogenic or energy enhancement substances.

24-hour urine measures free cortisone to cortisol ratio, which is useful to identify issues related to 11-beta-hydroxysteroid dehydrogenase, the enzyme that converts active cortisol to inactive cortisone.

The 24-Hour Urine Free-Hormone Profiles

ACTH is part of a complex pathway of biochemical messengers. It is, therefore, difficult to identify where, exactly, in this ''pathway'' dysfunction may be occurring. In response to this

complexity, comprehensive testing laboratories have developed methods for evaluating primary and secondary steroid hormones and their most important metabolites. This provides practitioners with a tool to examine the stress response more fully in the context of overall hormonal balance including precursors and metabolites of the hormones.[75]

sIgA

A protein modulator of immune activity, sIgA is intimately linked to the activity of the autonomic nervous system. Alterations and dysfunctions in the autonomic nervous system can be measured directly by changes in salivary composition and excretion. Medical researchers have recently theorized that factors such as exercise and chronic stress might induce changes in several components of saliva, such as immunoglobulins and proteins. Acute stress increases sIgA secretion immediately after the stressor, while the chronic stress causes a decrease in sIgA secretion several days after the stressor.

Plasma Glutamine

Glutamine is considered to be a conditionally essential amino acid because it can be synthesized in the body from glutamic acid. Glutamine is an important modulator of many homeostatic functions and optimal functioning of specialized tissues within the body. These tissues are key to gut and immune system function. Researchers have recognized certain conditions in which the body's demand for glutamine exceeds its ability to synthesize it. Such conditions are associated with high levels of physiologic stress. Under such chronic, catabolic conditions, the body takes its supply of glutamine from muscle tissue.[76] Glutamine may be decreased after surgery and other stressors.

Total Blood Cholesterol

Researchers theorize that because the body alters its ability to compensate for a shift in adrenal function, stress has a deleterious influence on cholesterol synthesis and specific lipoprotein molecules. Measuring total body cholesterol will allow researchers to correlate changes in adrenal function with shifts in cholesterol levels. Chronic stress is associated with high LDL-cholesterol and low HDL-cholesterol.

Serum Ferritin

Ferritin reflects the body's iron stores and is a good indicator of iron storage status. The ferritin test is more sensitive than the iron or total iron binding capacity test for diagnosing iron deficiency or overload. Measuring ferritin levels will provide an additional means of assessing immune function and physiologic adaptation to stress. Serum ferritin concentrations can be significantly depressed under physical stress.

Morning Basal Body Temperature

Cortisol has a profound suppressive effect on thyroid-axis function. In the presence of elevated cortisol, thyroid functioning can become significantly impaired. The resultant changes in thyroid metabolism can include suppression of thyroid-stimulating hormone (thyrotropin; TSH) and decreased conversion of thyroid hormone from thyroxine (T4) to the more potent

form of triiodothyronine (T3) in peripheral tissues. It has been hypothesized that these effects arise from inhibition of the enzyme 5-deiodinase, affecting the T4 to T3 conversion and suppression of TSH by endogenous somatostatin. Increased cortisol can cause peripheral tissues to no longer respond to the thyroid hormone signal. It creates a condition of thyroid resistance, meaning that thyroid hormone levels can be normal, but tissues fail to respond efficiently to the thyroid signal, causing symptoms of hypothyroidism such as low basal body temperature.

Postural Muscle Assessment

Research has identified restricted muscular sodium=potassium adenosine triphosphatase (ATPase) activity and reduced cortisol levels in chronically stressed rats. Studies suggest that it is necessary to have an "intact pituitary–adrenal axis for adequate function of the sodium= potassium pump."[77,78] An ion shift with an increased extracellular potassium concentration has also been proposed as a possible cause of muscular complaints during exercise in patients who use beta-blockers. Postural muscles (gastrocnemius, soleus, medial hamstrings, short adductors of the thigh, hamstrings, psoas, piriformis, tensor fascia lata, quadratus lumborum, erector spinae, latissimus dorsi, upper trapezius, sternomastoid, levator scapulae, pectoralis major, and the flexors of the forearm) shorten under stress. Therefore, evaluation of the postural muscles may be applicable to stress-induced health conditions.

HERBAL TREATMENTS FOR ADRENOCORTICAL DYSFUNCTION

To compensate for increased stressors, many individuals have turned to ergogenic or energy enhancement substances. These herbal and nutritional supplements are thought to have some type of ergogenic activity and are among the best-selling natural products in nutrition stores, with a financial impact in the $2–$3 billion per year range. Although there is a body of scientific literature on a variety of natural ergogenic substances—such as pyruvate, creatine, ephedra (ma huang; Ephedra sinica), ginseng (Panax spp.), and guarana (Paullinia cupana)—using animal models, there are few well-designed human clinical trials. This lack of legitimate research and the high over-the-counter use of natural products suggest an urgent need to conduct studies on the long-term effectiveness and safety of these natural ergogenic aids. Natural products (such as phytopharmacologic agents), which appear to enhance performance capacity (as demonstrated in animal and human studies), include such nutrients as creatine and pyruvate and such herbs as guarana, ginseng, Siberian ginseng (eleuthero; Eleutherococcus senticosus), schisandra (Schisandra chinensis), and ashwagandha (Withania somnifera).[79–81] Other botanicals with purported ergogenic efficacy include regular coffee (Coffea arabica), cola nut (Cola accuminata), and ephedra. These herbs are thought to have ergogenic effects because they contain methylxanthine compounds (cola nut and coffee beans), which have been shown to mimic the effects of endogenous epinephrine (ephedra). Caffeine, a methylxanthine, has been shown, in human trials, to enhance endurance and exercise performance.[82] Perhaps the most misunderstood of all adrenal tonic herbs are the adaptogens. The term adaptogen, coined by Dr. Israel Brekhman, was proposed as a more appropriate description for isolated phytochemical compounds. Adaptogens, first identified in 1966 by Brekhman, are, collectively, a group of medically effective substances that put organisms into nonspecific heightened resistance states to help organisms to combat stressors and adapt to extraordinary

Table 1–1. Botanicals for Treating Adrenocortical Dysfunction

Botanical Agent	R_x	Mechanism of Action
Licorice (Glycyrrhiza glabra)	1–2 g per day (can go as high as 30 g)	Suppresses 5b-reductase activity; inhibits 11b-hydroxysteroid-dehydrogenase, which converts active cortisol into inactive cortisone; may cause blood pressure elevations requiring monitoring
Hog weed (Boerhaavia diffusa)	Unknown	Buffers plasma cortisol elevation; reverses adrenal cortisol depletion under high levels of stress
Ashwagandha (Withania somnifera)	10–60 drops 3–4 times per day of fresh plant-liquid extract or 1–6 g daily of the whole herb in capsule or tea[a]	Glucocorticoid-like effects from plant sterols
Siberian ginseng (Eleutherococcus senticosus)	Dry strength liquid extract: 20–60 drops 1–4 times per day	Binds to mineral and extract: 20–60 glucocorticoid-receptors

[a]Tilgner S. Herbal Medicine: From the Heart of the Earth. Cottage Grove, OR: Wise Acres Press, 1999.

challenges. These herbs are of most interest to nutritionally minded physicians as substances that can enhance an individual's resistance to the long-term, cumulative effects of high-volume and high-intensity stress (such as exercise). Perhaps the most studied of the adaptogenic herbs are Siberian ginseng (Eleuthero) and licorice (Glycyrrhiza glabra). The purported mechanism of action of licorice is to reduce the amount of hydrocortisone broken down via inhibition of 11-beta-hydroxysteroid-dehydrogenase, which converts active cortisol into inactive cortisone. Eleuthero may act as an adaptogen by regulation of glucose metabolism and enhancement of immune function. These herbs were the first to be studied as adaptogens. Additional first-generation adaptogens include schisandra and reishi (Ganoderma lucidum).[83] There are additional botanical agents that have been reported to have adaptogenic qualities, but these agents have not been studied extensively for their support of the adrenal system. These include: ashwaganda, gotu kola (Centella asiatica), wild oats (Avena sativa), astragalus (huang chi; Astragalus membranaceous), fo-ti or hoshouwu (Polygonum multiflorum), burdock (Arctium lappa), Siberian Ginseng (Eleutherococcus senticosus) and suma (Pfaffia paniculata).

Withania somnifera (Ashwagandha)

Withania somnifera is a medicinal plant used in Ayurvedic medicine. Historically, this adaptogenic herb has been used to modulate the stress response as well as for immune modulation, and anti-inflammatory, anti-tumor, and antioxidant activity.[84] Research using animal models indicates that supplementation with ashwagandha moderates the stress response when exposed to chronic environmental stressors, including attenuation of symptoms such as

depression, increased blood sugar, glucose intolerance, increased cortisol, cognitive deficits and stomach ulcers.[85] Additional studies have shown that ashwagandha exhibits anti-anxiety and antidepressant activity comparable to pharmaceutical agents.[86] Research has also demonstrated that ashwagandha exhibits neuroprotective activity in the hippocampus with induced environmental stress. This study showed an 80% decrease in the number of degenerating cells in the hippocampus with ashwagandha compared to controls.[87] Studies using animal models have also demonstrated ashwagandha supplementation increases antioxidant enzymes as well as decreases stress-induced gastric ulcers.[88] Research has revealed immune modulating effects by up-regulation of Th-1 immune response measured by significant increases in CD4 and CD8 levels with ashwagandha root supplementation.[89] Ashwagandha root also has been shown to decrease total plasma lipids, cholesterol, triglycerides, and lipid peroxidation and increase HDL levels in hypercholesterolemic animals.[90]

Eleutherococcus senticosus (Eleuthero; Siberian Ginseng)

Siberian ginseng is another adaptogenic herb used for various immune and stress modulating effects. Studies with animal models indicate that Siberian ginseng supplementation combined with induced physical stress showed inhibition of elevation in serum cortisol, inhibition of the reduction in natural killer cell activity, and increased physical endurance.[91] Studies indicate that the constituents in Siberian ginseng also exhibit immune stimulating, antibacterial, cholesterol lowering, antioxidant, anti-cancer, and insulin modulating activity.[92]

Panax Ginseng (Korean Ginseng)

Panax ginseng has been traditionally used in Asian countries as an adaptogenic herb to modulate stress, fatigue, and immune function. Ginseng has numerous active constituents, most notably are the triterpenoid saponins referred to collectively as ginsenosides. Research shows that ginseng saponins directly influence the HPA axis. Animal models show that these saponins increase plasma levels of ACTH and cortisol, and this stimulation is suppressed by dexamethasone suggesting they act via the hypothalamus.[93] Panax has also been shown to increase DHEA sulfate and improve the cortisol : DHEA ratios in menopausal women. Panax also stimulates the Th-1 immune response. Studies show an increase in IgA production, and the Th-1 cytokines interleukin-2 and interferon-gamma as well as interleukin-10. Also, the activity of natural killer cells was increased.[94] Evidence suggests that Panax ginseng exhibits antioxidant, anti-cancer, and anti-inflammatory activity. Research shows that Panax provides protection of neurons from toxicity and hypoxia, improve cognitive performance, exhibits anti-atherosclerotic and antihypertensive activity, improves wound healing, decreases allergic response, and enhances insulin sensitivity.[95]

Rhodiola rosea

Rhodiola is another medicinal plant used to tonify and for general balancing. A double-blind crossover study performed with humans showed that Rhodiola supplementation improved mental fatigue and cognition under stressful conditions.[96] Investigation of Rhodiola also demonstrates that this herb prevents stress-induced cardiac damage by preventing catacholamine release and higher cAMP levels in the myocardium associated with increased stress.[97] Rhodiola has numerous other traditional uses as well. It exhibits antidepressant and anti-cancer activity, improves physical and mental performance, and increases endogenous opioid peptides.[98]

Botanicals with Purported Adaptogenic Properties

American ginseng (Panax quinquefolium)
Ashwagandha (Withania somnifera)
Astragalus (Astragalus membranaceus) root
Borage (Borago officinalis)
Bupleurum (Bupleurum chinense)
Cola nut (Cola nitida)
Devil's club (Oplopanax horridum)
Echinacea (Echinacea spp.)
Ginseng (Panax spp.)
Korean ginseng (Panax Ginseng)
Licorice (Glycyrrhiza glabra)
Matricaria chamomile
Oats (Avena sativa)
Prickly ash (Xanthoxylum clava-herculis) bark
Siberian ginseng (Eleutherococcus senticosus)
Scullcap (Scutellaria lateriflora)
Suma (Pfaffia paniculata)
Turmeric (Curcuma longa)

From: Tilgner S. Herbal Medicine: From the Heart of the Earth. OR: Wise Acres Press, 1999.

Camellia sinensis

Camellia sinensis, commonly known as green tea, is well known for its antioxidant, anti-inflammatory, and anti-cancer properties. Additionally, it is believed to improve cardiovascular health, protect the skin from ionizing radiation, and enhance weight loss.[99] The amino acid theanine is one of the constituents of green tea. Human studies show that oral intake of theanine attenuates the sympathetic response to an acute stressor. Specifically, a decrease in heart rate and salivary immunoglobulin A was demonstrated.[100] Theanine increases dopamine and serotonin levels in the brain, which may account for its anxiolytic activity.[101] Also, animal models also show that theanine decreases blood pressure in spontaneously hypertensive rats.[102]

Matricaria chamomile

Matricaria chamomile, also known as Chamomilla recutita, has been shown to modulate the HPA axis. Animal models have shown that chamomile supplementation reduced cortisol levels in response to an acute stressor.[103] Additionally, chamomile inhalation decreased the stress-induced increase in ACTH levels.[104] The constituent in chamomile apigenin has been shown to bind the central benzodiazepine receptors inducing anxiolytic and slight sedating effects.[105]

Holy Basil

Research has documented that holy basil (Ocimim sanctum) acts as an antioxidant and may decrease levels of stress hormones.[106] This herb is a powerful anti-inflammatory that has an effec-

tiveness that is similar to aspirin and ibuprofen. However, unlike aspirin and ibuprofen, this herb is not irritating to the lining of the stomach. Animal studies have found that holy basil has similar effects to a variety of mood-enhancing pharmaceuticals, such as stimulants and antidepressants.

NUTRACEUTICALS FOR TREATING ADRENOCORTICAL DYSFUNCTION

Phophatidylserine

Phosphatidylserine is an endogenous phospholipid found in high levels in the brain and is important in neuron function. Soy lecithin phosphatidylserine has been shown to have adaptogenic properties and modulates the HPA axis. Studies show that in the presence of a

Table 1–2. Nutraceuticals for Treating Adrenocortical Dysfunction

Nutraceutical	R_x	Mechanism of Action
Vitamin C	1,000 mg, 3 times per day	Acts as a reducing agent for the mixed function oxidase used in the synthesis of steroid hormones[a]
Pantothenic acid	500 mg, 2 times per day	Increases corticosteroid production and normalizes response to ACTH[b]
Vitamin B complex	50–100 mg, per day	Helps to transfer methyl groups and regenerate methionine
Phosphatidylserine	500 mg, 2 times per day, 15 minutes prior to eating	Orally, prescribed PS product has decreased plasma cortisol and ACTH levels in healthy research subjects[c]
Magnesium	150 mg, 3 times per day	A cofactor for most ATP-dependent reactions and activation of intracellular secondary messenger cAMP
Zinc	15 mg, 2 times per day, with food	Zinc deficiency increases membrane susceptibility to oxygen free-radical damage
a-lipoic acid	150 mg, 3 times per day	Cofactor for the citric-acid cycle; potent antioxidant; partially restores the hydrocortisone suppression of T-helper cell activity[d]
Adrenal glandular support	400–500 mg, per day or as directed by manufacturer	Unknown; further research is needed

[a]Kodama M, Inoue F, Kodama T. Intraperitoneal administration of ascorbic acid delays the turnover of labeled cortisol in plasma of ODA rat, but not Wistar rat: Evidence in support of the cardinal role of vitamin C in the progression of glucocorticoid synthesis. In Vivo 1996;10:97–110

[b]Pietrzik K, Ginta E. Response of hepatitis drug–metabolizing enzymes to immobilization stress in rats of various ages. Acta Physiol Hungarica 1993;81:29–35.

[c]Monteleone P, Maj M, Beinert L, et al. Blunting by chronic phosphatidylserine administration of the stress-induced activation of the hypothalamo-pituitary-adrenal axis in healthy men. Eur J Clin Pharmacol 1992;41:385–388.

[d]Ohmori H, Yamauchi T, Yamamoto I. Augmentation of the antibody response by lipoic acid in mice. Jpn J Pharmacol 1986;42:275–280.

ACTH, adrenocoricotropic hormone; ATP, adenosine triphosphate; cAMP, cyclic adensosine monophosphate; PS, phosphatidylserine.

psychological stressor, phosphatidylserine supplementation blunts serum cortisol, ACTH, and salivary cortisol levels.[107] Additionally, research has shown that phosphatidylserine supplementation in individuals with above-average neuroticism scores reported better moods and feeling less stressed.[108] Results also indicate that phosphatidylserine improves cognitive function on tasks such as learning and memory skills in elderly individuals.[109] In addition, studies demonstrate improvement in depression, cognition, and behavior in elderly individuals with phosphatidylserine.[110]

L-Tyrosine and L-Phenylalanine

Tyrosine is a nonessential amino acid synthesized from phenylalanine. It is the precursor used for the synthesis of thyroxine, catecholamines, norepinephrine, epinephrine, and dopamine. Studies have associated stress-induced impairment of performance with depletion of brain stores of norepinephrine. Tyrosine supplementation has been shown to improve stress-associated declines in both neural norepinephrine levels and performance.[111] Also, individuals given tyrosine supplementation performed better on a memory and a tracking task under psychosocial and physical stress. In addition, the supplementation of tyrosine decreased systolic blood pressure in these individuals.[112]

Ascorbic Acid

Ascorbic acid, or vitamin C, is a water-soluble vitamin important for numerous physiological functions. In addition to antioxidant and immune-stimulating activity, it is also involved with tyrosine, tryptophan, norepinephrine, dopamine, thyroxine, and carnitine metabolism. A study was performed to evaluate the effect of ascorbic acid supplementation with psychological stress. The group given the ascorbic acid showed less increase in blood pressure, decreased subjective stress response, and a faster cortisol recovery.[113] In one study, ascorbic acid supplementation was given to individuals undergoing prolonged exercise. Cortisol was significantly reduced immediately post-exercise, as well as epinephrine, interleukin-10, and interleukin-1 receptor antagonist.[114] Evidence also shows that animals deficient in ascorbic acid have significantly higher serum and saliva cortisol levels.[115]

B Vitamins

B vitamins, such as pyridoxine, pantothenic acid, thiamine, and cobalamin, have been shown to improve aspects of the stress response and stress-related disease. Pyridoxine, or vitamin B6, is required for amino acid, carbohydrate, and lipid metabolism. Pyridoxine has been shown by numerous studies to modulate the stress response. Animal studies indicate that pyridoxine deficiency causes hypertension and increased sympathetic stimulation and decreased serotonin, gamma-aminobutyric acid (GABA) and pyridoxal phosphate. Pyridoxine supplementation in these animals reversed these finding demonstrating normal GABA, serotonin, epinephrine and norepinephrine levels.[116] Vitamin B6 is associated with increased risk of cardiovascular disease. Low levels of pyridoxal 5$^{\text{ø}}$-phosphate, the active form of vitamin B6, is associated with elevation in the inflammatory marker CRP independent of homocysteine levels.[117] Low levels of vitamin B6, B12, and folate are associated with increased homocysteine and risk for coronary heart disease.[118] Thiamine, or vitamin B1, has also shown anti-stress activity in animals by protecting cardiac tissue from stress-induced ischemia.[119] Deficiency of thiamine is also associated with memory and learning deficits.[120]

Omega-3 Fatty Acids

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 fatty acids found in high concentration in fish, such as salmon, cod, mackerel, trout, sardines, and herring. Research has shown that supplementation with omega-3 fatty acids blunt the stress response elicited by mental stress. In fact, epinephrine, cortisol, plasma nonesterified fatty acids, and energy expenditure were all significantly decreased with dietary fish oil supplementation.[121] Fish oil also has anti-inflammatory activity by inhibiting the pro-inflammatory cytokines interleukin-1 alpha and TNF-alpha as well as decrease COX-2 expression.[122] Studies also show that omega-3 deficiency adversely affects learning and cognitive behavior.[123] Evidence suggests that fish oil is beneficial for prevention of cardiovascular disease, type 2 diabetes, metabolic syndrome, hyperlipidemia, and depression.[124]

CONCLUSIONS

A particularly interesting study revealed that cortisol strongly fluctuates with increases and decreases in negative affect. The parameters of this research included testing salivary cortisol levels of 30 healthy young men experiencing an activating and humorous video, a speech stressor, and a resting control. The study researchers found that negative affect increased during the speech but strongly decreased during the video. The researchers concluded that their results suggested that the HPA axis is a dynamic system that is influenced by changes in negative affect independently of the experience of generalized activation.[125] An increasing amount of research points to the relation between some emotional states and sympathetic nervous system over-activity.[3,126] This research confirms that the mind and body can no longer be looked on as separate moieties. Whatever the underlying mechanism that connects mind and body, the writing on the wall is quite clear—medicine can no longer separate the structure of the human body from the function of the human body. Ultimately, as we have known for a very long time empirically, restoration of homeostasis requires treatment of the whole organism, not just one part of it.[127] With regard to adrenocortical function, even on the purely physical level, many physicians who practice nutritionally oriented medicine have noted that certain conditions improve with treatment for adrenal fatigue. Some of the more common conditions that respond to this kind of treatment are acute viral illnesses, allergies, gastritis, osteoarthritis, rheumatoid arthritis, eczema, contact dermatitis, urticaria, psoriasis, and allergic rhinitis.

REFERENCES

[1]Randolfi EA. Developing a stress management and relaxation center for the worksite. Worksite Health. 1997 Summer;4,(2):40–44.

[2]Sapolsky R. Stress and disease: Who gets sick and who stays well. Institute for CorTexT Research and Development, Stanford University, Department of Biological Sciences and Neuroscience. Spring 1995 lecture.

[3]Kovacs K, Selye H. The original and creative scientist. Ann NY Acad Sci. 1998;851:13–15.

[4]Terzolo M, Osella G, Ali A, Borretta G, Cesario F, Paccotti P, Angeli A. Subclinical Cushing's syndrome in adrenal incidentaloma. Clin Endocrinol. 1998;48(1):89–97.

[5]Tintera JW. Hypoadrenocorticism. Troy, NY: Hypoglycemia Foundation, Inc., 1980.

[6]Opstad K. Circadian rhythm of hormones is extinguished during prolonged physical stress, sleep and energy deficiency in young men. Eur J Endocrinol. 1994;131:56–66.

[7]Ronizo RA. Nutritional support for adrenal function. Am J Nat Med. 1998;5:12–17.

[8]Morgan WP, Brown DR, Raglin JS, O'Connor PJ, Ellickson KA. Psychological monitoring of overtraining and staleness. Br J Sports Med. 1987;21:408–414.

[9]Chrousos GP. Stressors, stress, and neuroendocrine integration of the adaptive response. Ann NY Acad Sci. 1998;851:311–356.
[10]Szabo S. Hans Selye and the development of the stress concept. Ann NY Acad Sci. 1998;851:19–27.
[11]Ronzio RA. Nutritional support for adrenal function. Am J Nat Med. 1998;5(5):12–17.
[12]Kelly GS. Nutritional and botanical interventions to assist with adaptation to stress. Alt Med Rev. 1999;4(4):249–265.
[13]Gleeson M, McDonald WA, Cripps AW, Pyne DB, Clancy RL, Fricker PA, Wlodarrczyk JH. Exercise, stress, and mucosal immunity in elite athletes. Adv Mucosal Immunol. 1995;2:571–574.
[14]Smith LL. Cytokine hypothesis of overtraining: A physiological adaptation to excessive stress? Med Sci Sports Exerc. 2000;32(2):317–331.
[15]Heiderscheit BC, Hamil J, Van Emmerik REA. Q-angle influences on the variability of lower extremity coordination during running. Med Sci Sports Exerc. 1999;31(9):1313–1319.
[16]Stone D, Green C, Rao U, Aizawa H, Yamaji T, Niyibizi C, Carlin G, Woo SL. Cytokine-induced tendinitis: A preliminary study in rabbits. J Orthoped Res. 1999;17(2):168–177.
[17]Kreider RB, Fry AC, O'Toole ML. Overtraining in Sport. Champaign, IL: Human Kinetics, 1988.
[18]Lehmann M, Foster C, Hans-Harmann D, Gastman U. Autonomic imbalance hypothesis and overtraining syndrome. Med Sci Sports Exerc. 1998;30(7):1140–1145.
[19]Demitrack MA, Crofford LJ. Evidence for the pathophysiological implications of hypothalamic–pituitary–adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. Ann NY Acad Sci. 1998;840(4):684–697.
[20]Greenspan FS, Strewler GJ. Basic and Clinical Endocrinology. Stamford, CT: Appleton and Lange= Simon & Schuster, 1997.
[21]Fry RW, Morton AR, Garcia-Webb P, Crawford GPM, Keast D. Biological responses to overload training in endurance sports. Eur J Appl Physiol. 1992;64:335–344.
[22]Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res. 2002 Oct;53(4):865–871.
[23]Vaananen I, Vasankari T, Mantysaari M, Vihko V. Hormonal responses to 100 km cross-country skiing during 2 days. J Sports Med Phys Fitness. 2004 Sep;44(3):309–314.
[24]Black PH. The inflammatory response is an integral part of the stress response: Implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. Brain Behav Immun. 2003 Oct;17(5):350–364.
[25]Black PH, Garbutt LD. Stress, inflammation and cardiovascular disease. J Psychosom Res. 2002 Jan; 52(1):1–23.
[26]von Kanel R, Dimsdale JE. Effects of sympathetic activation by adrenergic infusions on hemostasis in vivo. Eur J Haematol. 2000 Dec;65(6):357–369.
[27]Ikarugi H, Taka T, Nakajima S, Noguchi T, Watanabe S, Sasaki Y, Haga S, Ueda T, Seki J, Yamamoto J. Norepinephrine, but not epinephrine, enhances platelet reactivity and coagulation after exercise in humans. J Appl Physiol. 1999 Jan;86(1):133–138.
[28]al'Absi M, Wittmers LE Jr. Enhanced adrenocortical responses to stress in hypertension-prone men and women. Ann Behav Med. 2003 Winter;25(1):25–33.
[29]Nishio K, Shigemitsu M, Kusuyama T, Fukui T, Kawamura K, Itoh S, Konno N, Katagiri T. Insulin resistance in nondiabetic patients with acute myocardial infarction. Cardiovasc Revasc Med. 2006 Apr–Jun;7(2):54–60.
[30]Dinan TG, Quigley EM, Ahmed SM, Scully P, O'Brien S, O'Mahony L, O'Mahony S, Shanahan F, Keeling PW. Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? Gastroenterology. 2006 Feb;130(2):304–311.
[31]Elsenbruch S, Holtmann G, Oezcan D, Lysson A, Janssen O, Goebel MU, Schedlowski M. Are there alterations of neuroendocrine and cellular immune responses to nutrients in women with irritable bowel syndrome? Am J Gastroenterol. 2004 Apr;99(4):703–710.
[32]Heitkemper M, Jarrett M, Cain K, Shaver J, Bond E, Woods NF, Walker E. Increased urine catecholamines and cortisol in women with irritable bowel syndrome. Am J Gastroenterol. 1996 May;91(5): 906–913.
[33]Quan C, Talley NJ. Management of peptic ulcer disease not related to Helicobacter pylori or NSAIDs. Am J Gastroenterol. 2002 Dec;97(12):2950–2961.
[34]Anda RF, Williamson DF, Escobedo LG, Remington PL, Mast EE, Madans JH. Self-perceived stress and the risk of peptic ulcer disease. A longitudinal study of US adults. Arch Intern Med. 1992 Apr;152(4): 829–833.
[35]Lazebnik LB, Arbuzova VG, Sokolova GN, Astaf 'eva OV, Petrako v AV, Nilova TV, Chikunova BZ. [Role of stress in the etiopathogenesis of duodenal ulcer in young patients] Eksp Klin Gastroenterol. 2002;(5):30–33, 126–127.

[36]Kuhlmann S, Piel M, Wolf OT. Impaired memory retrieval after psychosocial stress in healthy young men. J Neurosci. 2005 Mar 16;25(11):2977–2982.

[37]Elzinga BM, Bakker A, Bremner JD. Stress-induced cortisol elevations are associated with impaired delayed, but not immediate recall. Psychiatry Res. 2005 Apr 30;134(3):211–223.

[38]Bremner JD. The relationship between cognitive and brain changes in posttraumatic stress disorder. Ann NY Acad Sci. 2006 Jul;1071:80–86.

[39]Lee BK, Glass TA, McAtee MJ, Wand GS, Bandeen-Roche K, Bolla KI, Schwartz BS. Associations of salivary cortisol with cognitive function in the Baltimore memory study. Arch Gen Psychiatry. 2007 Jul;64(7): 810–818.

[40]Swaab DF, Bao AM, Lucassen PJ. The stress system in the human brain in depression and neurodegeneration. Ageing Res Rev. 2005 May;4(2):141–194.

[41]Wheatland R. Chronic ACTH autoantibodies are a significant pathological factor in the disruption of the hypothalamic-pituitary-adrenal axis in chronic fatigue syndrome, anorexia nervosa and major depression. Med Hypotheses. 2005;65(2):287–295.

[42]Penninx BW, Beekman AT, Bandinelli S, Corsi AM, Bremmer M, Hoogendijk WJ, Guralnik JM, Ferrucci L. Late-life depressive symptoms are associated with both hyperactivity and hypoactivity of the hypothalamo-pituitary-adrenal axis. Am J Geriatr Psychiatry. 2007 Jun;15(6):522–529.

[43]Erhardt A, Ising M, Unschuld PG, Kern N, Lucae S, Pütz B, Uhr M, Binder EB, Holsboer F, Keck ME. Regulation of the hypothalamic-pituitary-adrenocortical system in patients with panic disorder. Neuropsychopharmacology. 2006 Nov;31(11):2515–2522. Epub 2006 Jul 12.

[44]Butcher SK, Killampalli V, Lascelles D, Wang K, Alpar EK, Lord JM. Raised cortisol:DHEA ratios in the elderly after injury: Potential impact upon neutrophil function and immunity. Aging Cell. 2005 Dec;4(6):319–324.

[45]Cohen S, Hamrick N, Rodriguez MS, Feldman PJ, Rabin BS, Manuck SB. Reactivity and vulnerability to stress-associated risk for upper respiratory illness. Psychosom Med. 2002 Mar–Apr;64(2):302–310.

[46]Eijsbouts AM, van den Hoogen FH, Laan RF, Hermus AR, Sweep CG, van de Putte LB. Hypothalamic-pituitary-adrenal axis activity in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2005 Sep–Oct; 23(5):658–664.

[47]Johnson EO, Vlachoyiannopoulos PG, Skopouli FN, Tzioufas AG, Moutsopoulos HM. Hypofunction of the stress axis in Sjogren's syndrome. J Rheumatol. 1998 Aug;25(8):1508–1514.

[48]Lima AP, Moura MD, Rosa e Silva AA. Prolactin and cortisol levels in women with endometriosis. Braz J Med Biol Res. 2006 Aug;39(8):1121–1127.

[49]Csemiczky G, Landgren BM, Collins A. The influence of stress and state anxiety on the outcome of IVF-treatment: Psychological and endocrinological assessment of Swedish women entering IVF-treatment. Acta Obstet Gynecol Scand. 2000 Feb;79(2):113–118.

[50]Charney DS. Psychobiological mechanisms of resilience and vulnerability: Implications for successful adaptation to extreme stress. Am J Psychiatry. 2004 Feb;161(2):195–216.

[51]Gluck ME, Geliebter A, Lorence M. Cortisol stress response is positively correlated with central obesity in obese women with binge eating disorder (BED) before and after cognitive-behavioral treatment. Ann NY Acad Sci. 2004 Dec;1032:202–207.

[52]Dagogo-Jack S, Umamaheswaran I, Askari H, Tykodi G. Leptin response to glucocorticoid occurs at physiological doses and is abolished by fasting. Obes Res. 2003 Feb;11(2):232–237.

[53]Otsuka R, Yatsuya H, Tamakoshi K, Matsushita K, Wada K, Toyoshima H. Perceived psychological stress and serum leptin concentrations in Japanese men. Obesity (Silver Spring). 2006 Oct;14(10):1832–1838.

[54]Casanueva FF, Dieguez C. Neuroendocrine regulation and actions of leptin. Front Neuroendocrinol. 1999 Oct;20(4):317–363.

[55]Rouach V, Bloch M, Rosenberg N, Gilad S, Limor R, Stern N, Greenman Y. The acute ghrelin response to a psychological stress challenge does not predict the post-stress urge to eat. Psychoneuroendocrinology. 2007 Jul;32(6):693–702. Epub 2007 Jun 8.

[56]Everson-Rose SA, Lewis TT. Psychosocial factors and cardiovascular diseases. Annu Rev Public Health. 2005;26:469–500.

[57]Olson MB, Krantz DS, Kelsey SF, Pepine CJ, Sopko G, Handberg E, Rogers WJ, Gierach GL, McClure CK, Merz CN; WISE Study Group. Hostility scores are associated with increased risk of cardiovascular events in women undergoing coronary angiography: A report from the NHLBI-Sponsored WISE Study. Psychosom Med. 2005 Jul–Aug;67(4):546–552.

[58]Boyle SH, Williams RB, Mark DB, Brummett BH, Siegler IC, Barefoot JC. Hostility, age, and mortality in a sample of cardiac patients. Am J Cardiol. 2005 Jul 1;96(1):64–66.

[59]Hillbrand M, Waite BM, Rosenstein M, Harackiewicz D, Lingswiler VM, Stehney M. Serum cholesterol concentrations and non-physical aggression in healthy adults. J Behav Med. 2005 Jun;28(3):295–299.

[60]Papageorgiou C, Pitsavos C, Panagiotakos DB, Kontoangelos K, Chrysohoou C, Papadimitriou GN, Rabavilas AD. Association between hostility and plasma total homocysteine concentrations in a general population sample. Neuropsychobiology. 2006;53(1):26–-32. Epub 2005 Nov 24.

[61]Coccaro EF. Association of C-reactive protein elevation with trait aggression and hostility in personality disordered subjects: a pilot study. J Psychiatr Res. 2006 Aug;40(5):460–465. Epub 2005 Jul 1.

[62]Suarez EC, Lewis JG, Krishnan RR, Young KH. Enhanced expression of cytokines and chemokines by blood monocytes to in vitro lipopolysaccharide stimulation are associated with hostility and severity of depressive symptoms in healthy women. Psychoneuroendocrinology. 2004 Oct;29(9):1119–1128.

[63]Anderson DE, Metter EJ, Hougaku H, Najjar SS. Suppressed anger is associated with increased carotid arterial stiffness in older adults. Am J Hypertens. 2006 Nov;19(11):1129–1134.

[64]Steptoe A, Marmot M. Psychosocial, hemostatic, and inflammatory correlates of delayed poststress blood pressure recovery. Psychosom Med. 2006 Jul–Aug;68(4):531–537.

[65]Todaro JF, Con A, Niaura R, Spiro A 3rd, Ward KD, Roytberg A. Combined effect of the metabolic syndrome and hostility on the incidence of myocardial infarction (the Normative Aging Study). Am J Cardiol. 2005 Jul 15;96(2):221–226.

[66]Suarez EC. Sex differences in the relation of depressive symptoms, hostility, and anger expression to indices of glucose metabolism in nondiabetic adults. Health Psychol. 2006 Jul;25(4):484–492.

[67]Pickering TG. Mental stress as a causal factor in the development of hypertension and cardiovascular disease. Curr Hypertens Rep. 2001 Jun;3(3):249–254.

[68]Dumitrascu DL, Acalovschi M, Pascu O. Hostility in patients with chronic constipation. Rom J Intern Med. 1998 Jul–Dec;36(3-4):239–243.

[69]Hyphantis TN, Triantafillidis JK, Pappa S, Mantas C, Kaltsouda A, Cherakakis P, Alamanos Y, Manousos ON, Mavreas VG. Defense mechanisms in inflammatory bowel disease. J Gastroenterol. 2005 Jan;40(1): 24–30.

[70]Marsden P, McCullagh AG. Endocrinology: Management of Common Diseases in Family Practice. fsLancaster, England. PSG Publishing, 1985.

[71]Lac G, Lac N, Robert A. Steroid assays in saliva: A method to detect plasmatic contaminations. Arch Int Physiol Biochem. 1993;101:257–262.

[72]Vining RF, McGinley RA. The measurement of hormones in saliva: Possibilities and pitfalls. J Steroid Biochem. 1987;27:81–94.

[73]Tunn S, Möllmann H, Barth J, Derendorf H, Krieg M. Simultaneous measurement of cortisol in serum and saliva after different forms of cortisol administration. Clin Chem. 1992;38:1491–1494.

[74]Peters JR, Walker RF, Riad-Fahmy D, Hall R. Salivary cortisol assays for assessing pituitary–adrenal reserve. Clin Endocrinol. 1982;17:583–592.

[75]Fitzgerald PA. Adrenal cortex physiology. In: Tierney Jr LM, McPhee J, Papadakis MA, eds. Current Medical Diagnosis and Treatment. Los Altos, CA: MA Lange Publishers, 1995.

[76]Marz RB. Medical Nutrition from Marz, 2nd Edition. Portland, OR. Omni-Press, 1997.

[77]Maffetone P. Complementary Sports Medicine. Champaign, IL: Human Kinetics, 1999.

[78]Davis JM. Carbohydrates, branched-chain amino acids, and endurance: The central fatigue hypothesis. Int J Sport Nutr. 1995;5:29–38.

[79]Saito H, Yoshido Y, Takagi K. Effect of Panax ginseng root on exhaustive exercise in mice. Jpn J Pharmacol. 1974;24:119–127.

[80]Luo YM, Cheng XJ, Yuan WX. Effects of ginseng root saponins and ginsenoside Rb1 on immunity in cold water swim stress mice and rats. Chung Kuo Yao Li Hsueh Pao. 1993;14:401–404.

[81]Nishibe S, Kinoshita H, Takeda H, Okano G. Phenolic compounds from stem bark of Acanthopanax senticosus and their pharmacological effect in chronic swimming stressed rats. Chem Pharm Bull. 1990; 38:1763–1765.

[82]Dionne JY. An overview of ginseng and other adaptogenic herbs. Int J Integrative Med. 2000;(2):39–43.

[83]Filaretov AA, Bogdanova TS, Mitushov MI, et al. Effect of adaptogens on the activity of the pituitary–adrenocortical system in rats. Biull Eksp Biol Med. 1986;101:573–574.

[84]Mishra LC, Singh BB, Dag enais S. Scientific basis for the therapeutic use of Withania somnifera (ashwagandha): A review. Altern Med Rev. 2000 Aug;5(4):334–346.

[85]Bhattacharya SK, Muruganandam AV. Adaptogenic activity of Withania somnifera: an experimental study using a rat model of chronic stress. Pharmacol Biochem Behav. 2003 Jun;75(3):547–555.

[86]Bhattacharya SK, Bhattacharya A, Sairam K, Ghosal S. Anxiolytic-antidepressant activity of Withania somnifera glycowithanolides: An experimental study. Phytomedicine. 2000 Dec;7(6):463–469.

[87]Jain S, Shukla SD, Sharma K, Bhatnagar M. Neuroprotective effects of Withania somnifera Dunn. in hippocampal sub-regions of female albino rat. Phytother Res. 2001 Sep;15(6):544–548.

[88]Bhatnagar M, Sisodia SS, Bhatnagar R. Antiulcer and Antioxidant activity of asparagus racemosus WILLD and Withania somnifera DUNAL in rats. Ann NY Acad Sci. 2005 Nov;1056:261–278.

[89]Bani S, Gautam M, Sheikh FA, Khan B, Satti NK, Suri KA, Qazi GN, Patwardhan B. Selective Th1 up-regulating activity of Withania somnifera aqueous extract in an experimental system using flow cytometry. J Ethnopharmacol. 2006 Aug 11;107(1):107–115. Epub 2006 Apr 5.

[90]Visavadiya NP, Narasimhacharya AV. Hypocholesteremic and antioxidant effects of Withania somnifera (Dunal) in hypercholesteremic rats. Phytomedicine. 2006 May 16;[Epub ahead of print]

[91]Kimura Y, Sumiyoshi M. Effects of various Eleutherococcus senticosus cortex on swimming time, natural killer activity and corticosterone level in forced swimming stressed mice. J Ethnopharmacol. 2004 Dec;95(2–3):447–453.

[92]Davydov M, Krikorian AD. Eleutherococcus senticosus (Rupr. & Maxim.) Maxim. (Araliaceae) as an adaptogen: a closer look. J Ethnopharmacol. 2000 Oct;72(3):345–393.

[93]Hiai S, Yokoyama H, Oura H, Yano S. Stimulation of pituitary-adrenocortical system by ginseng saponin. Endocrinol Jpn. 1979 Dec;26(6):661–665.

[94]Liou CJ, Huang WC, Tseng J. Short-term oral administration of ginseng extract induces type-1 cytokine production. Immunopharmacol Immunotoxicol. 2006;28(2):227–240.

[95]Radad K, Gille G, Liu L, Rausch WD. Use of ginseng in medicine with emphasis on neurodegenerative disorders. J Pharmacol Sci. 2006 Mar;100(3):175–186. Epub 2006 Mar 4.

[96]Darbinyan V, Kteyan A, Panossian A, Gabrielian E, Wikman G, Wagner H. Rhodiola rosea in stress induced fatigue—a double blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. Phytomedicine. 2000 Oct;7(5): 365–371.

[97]Maslova LV, Kondrat'ev BIu, Maslov LN, Lishmanov IuB. [The cardioprotective and antiadrenergic activity of an extract of Rhodiola rosea in stress] Eksp Klin Farmakol. 1994 Nov–Dec;57(6):61–63.

[98]Kelly GS. Rhodiola rosea: a possible plant adaptogen. Altern Med Rev. 2001 Jun;6(3):293–302.

[99]Nagle DG, Ferreira D, Zhou YD. Epigallocatechin-3-gallate (EGCG): chemical and biomedical perspectives. Phytochemistry. 2006 Sep;67(17):1849–1855. Epub 2006 Jul 31.

[100]Kimura K, Ozeki M, Juneja LR, Ohira H. l-Theanine reduces psychological and physiological stress responses. Biol Psychol. 2006 Aug 21;[Epub ahead of print]

[101]Yokogoshi H, Kobayashi M, Mochizuki M, Terashima T. Effect of theanine, r-glutamylethylamide, on brain monoamines and striatal dopamine release in conscious rats. Neurochem Res. 1998 May;23(5): 667–673.

[102]Yokogoshi H, Kato Y, Sagesaka YM, Takihara-Matsuura T, Kakuda T, Takeuchi N. Reduction effect of theanine on blood pressure and brain 5-hydroxyindoles in spontaneously hypertensive rats. Biosci Biotechnol Biochem. 1995 Apr;59(4):615–618.

[103]Reis LS, Pardo PE, Oba E, Kronka Sdo N, Frazatti-Gallina NM. Matricaria chamomilla CH12 decreases handling stress in Nelore calves. J Vet Sci. 2006 Jun;7(2):189–192.

[104]Yamada K, Miura T, Mimaki Y, Sashida Y. Effect of inhalation of chamomile oil vapour on plasma ACTH level in ovariectomized-rat under restriction stress. Biol Pharm Bull. 1996 Sep;19(9):1244–1246.

[105]Viola H, Wasowski C, Levi de Stein M, Wolfman C, Silveira R, Dajas F, Medina JH, Paladini AC. Apigenin, a component of Matricaria recutita flowers, is a central benzodiazepine receptors-ligand with anxiolytic effects. Planta Med. 1995 Jun;61(3):213–216.

[106]Jeffries W. The present status of ACTH, cortisone, and related steroids in clinical medicine. N Eng J Med 1955;253:441–446.

[107]Hellhammer J, Fries E, Buss C, Engert V, Tuch A, Rutenberg D, Hellhammer D. Effects of soy lecithin phosphatidic acid and phosphatidylserine complex (PAS) on the endocrine and psychological responses to mental stress. Stress. 2004 Jun;7(2):119–126.

[108]Benton D, Donohoe RT, Sillance B, Nabb S. The influence of phosphatidylserine supplementation on mood and heart rate when faced with an acute stressor. Nutr Neurosci. 2001;4(3):169–178.

[109]Crook TH, Tinklenberg J, Yesavage J, Petrie W, Nunzi MG, Massari DC. Effects of phosphatidylserine in age-associated memory impairment. Neurology. 1991 May;41(5):644–649.

[110]Maggioni M, Picotti GB, Bondiolotti GP, Panerai A, Cenacchi T, Nobile P, Brambilla F. Effects of phosphatidylserine therapy in geriatric patients with depressive disorders. Acta Psychiatr Scand. 1990 Mar; 81(3):265–270.

[111]Salter CA. Dietary tyrosine as an aid to stress resistance among troops. Mil Med. 1989 Mar;154(3): 144–146.

[112]Deijen JB, Wientjes CJ, Vullinghs HF, Cloin PA, Langefeld JJ. Tyrosine improves cognitive performance and reduces blood pressure in cadets after one week of a combat training course. Brain Res Bull. 1999 Jan 15;48(2):203–209.

[113]Brody S, Preut R, Schommer K, Schurmeyer TH. A randomized controlled trial of high dose ascorbic acid for reduction of blood pressure, cortisol, and subjective responses to psychological stress. Psychopharmacology (Berl). 2002 Jan;159(3):319–124. Epub 2001 Nov 20.

[114]Peters EM, Anderson R, Nieman DC, Fickl H, Jogessar V. Vitamin C supplementation attenuates the increases in circulating cortisol, adrenaline and anti-inflammatory polypeptides following ultramarathon running. Int J Sports Med. 2001 Oct;22(7):537–543.

[115]Enwonwu CO, Sawiris P, Chanaud N. Effect of marginal ascorbic acid deficiency on saliva level of cortisol in the guinea pig. Arch Oral Biol. 1995 Aug;40(8):737–742.

[116]Paulose CS, Dakshinamurti K, Packer S, Stephens NL. Sympathetic stimulation and hypertension in the pyridoxine-deficient adult rat. Hypertension. 1988 Apr;11(4):387–391.

[117]Friso S, Jacques PF, Wilson PW, Rosenberg IH, Selhub J. Low circulating vitamin B(6) is associated with elevation of the inflammation marker C-reactive protein independently of plasma homocysteine levels. Circulation. 2001 Jun 12;103(23):2788–2791.

[118]Folsom AR, Nieto FJ, McGovern PG, Tsai MY, Malinow MR, Eckfeldt JH, Hess DL, Davis CE. Prospective study of coronary heart disease incidence in relation to fasting total homocysteine, related genetic polymorphisms, and B vitamins: The Atherosclerosis Risk in Communities (ARIC) study. Circulation. 1998 Jul 21;98(3):204–210.

[119]Vinogradov VV, Shneider AB, Senkevich SB. Thiamine cardiotropism. Cor Vasa. 1991;33(3):254–262.

[120]Nakagawasai O, Yamadera F, Iwasaki K, Arai H, Taniguchi R, Tan-No K, Sasaki H, Tadano T. Effect of kami-untan-to on the impairment of learning and memory induced by thiamine-deficient feeding in mice. Neuroscience. 2004;125(1):233–241.

[121]Delarue J, Matzinger O, Binnert C, Schneiter P, Chiolero R, Tappy L. Fish oil prevents the adrenal activation elicited by mental stress in healthy men. Diabetes Metab. 2003 Jun;29(3):289–295.

[122]Curtis CL, Hughes CE, Flannery CR, Little CB, Harwood JL, Caterson B. N-3 fatty acids specifically modulate catabolic factors involved in articular cartilage degradation. J Biol Chem. 2000 Jan 14;275(2): 721–724.

[123]Moriguchi T, Greiner RS, Salem N Jr. Behavioral deficits associated with dietary induction of decreased brain docosahexaenoic acid concentration. J Neurochem. 2000 Dec;75(6):2563–2573.

[124]Hutchins H, Vega CP. Omega-3 fatty acids: Recommendations for therapeutics and prevention. MedGenMed. 2005 Oct 19;7(4):18.

[125]Pagani M, Lucini D, Mela GS, Langewitz W, Malliani A. Sympathetic overactivity in subjects complaining of unexplained fatigue. Clin Sci. 1994;87(6):655–661.

[126]Urhausen A, Gabriel HH, Kindermann W. Impaired pituitary hormonal response to exhaustive exercise in overtrained endurance athletes. Med Sci Sports Exerc. 1998;30(3):407–414.

[127]DiGiovanna EL, Schiowitz S. An Osteopathic Approach to Diagnosis and Treatment. Philadelphia: JB Lippincott, 1997.

2

HOLISTIC APPROACHES TO TREATING ANDROPAUSE

Andropause has been increasingly discussed in the media in recent years. Originally described as the ''male climacteric'' in a Journal of the American Medical Association (JAMA)[1] paper in the mid-1940s, andropause has gained much attention lately among medical providers. In the JAMA study, Heller and Myers reported the benefits of testosterone replacement for relieving andropausal symptoms, thereby establishing the condition as an actual medical problem warranting replacement=treatment. Although the case for andropause was established so long ago, several conflicting theories about the validity of andropause as an actual medical condition have prevented it from receiving much-needed attention, and a confusing label—''male menopause''—has also created problems with recognition. In addition, relatively inconvenient treatments coupled with men's notorious discomfort with seeking medical care (women visit the doctor roughly 150% more frequently than men) have kept andropause on the ''back burner'' of medicine. The term andropause refers to a condition of lowered androgens, including testosterone, dehydroepiandrosterone (DHEA), and androstenedione. Incorrectly referred to as ''male hormones,'' these substances are found in both men and women. Peaking in the early to mid 20s, testosterone then begins a slow decline; each year thereafter the body's total testosterone level declines roughly by 1.6%, free testosterone by 2%, and bioavailable testosterone by 2.5%. Further compounding of this problem is a rise in sex hormone–binding globulin (SHBG) of roughly 1.6% per year.[2] Based on measurements of total testosterone, approximately 20% of men over 55 are considered hypogonadal[3] and, when this condition is based on levels of bioavailable testosterone, 50% of men age 50 and over are considered hypogonadal.[4] Recent research estimates that approximately one in four men over age 30 have low levels of testosterone.[5]

THE BIOCHEMISTRY OF ANDROPAUSE

The testes in a healthy young man will produce nearly 95% of his androgens, most of which is testosterone, at a rate of roughly 10 mg per day. The other 5% of androgens are derived from adrenal-gland production of DHEA, a precursor molecule. The stimulus for production originates in the hypothalamic-pituitary axis, where gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the release of two hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), in the pituitary gland. Luteinizing hormone drives the production of testosterone in the testes while FSH hormone affects spermatogenesis. Testosterone is metabolized further to dihydrotestosterone (DHT) by the ever-demonized enzyme 5-alpha-reductase (DHT is considered to be responsible for prostatic hypertrophy as well as male-pattern hair loss in genetically susceptible men)[6] or it undergoes transformation into estradiol via the enzyme aromatase. DHT binds with greater affinity to androgen receptors and therefore acts as a more potent activator (up to four times the strength) of testosterone receptors. Estrogens are also

a factor in andropause; 25% of the estradiol (the most biologically active form of estrogen) produced in the male is derived from the testicles while the remaining 75% is produced mainly in adipose tissue, the brain, and the liver. Nearly 98% of testosterone circulates bound to plasma proteins (and is thereby ''unavailable'') whereas the remaining 2%, known as free testosterone, accounts for nearly all of the biologic activity of the hormone. Of the bound testosterone, 40% is tightly bound to SHBG while the remainder is relatively weakly bound to albumin and is therefore more readily available. The term bioavailable refers to both the free testosterone and that which is bound to albumin.[7] The amount of testosterone that binds with SHBG increases with aging thereby decreasing the amount of free testosterone.[8] As testosterone levels fall, this stimulates increased production of SHBG by the liver; the estrogens in a man's body will also increase SHBG. Increased levels of SHBG-bound testosterone lead to normal serum ranges of total testosterone, despite a relative deficiency in bioavailable testosterone.

When the body has excess androgens, SHBG will tend to be low, which results in normal levels of total testosterone but elevated levels of bioavailable testosterone.

THE AGING PROCESS

Aging is undeniably related to lowered androgen levels. Compared to female menopause in which hormone levels are attenuated in a much narrower period of time over 5–10 years, andropause is marked by a more gradual decline of androgens. Because of the gradual nature of the decline, other phrases, such as ''androgen decline in aging males'' (ADAM) or ''alternative partial androgen decline in aging males'' are used because the decline does not result in complete deficiency. When androgen levels are low enough to become symptomatic, this condition is then called andropause,[9] which is technically defined as the natural cessation of the sexual function in older men. The decline of testosterone in males that occurs with aging is associated with an increase in FSH and LH, albeit to a much lesser extent than seen in women. A low testosterone level with a transient rise in LH is suggestive of age-related impairment of gonadotropin releasing hormone (GnRH).[10] Because testosterone has only a supportive role in regulating spermatogenesis, the fertility of andropausal men may be minimally affected; this is evidenced mostly by increased numbers of sperm with abnormal morphology and impaired mobility.[11] This situation is very different than that of women, in whom reproductive function is effectively ceased by menopausal-induced ovarian shutdown. The end result of sex-hormone deprivation in both genders is similar; loss of muscle, bone density, and cognitive function are common in aging patients, and they also develop increased risks for coronary artery disease and myocardial infarctions. The exact mechanism by which androgens affect bone development and cognition are relatively unclear at this time; however, a definite protective effect has been observed.[12]

Responsible for structural regulation of body proteins (and the development and maintenance of male genitalia), testosterone, at suboptimal levels, will initially lead to modest physical changes, including weakening muscles, bone loss, weight gain (primarily adipose tissue), and progressive facial aging. If testosterone is continually low, changes in memory, impotence, general fatigue, and irritability result. Decreased libido may be one of the first noted changes of age-associated testosterone decline in men. Declining testosterone and resultant loss of libido is not typically manifested by frustrated sexual urges, or complaints of frustration; most often this condition manifests as passivity. This can often lead to lack of interest in sex, visual sexual stimulation, business, competitive sports, and physical activity. Typically, during a man's 40s or 50s, and sometimes even the 30s, testosterone production begins to

decline noticeably. This is most often noted between ages 50 and 55. Symptoms are not universally experienced during andropause; however, the most frequently noted symptoms include mood changes accompanied by decreased well-being and changes in sexual function. One study of men age 60 and above revealed a 46% occurrence of loss of libido and erectile dysfunction, a 41% occurrence of general fatigue, and a 36% occurrence of memory loss.[13] The investigators noted, however, that correlation of symptoms with testosterone levels was highly variable and warrants further research.

CLINICAL ASSESSMENT

A detailed history, physical examination, and laboratory testing are necessary to rule out confounding factors and diagnose andropause correctly. Pertinent history questions should focus on the difference between loss of libido and impotence that results from erectile dysfunction. Excessive alcohol intake can suppress androgen production. Several factors act as diagnostic confounders. Chronic illness and stress (physical and mental) can lead to a decline in testosterone levels. Pharmaceuticals, such as spironolactone, digoxin, and cimetidine, also may produce this effect. Conditions, such as insulin resistance, obesity, and diabetes, are associated with hypogonadism[10,14,15] while anemia and hypothyroidism can produce fatigue and decreased libido. Other, rarer conditions, such as Kallman's syndrome, Klinefelter's syndrome, and Prader-Willi syndrome, that result in hypogonadism should also be ruled out.

TREATMENTS

Quite often, men suffering from symptoms of andropause are often treated for a specific, sometimes related, medical condition only. For instance, an andropausal man may be diagnosed with depression and given an antidepressant, rather than the doctor truly discerning the origin of the depression. With today's rampant prescribing of antidepressants to people who are not otherwise happy and content 100% of the time, this problem continues to be compounded (not to mention that antidepressants exaggerate loss of libido). Physicians may not see the entire pattern; but a holistic approach to the patient's entire symptomatology may include treatment with hormone replacement therapy (HRT), botanical medicines, nutrition, and exercise. Therapy is primarily focused on supporting and balancing hormone levels in the body.

Associated Andropausal Symptoms

- Erectile dysfunction
- Decreased libido
- Mood disturbances, including depression, irritability, tiredness
- Sleep difficulties
- Loss of muscle size and strength
- Osteoporosis
- Increased body fat
- Difficulty with concentration
- Memory loss

HORMONE REPLACEMENT

HRT Controversies

Similar to menopause, andropause can be treated with a combination of lifestyle, nutritional, botanical, and HRT approaches. The recent backlash against esterified estrogens used in combination with synthetic progesterone (progestin) molecules for treating menopause[16] has led to a near-revolution and altered prescribing habits by physicians. Several events (popular media and research evidence) have led to a wave of interest in using bioidentical hormones to achieve hormonal balance. An offshoot of this trend involves the use of hormone replacement in men. Among these are pro-hormones (DHEA, androstenedione, and pregnenolone) and testosterone. Combined with other natural medicines, treatment of andropause symptoms is rather successful but, as will be discussed, is not without controversy.

Testosterone Replacement

The knowledge base surrounding replacement of testosterone and androgens at physiologic levels in men with andropausal symptoms is much newer and less widely accepted in conventional medicine compared to the many accepted allopathic choices available to women. It is true that women, without a doubt, experience greater fluctuations and resultant symptoms because of the cyclical nature of female hormones. This has led in part to the vast ''medicalization'' of both the menses and menopause, wherein a solution to nearly any type of perturbation can be answered with one or more combinations of hormone replacement. Protocols and forms of HRT for men are quite limited by comparison. Medicine has long held that prostate-specific problems, such as hypertrophy and cancer, are solely initiated by testosterone. However, a small body of evidence is accumulating that these problems may not be solely related to this hormone. This evidence indicates that accumulation of estrogen in aging may be the primary factor in the development of prostate disease later in life whereas testosterone and DHT play a secondary role, or act as promoters.[17] Another study showed that there were no associations between testosterone, SHBG, or androstenedione concentrations and the incidence of prostatic carcinoma, further refuting the notion that androgens are the sole determinants of future prostate disease.[18] What is more, with aging, testosterone levels begin to decline; yet at the same time, prostatic hypertrophy incidence elevates. The standard argument for this is that

Table 2–1. Dosing Table

Treatment	Doses
Hormone replacement	Should be evaluated on an individual therapy basis following extensive testing; typically introduced after all other means have been used
Testosterone replacement	Typical starting dose is 5–10 mg, topically
Dehydroepiandrosterone	25–50 mg per day
Chrysin	500–750 mg per day
Zinc	30 mg per day[a]
Puncture vine or tribulus (Tribulus terrestris)	Variable; 250–1,500 mg per day; standardized to 30%–45% steroidal saponins (also known as furostanol)
Potency wood (Muira puama)	1–2 mL, extract, 2 times per day

[a]Patients should always supplement with copper when taking extra zinc.

Diagnostic Confounders of Andropause

Diabetes, renal failure, cirrhosis, anemia, or hypothyroidism
Depression
Alcohol abuse=poor nutrition leading to decreased albumin levels
Abnormal circadian rhythm of testosterone
Medications, such as cimetidine [Tagamet], digoxin [Digitek, Lanoxicaps , Lanoxin], spironolactone [Aldactone], or antidepressants
Acute stressors, such as surgery, severe burns, or accidents
Vigorous athleticism
Other confounders, including hypothalamic-pituitary tumors, Cushing's syndrome, hemochromatosis, Kallmann's syndrome, Klinefelter's syndrome, or Prader-Willi syndrome

hypertrophy results from the cumulative effect of testosterone on the prostate gland. However, when focusing on incidence rates during the years of highest testosterone levels (20s, 30s, and 40s), when most of the exposure has occurred, this time period is associated with the lowest risk of prostate disease.[19]

The transformation (aromatization) of testosterone to estrogen occurs most readily in the fat stores of the body. Therefore, as one ages and gains weight, the aromatase enzyme system is fueled, resulting in elevated levels of estradiol, perhaps promoting prostatic disease. Conversely, as testosterone is metabolized via 5-alpha reductase, it is transformed into DHT, a molecule that androgen-related disease is currently blamed on. When viewing the routes of metabolization of testosterone, we noticed that the two main avenues are via aromatase, leading to estradiol and 5-alpha reductase, leading to DHT. An unproven idea worth considering is the possibility that by blocking the 5-alpha reductase enzyme, one essentially creates a ''backup'' at this point in testosterone metabolism, forcing testosterone to be dismantled via aromatase, possibly leading to greater levels of estradiol and exacerbating the problem. The problem is addressed by attempting to restore a more youthful balance between estrogen and testosterone by decreasing estrogen influence and increasing testosterone influence in the male body. This is referred to as increasing the testosterone–estrogen ratio. This is achieved with testosterone supplementation, often at doses of 5–10 mg per day, and taking steps to reduce estrogen load in the body, such as using phytoestrogens, dietary strategies, exercise, and nutraceutical options. In addition, some physicians may augment this process by prescribing progesterone to men, further blunting estrogen's effect in the body. Prior to, and during, androgen replacement, a prostate examination should be conducted at the outset of therapy, and baseline and prostate-specific antigen levels should be measured, three and six months later and then every six months thereafter, if latent prostate symptoms develop.

DHEA

DHEA has been promoted as a way to slow the aging process and several ''symptoms'' concomitant with the process. DHEA's effects include reversing weight gain and increasing strength, endurance, cognitive function, immune function, and overall energy levels. More specifically, however, DHEA is used to treat adrenal and androgen deficiency in aging adults.

DHEA is produced in the liver and adrenal glands and testes in men. The majority of DHEA in the body exists in the sulfated storage form, DHEA-S. DHEA is converted into androstenedione, a main precursor of both androgens and estrogens.[20] DHEA levels are typically higher in men than in women and tend to decline with aging in both genders. Interestingly, not all aging members of the population experience this effect; in approximately one-third of adults, DHEA will increase with age.[21] DHEA supplementation appears to alter the gender-specific androgen–estrogen ratios; however, the amount of hormone that is elevated in each gender is different.

Men may experience an increase in estrogens but not as much in androgens when taking DHEA, and women who take the supplement will experience large increases in androgens but not in estrogens.[22] The androgen- and estrogen-producing effects of DHEA are thought to be responsible for the pro-hormone's beneficial effects.[23] In men who took DHEA for more than 24 weeks, erectile dysfunction was reduced and the men had improved orgasm function, libido, and overall sexual satisfaction.[24] Much controversy surrounds the use of DHEA in both genders; studies to date have been generally small and of short duration. DHEA is a potent agonist of estrogen receptor–positive breast cancer cells in vitro (and should therefore be used with caution in women), although it is difficult to extrapolate such data to in vivo activity.[25]

EXERCISE

Declining testosterone has multifaceted origins and levels of the hormone can be augmented in numerous ways. Perhaps the most neglected medicine of all, exercise can improve an aging man's testosterone levels (in addition to offsetting andropause-related bone loss, weight gain, muscle loss, and sleep and mood disturbances). Moderate physical activity was shown to increase serum testosterone levels by 39%, SHBG by 19%, free testosterone by 23%, and total serum proteins by 13%, mainly during a period of exercise in one study.[26] The transient elevation of testosterone observed in this study was thought to be partly the result of increased SHBG concentration. Testosterone levels returned to baseline in the subjects after the exercise, indicating that hemoconcentration may have contributed partially to the subjects' increased testosterone levels. However, a separate study sought to challenge the observation that perhaps this testosterone elevation was only related to increases in SHBG; investigators in this study concluded that, indeed, free testosterone does increase with moderately prolonged endurance-type exercise, and this increase was not associated with a change in the binding affinity of SHBG.[27] Furthermore, the data from this study suggested that exercise-induced increases in testosterone were mediated by sympathetic stimulation of the testicles. This effect has been demonstrated in studies that evaluated pre- and post-exercise levels of LH, FSH, prolactin, testosterone, and free testosterone, showing no significant changes in LH, FSH, or prolactin either before or after exercise but showing an activity-related increase in both free and total testosterone.[28] Physical fitness has such far-reaching benefits for patients in nearly all conditions that it can, most assuredly, help the andropausal man. Exercise can not only offset associated andropausal changes but, at least temporarily, increase testosterone levels in serum. This may explain in part the widely observed exercise-related increase in mood seen among older athletes as well.

AROMATASE INHIBITORS

The previously mentioned enzyme, aromatase, is partially responsible for lowered levels of testosterone in men; it achieves this by converting the testosterone molecule into the closely related but vastly different estradiol molecule. Aromatase is a cytochrome P-450 enzyme that

catalyzes the rate-limiting step in estrogen synthesis, from the conversion of androgens (androstenedione and testosterone) to estrogens. (Aromatase is also known as estrogen synthetase.) By inhibiting this enzyme, the transformation of testosterone into estradiol (and resultant decreased levels of testosterone) can be slowed. Aromatase inhibitors are useful for both men and women; in women, aromatase transforms stored androgens into estrogens. For this purpose, aromatase inhibitors are now used as anti-cancer agents for treating estrogen-dependent cancers. Currently, three aromatase inhibitors are approved by the U.S. Food and Drug Administration: anastrazole (Arimidex), exemestane (Aromasin), and letrozole (Femara) mainly for treating estrogen-dependent breast cancers when they first arise and when they recur.

Chrysin

Perhaps the most powerful of the naturally derived aromatase inhibitors in vitro, chrysin is thought to be one of the most potent inhibitors of human estrogen aromatase. Chrysin belongs to the flavone class of flavonoids and is derived from several plant species, the primary of which is Passiflora coerulea. Other sources include geranium species, such as lemon geranium (Pelargonium crispum), honey and bee propolis, and the Pinaceae species, which include pine trees. The ability of chrysin to inhibit aromatization of androstenedione and testosterone has been demonstrated in vitro; however, in vivo studies are necessary. Other investigators have noted a phytoestrogenic effect[29] (binds weakly to alpha and beta estrogen receptors), and antioxidant [30] (inhibits xanthine oxidase and the consequent formation of uric acid and related reactive oxygen species) and anxiolytic[31] actions (binds to the ''benzodiazepine receptor'' portion of gamma-aminobutyric acid [a] receptors. Much of the research on chrysin has been performed in vitro; this shows the potential for chrysin to inhibit the aromatase enzyme,[32] but human research has not shown that chrysin increases testosterone levels when used with androgen precursor molecules, such as androstenedione and DHEA.[33] Chrysin is suspected of having low oral bioavailability. In fact, this flavone is thought to induce the very enzyme (UGT1A1) that hastens its own elimination in the intestine and liver.[34] Nonetheless, due to presumptive marketing, chrysin is widely used by athletes who tend to welcome any product with promise to enhance physical performance. The end result of using aromatase inhibitors is to preserve testosterone by preventing its transformation into estrogens.

Lignans and Flavonoids

Various lignans and flavonoids have been shown to inhibit the aromatase enzyme. Lignans are phytoestrogens with weak estrogenic effects and possibly antiestrogenic effects. Numerous flavonoids and lignans such as apigenin, quercetin, genistein, biochanin A, daidzein, and zearalenone have shown the ability to inhibit aromatase in vitro.[35] The isoflavone genistein, found in soy and red clover, and the lignans enterolactone and enterodiol found in flaxseeds, have been shown to inhibit aromatase in breast cancer cells in vitro, resulting in decreased production of estradiol and estrone.[36] Due to the increased absorption of flaxseed and soy, among other sources of lignans and flavonoids, these are areas of increased research for aromatase inhibition and hormone-dependent cancer prevention.

ZINC

Zinc is a long-hailed nutrient for prevention and treatment of men's health problems. Zinc is rather abundant in the body (totaling nearly 2 g) and is incorporated into many different

enzyme systems in the body, underlying this mineral's importance in overall health. More specifically, suboptimal volumes of zinc appear to have a negative influence on serum testosterone concentrations as well as on seminal volume.[37] Not necessarily specific to andropause, zinc concentrations in the semen are directly correlated with sperm numbers.[38] Because of the large amount of zinc that is stored in the prostate gland and the relationship between prostate tissue levels and benign prostatic hyperplasia,[39] this mineral is lionized among people who use nutritional treatment to address prostate diseases. Zinc is also thought to serve as an inhibitor of 5-alpha reductase, the enzyme that converts testosterone to DHT.[40]

OTHER BOTANICAL MEDICINES

Puncture Vine

Tribulus (Tribulus terrestris), commonly known as puncture vine, has been used historically as a ''tonic'' herb for treating impotence. Tribulus is thought to increase testosterone levels indirectly by raising LH levels that come from the pituitary gland; the active component of tribulus is thought to be a type of saponin.[41] Specific research on tribulus in relation to its ability to elevate androgen levels is minimal. One experiment compared the sexual behavior of castrated laboratory animals that were untreated to those treated with either testosterone or tribulus extract. The researchers noted that, in both testosterone- and tribulus-treated groups, indicators of androgen activity were evident. These included increased prostate weight and measures of intracavernous pressure (degree of erection). The investigators concluded that the herb does have the ability to increase androgens (although measurement of actual levels was not performed).[42] The reputation of this herb (evidenced by historical use as an elevator of energy and vitality in indigenous medical systems) greatly precedes medical evidence. While the herb has promise as a promoter of libido and possibly androgen levels, more research is needed on its effects.

Potency Wood

Muira puama, also known as ''potency wood,'' is derived from the Brazilian Amazon and other parts of the Amazon rain forest. Long used by the indigenous people of South America, muira has a reputation for treating sexual debility and baldness, among other conditions. Still highly valued in the Brazilian Pharmacopoeia (included since the 1950s), the herb is considered to be a powerful aphrodisiac. Active constituents are thought to include fatty acids, sesquiterpenes, monoterpenes, and alkaloids.[43] Relatively few clinical trials exist on the action of this herb, especially those that may be applicable to andropausal symptoms. One trial investigated the herb's effects in men who were experiencing decreased libido and impotence. The researchers found that 62% of subjects who took the herb in supplement form reported positive results in regard to libido, while 51% of those with erectile dysfunction felt that the herb was helpful.[44] A second trial involving men with decreased libido used 1.5 g of Muira puama extract per day; according to the investigators 85% of test subjects experienced enhanced libido, 90% experienced improved ability to maintain an erection, while 100% of subjects experienced an increase in frequency of intercourse.[45] This herb appears to display possible benefits for the andropausal man in regard to improving sexual performance; more studies are needed to discern the mechanism by which this occurs.

CONCLUSIONS

Andropause, although more subtle than menopause, can be addressed in a number of ways, including hormone replacement, exercise, or supplementation. It is vital to individualize treatment after a careful examination and testing to rule out confounding factors.

REFERENCES

[1]Heller CG, Myers GB. The male climacteric: Its symptomatology, diagnosis and treatment. JAMA. 1944;126:472.

[2]Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: Longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002;87:589–598.

[3]Tenover JS. Androgen administration to aging men. Endocrinol Metab Clin North Am. 1994;23:877–892.

[4]Sih R, Morley JE, Kaiser FE. Testosterone replacement in older hypogonadal men: A 12-month randomized controlled trial. J Clin Endocrinol Metab. 1997;82:1661–1667.

[5]Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, Clark RV, McKinlay JB. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab. 2007 Nov;92(11): 4241–4247. Epub 2007 Aug 14.

[6]Nieschlag E, Behre HM, eds. Testosterone: Action, Deficiency, Substitution, 2nd Edition. Berlin: Springer-Verlag, 1998:58–66.

[7]Basaria S, Dobs AS. Hypogonadism and androgen replacement therapy in elderly men. Am J Med. 2001;110:563–572.

[8]Gray A, Feldman HA, McKinlay JB. Age, disease, and changing sex hormone levels in middle-aged men: Results of the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 1991;73:1016–1025.

[9]Morales A, Heaton JP, Carson CC III. Andropause: A misnomer for a true clinical entity. J Urol. 2000;163:705–712.

[10]Vermeulen A, Kaufman JM. Ageing of the hypothalamo-pituitary-testicular axis in men. Horm Res. 1995;43(1–3):25–28.

[11]Gallardo E, Simon C, Levy M. Effect of age on sperm fertility potential: Oocyte donation as a model. Fertil Steril. 1996;66:260–264.

[12]Barrett-Connor E, Goodman-Gruen D, Patay B. Endogenous sex hormones and cognitive function in older men. J Clin Endocrinol Metab. 1999;84:3681–3685.

[13]Tan RS. Andropause: Introducing the concept of ''relative hypogonadism'' in aging males [letter]. Int J Impot Res. 2002;14:319.

[14]Smith KW, Feldman HA, McKinlay JB. Construction and field validation of a self-administered screener for testosterone deficiency (hypogonadism) in ageing men. Clin Endocrinol (Oxf). 2000;53:703–711.

[15]Marin P, Holmang S, Jonsson L. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. Int J Obes Relat Metab Disord. 1992;16:991–997.

[16]Bestul MB, McCollum M, Hansen LB, Saseen JJ. Impact of the women's health initiative trial results on hormone replacement therapy. Pharmacotherapy. 2004;24:495–499.

[17]de Lignieres, B. Transdermal dihydrotestosterone treatment of ''andropause.'' Ann Med. 1993;25: 235–241.

[18]Heikkila R, Aho K, Heliovaara M, Hakama M, Marniemi J, Reunanen A, Knekt P. Serum testosterone and sex hormone–binding globulin concentrations and the risk of prostate carcinoma: A longitudinal study. Cancer. 1999;86:312–315.

[19]Vermeulen A. Dehydroepiandrosterone sulfate and aging. Ann NY Acad Sci. 1995;774:121–127.

[20]Oelkers W. Dehydroepiandrosterone for adrenal insufficiency [editorial]. N Engl J Med. 1999;341: 1073–1074.

[21]Tilvis RS, Kahonen M, Harkonen M. Dehydroepiandrosterone sulfate, diseases and mortality in a general aged population. Aging (Milano). 1999;11:30–34.

[22]Arlt W, Haas J, Callies F. Biotransformation of oral dehydroepiandrosterone in elderly men: Significant increase in circulating estrogens. J Clin Endocrinol Metab. 1999;84:2170–2176.

[23]Ebeling P, Koivisto VA. Physiological importance of dehydroepiandrosterone. Lancet. 1994;343:1479–1481.

[24]Reiter WJ, Pycha A, Schatzl G, et al. Dehydroepiandrosterone in the treatment of erectile dysfunction: A prospective, double-blind, randomized, placebo-controlled study. Urol. 1999;53:590–595.

[25]Calhoun KE, Pommier RF, Muller P, et al. Dehydroepiandrosterone sulfate causes proliferation of estrogen receptor–positive breast cancer cells despite treatment with fulvestrant. Arch Surg 2003;138: 879–883.

[26]Zmuda JM, Thompson PD, Winters SJ. Exercise increases serum testosterone and sex hormone–binding globulin levels in older men. Metabolism. 1996;45:935–939.

[27]Fahrner CL, Hackney AC. Effects of endurance exercise on free testosterone concentration and the binding affinity of sex hormone binding globulin (SHBG). Int J Sports Med. 1998;19:12–15.

[28]Vogel RB, Books CA, Ketchum C, Zauner CW, Murray FT. Increase of free and total testosterone during submaximal exercise in normal males. Med Sci Sports Exerc. 1985;17:119–123.

[29]Jeong HJ, Shin YG, Kim IH, Pezzuto JM. Inhibition of aromatase activity by flavonoids. Arch Pharm Res. 1999;22:309–312.

[30]Nagao A, Seki M, Kobayashi H. Inhibition of xanthene oxidase by flavonoids. Biosci Biotechnol Biochem. 1999;63:1787–1790.

[31]Wolfman C, Viola H, Paladini A, et al. Possible anxiolytic effects of chrysin, a central benzodiazepine receptor ligand isolated from Passiflora coerulea. Pharmacol Biochem Behav. 1994;47:1–4.

[32]Kellis JT Jr, Vickery LE. Inhibition of human estrogen synthetase (aromatase) by flavones. Science. 1984;225:1032–1034.

[33]Brown GA, Vukovich MD, Reifenrath TA, et al. Effects of anabolic precursors on serum testosterone concentrations and adaptations to resistance training in young men. Int J Sport Nutr Exerc Metab. 2000; 10:340–359.

[34]Walle T, Otake Y, Galijatovic A. Induction of UDP-glucuronosyltransferase UGT1A1 by the flavonoid chrysin in the human hepatoma cell line hep G2. Drug Metab Dispos. 2000;28:1077–1082.

[35]Lacey M, Bohday J, Fonseka SM, Ullah AI, Whitehead SA. Dose-response effects of phytoestrogens on the activity and expression of 3beta-hydroxysteroid dehydrogenase and aromatase in human granulosa-luteal cells. J Steroid Biochem Mol Biol. 2005 Aug;96(3-4):279–286.

[36]Brooks JD, Thompson LU. Mammalian lignans and genistein decrease the activities of aromatase and 17beta-hydroxysteroid dehydrogenase in MCF-7 cells. J Steroid Biochem Mol Biol. 2005 Apr;94(5):461–467. Epub 2005 Mar 16.

[37]Hunt CD, Johnson PE, Herbel J, Mullen LK. Effects of dietary zinc depletion on seminal volume and zinc loss, serum testosterone concentrations, and sperm morphology in young men. Am J Clin Nutr. 1992;56:148–157.

[38]Fuse H, Kazama T, Ohta S, Fujiuchi Y. Relationship between zinc concentrations in seminal plasma and various sperm parameters. Int Urol Nephrol. 1999;31:401–408.

[39]Miller AL. Benign prostatic hyperplasia: Nutritional and botanical therapeutic options. Alt Med Rev. 1996;1:18–25

[40]Om AS, Chung KW. Dietary zinc deficiency alters 5 alpha-reduction and aromatization of testosterone and androgen and estrogen receptors in rat liver. J Nutr. 1996;126:842–848.

[41]Cai L, Wu Y, Zhang J, Pei F, Xu Y, Xie S, Xu D. Steroidal saponins from Tribulus terrestris. Planta Med. 2001;67:196–198.

[42]Gauthaman K, Adaikan PG, Prasad RN. Aphrodisiac properties of Tribulus terrestris extract (Protodioscin) in normal and castrated rats. Life Sci. 2002;71:1385–1396.

[43]Auterhoff, H. Lipophilic constituents of Muira puama. Arch Pharm Ber Dtsch Pharm Ges. 1971;304: 223–228.

[44]Waynberg J. Contributions to the clinical validation of the traditional use of Ptychopetalum guyanna [presentation]. First International Congress on Ethnopharmacology. Strasbourg, France, June 5–9, 1990.

[45]Waynberg J. Male sexual asthenia—interest in a traditional plant-derived medication. Ethnopharmacology. Mar 1995.

3

NUTRITIONAL AND BOTANICAL APPROACHES TO ANTI-AGING

As the human population ages and increases in longevity, the study of biological aging is emerging. According to the Centers for Disease Control and Prevention, for 2003, an estimated 35.9 million Americans were over the age of 65 and more than 25% of this population was in fair-to-poor health.[1] According to the U.S. Census Bureau, by 2030, 20% of the U.S. population will be over 65, compared to just 4% 100 years ago.[2] The mechanism of cellular aging is elusive, and many theories have been proposed to explain the decrease in physiologic function that occurs with aging. As a result of increased risks of disease and mortality, decreases in quality of life, and rising health care costs, aging and longevity research is necessary to address problems related to aging. A wide range of nutrients and interventions have been shown to decrease cellular aging and age-related disease.

THEORIES OF AGING

There are several theories of cellular aging. These theories are not mutually exclusive, and many complement each other. Aging was initially believed to be a result of genetically programmed cell death. Subsequently, it was proposed that aging might be a result of accumulation of cellular damage and mutation of nuclear and mitochondrial DNA. Given that evidence has surfaced suggesting that aging may be a result of cellular damage, this implies that interventions to influence aging are possible.

Oxidative Stress and Free Radicals

Damage caused by free radicals is the most popular and universal theory of cellular aging. These highly reactive molecules are formed in many biochemical reactions as well as being introduced via exogenous exposures. The basic idea of this theory is that a shift occurs between the amounts of pro-oxidants (which are needed for tasks such as immune defense and cell communication) and antioxidants (which keep the pro-oxidants from doing too much damage to the human body). This shift leads to increased oxidative stress, less well-controlled cell functioning, and aging. The theory is based primarily on three observations: (1) free radicals are extremely reactive, (2) they are constantly being produced from oxygen and nitrogen in the body, and (3) natural defense systems exist to control the unwanted effects of free radicals.[3] Free radicals react with molecules causing damage and DNA mutations, and have been implicated in many disease processes.[4] Studies indicate that an increase in the accumulation of oxidative damage increases functional deficits during aging, and treatments that decrease oxidative damage have been shown to delay age-related loss of function.[5] Other evidence suggests that increases in oxidative stress cause increases in inflammatory mediators, leading to age-related inflammatory diseases, such as arthritis, atherosclerosis, osteoporosis, and dementia.[6]

Mitochondrial Damage

Mitochondria produce most of the energy used by the body in the form of adenosine triphosphate (ATP). Oxidative phosphorylation provides the majority of ATP production via the electron transport chain. Aging has been shown to decrease the efficiency of mitochondrial oxidative phosphorylation. Specifically, aging decreases cellular energy production, impairs substrate oxidation, and increases the production of free radicals.[7] Loss of muscle mass and function seen with aging is associated with mitochondrial damage in muscle cells.[8] Studies indicate that aging is associated with a decrease in number and increase in size of mitochondria, making them less efficient with age.[9] Small amounts of reactive oxygen species (ROS) are formed via energy production that regulates some cellular functions, and that can act as a second messenger for transcription factors.[10] Cells have several antioxidant enzymes to prevent excess ROS from causing damage. Enzymes required for oxidative phosphorylation and antioxidant enzymes decrease with age as the number of cells completely lacking the enzyme cytochrome oxidase increases.[11] In addition, mitochondrial DNA is more susceptible to free-radical damage and mutation than nuclear DNA.[12] Research indicates that mitochondrial DNA mutation in post-mitotic cells begins accumulating in individuals after the mid 30s.[13] These mutations may lead to impaired protein transcription and translation causing the decrease in cellular respiration. Studies have shown that human cells with increased levels of mutant mitochondrial DNA produce less ATP and release increased levels of ROS.[14] Studies also show a decrease in mitochondrial membrane potential with aging. This causes an increase in proton leakage and a decrease in ATP production, thus affecting the efficiency of cellular respiration.[15] Mitochondrial defects and the resultant decline in mitochondrial function are implicated in the induction of apoptosis. Increased oxidant levels have been shown to cause an increase of events such as increased activation of the mitochondrial permeability transition pore leading to an increase in the release of pro-apoptotic proteins from the mitochondria.[16]

Telomeres

Telomeres are repeat sequences at the ends of eukaryotic chromosomes that provide protection and stabilization. Telomeres generally shorten with each replication because of the inability of DNA polymerase to copy the lagging DNA strand. Telomerase is a reverse transcriptase that synthesizes the telomere. Most human cells are deficient in telomerase, allowing the attrition of the telomere. Short telomeres activate irreversible cell-cycle arrest (cellular senescence and apoptosis).[17] Cancer cells have been shown to up-regulate telomerase, prolonging the lifespan of the tumor cells.[18] Approximately 90% of cancer cells have high levels of telomerase activity.[19] Oxidative damage has been shown to accelerate telomere shortening, and antioxidants have been shown to slow telomere attrition.[20] Research suggests that telomere length is a highly heritable trait and that telomeres are longer in women than in men.[21] Obesity and smoking have also been shown to decrease telomere length.[22] A study done with long-term estrogen and progesterone hormone therapy in postmenopausal women showed that longer telomeres appeared in women on hormone replacement than in women without hormone therapy.[23] In addition, individuals with mood disorders have been shown to have significantly shorter telomeres, possibly providing the link between mood disorders and increased morbidity and mortality.[24] Another study revealed that women with the most chronic and highest levels of perceived stress had lower telomerase activity and shorter telomeres.[25] Research has also shown that telomere shortening in vascular cells is associated with endothelial dysfunction and atherosclerosis formation.[26]

Neurologic and Endocrine Dysfunction

This theory suggests that aging is caused by endocrine dysfunction, which is common in elderly people. Changes in hormonal secretion, loss of receptor sensitivity to stimulatory or inhibitory stimuli, anatomic changes of endocrine glands, and altered transport of hormones occur with aging.[27] Many hormones decrease with aging. Studies have shown that melatonin secreted from the pineal gland (responsible for regulation of circadian rhythms) decreases with age. Specifically, increasing age is directly proportional to decreasing levels of plasma melatonin and delayed melatonin elevation.[28] Growth hormone decreases at approximately 14% per decade. After age 60, growth hormone is decreased by approximately 50%–70% compared with levels in the third and fourth decade of life.[29] Steroid hormones, such as estrogen and testosterone, also decrease with age.[30] Interestingly, estrogen has been shown to up-regulate telomerase activity.[31] Animal studies have also demonstrated that testosterone may decrease telomerase activity.[32]

Cross-linkages

Proteins and other macromolecules can undergo cross-linking reactions. Proteins that undergo these reactions become less elastic, less soluble, and less digestible by enzymes. This theory suggests that large molecules undergo cross-linkage when exposed to a cross-linking agent causing cellular damage and cell death. Advanced glycosylation end-products (AGEs) are formed by a reaction between reducing sugars and biologic proteins. Glycated proteins are stable and accumulate over time. AGEs react with molecules creating cross-linkages. These reactions have been implicated in the pathology of several diseases. Hyperglycemic conditions, such as diabetes, have an increase in glycosylation of proteins, which may explain the increase in chronic diseases that occur with these conditions.[33] Collagen cross-linkage has been shown to cause increased stiffness in cartilage possibly leading to decreased resistance to damage and osteoarthritis.[34] Decreases in vascular and myocardial elasticity, hypertension, endothelial dysfunction, and atherosclerosis formation are associated with increased AGE accumulation.[35] Protein cross-linking is also found in the brains of individuals with Alzheimer's disease.[36] Research also suggests that cataracts may be associated with cross-linkage in eye lenses.[37]

NUTRITIONAL AND SUPPLEMENT-BASED ANTI-AGING INTERVENTIONS

Calorie Restriction

Calorie restriction is one of the most supported interventions in aging and longevity research. Studies with numerous animal types have demonstrated that calorie restriction increases longevity and decreases age-related diseases. Calorie restriction is widely studied in attempts to define which biochemical pathways are affected by fasting and the induced stress response. Research with humans indicates that calorie restriction modulates energy metabolism, reduces free-radical production, and alters endocrine function.[38] A study with monkeys demonstrated that a 30% reduction in calories lowered core body temperature and decreased energy expenditure.[39] Calorie restriction also increases the levels of nicotinamide adenine dinucleotide (NAD)–dependent protein deacetylases (known as sirtuins), which are involved in energy metabolism and gene silencing, and are associated with increased longevity.[40] Specifically,

Potential Anti-aging Supplements

Dimethylaminoethanol (DMAE)
Dehydroepiandrosterone (DHEA)
Growth hormone
Melatonin
Carnosine
Niacinamide
Coenzyme Q10
Resveratrol
Glutathione
Vitamin E
Vitamin C
b-carotene
a-lipoic acid.
Astragalus membranaceus (astragalus)
Ginkgo biloba (ginkgo)

Evidence suggests that, although antioxidants may not be able to prolong life, they may improve quality of life as they provide benefit for patients who have cancer and age-related diseases, such as atherosclerosis, neurodegenerative, and ocular diseases.[a]

[a]From ref. 96.

these proteins deacetylate and inactivate p53, allowing cells to bypass apoptosis and survive DNA damage, giving cells time to repair damage.[41] The protein p53 is a primary tumor suppressor, indicating the importance of balance between aging and cancer. Another study showed that calorie restriction decreased mitochondrial proton leakage, cellular oxygen consumption, and ROS production in rat muscle.[42] In addition, insulin and tri-iodothyronine are decreased with calorie restriction.[43] Insulin replacement reverses the beneficial effects of calorie restriction in the mitochondria by increasing ROS formation.[44] A study with rats also revealed that calorie restriction decreases the age-related decline of the glutathione and thioredoxin systems, supporting the antioxidant function of calorie restriction.[45] This intervention also reduces DNA damage and mutations and increases DNA repair by increasing the activity and reliability of DNA polymerases, which decline with aging.[46] Cancer and age-related immunologic defects, which are associated with DNA damage, also decrease with calorie restriction.[47] Calorie reduction decreases the release of leptin, a peptide hormone secreted from adipocytes. This alteration in leptin levels has been shown to activate the adrenal axis while suppressing the thyroid, gonadal, and somatotropic axes. Researchers suggest that this indicates that leptin plays an integral role in stress-induced metabolic and endocrine adaptation pathways, and leptin may be the link between calorie restriction and increased longevity.[48] Studies have also shown that calorie restriction alters levels of heat-shock proteins, which are protective for cells and which are induced by stressful stimuli. Heat-shock proteins decrease with age, and dietary restriction has reversed this process in the cardiac tissue of animals.[49]

Maintaining Adequate Absorption

Another important aspect of aging well is maintaining adequate absorption of the food that is consumed. A key to proper absorption is sufficient hydrochloric acid (HCl). An acidic environment is needed not only to optimize the absorption of minerals, such as zinc, iron,[50,51] and calcium,[52] but is also needed for the absorption of vitamin B_{12}. In one study, an acid-reducing drug, Prilosec , (AstraZeneca, L.P., Wayne, Pennsylvania) was shown to decrease vitamin B_{12}

Table 3–1. Prevention Strategies for Overcoming Common Health Problems in Aging Patients

Problem	Tell your Patients
Heart disease	Increase consumption of dark purple and red, bioflavonoid-rich fruits and vegetables containing resveratrol. These help to prevent damage to blood vessel linings by providing antioxidant protection. (See Chapter 8 on cardiovascular disease.)
Cerebrovascular accidents	Maintain adequate thinness of blood by consuming foods such as garlic and cold-water fish on a regular basis. Also supplements such as Nattokinase, serrapeptase, and turmeric. (See Chapter 8 on cardiovascular disease.)
Diabetes	Ensure adequate intake of minerals, whole grains; avoid over consumption of carbohydrates with too little protein or fiber; take chromium supplements. (See Chapter 11 on diabetes.)
Osteoarthritis	Consider supplementation with products that support healthy joint tissue, such as glucosamine sulfate and hyaluronic acid.
Cancers	Encourage sufficient detoxification by eating fruits and vegetables that are rich in phytochemicals such as limonene, and dietary glucosinolates such as indole-3 carbinol and sulforaphane that stimulate the liver's and intestinal tract's detoxification pathways. Men should consider increasing lycopene to support prostate health, and women should consider increasing their isoflavone intake. This prevents genetic damage by supporting antioxidant pathways.
Lung infections	Increase water consumption to maintain moisture and integrity of mucous membranes; quit smoking and avoid secondhand smoke, and environmental irritants, such as dust and chemical fumes.

absorption, a trend that was reversed when cranberry juice, well-known for its acidity, was introduced.[53] This interaction between vitamin B_{12} and Prilosec may extend to other acid-lowering drugs as well. Failure to absorb iron and vitamin B_{12} could lead to easily preventable anemia in elderly patients, causing unnecessary fatigue and depression. In addition, there is evidence that more than a quarter of older patients already consume less than 75% of the recommended daily allowance of not only vitamin B_{12}, but of folate and vitamin B_6 as well.[54] This is certainly relevant when we view the data demonstrating that lower levels of these B vitamins, which are needed to limit production of homocysteine, correlate with both higher homocysteine levels and an increased incidence of carotid-artery stenosis.[55–57] Finally, a proper acidic environment in the stomach probably aids in killing a number of bacteria that may enter our bodies contained in the food that humans eat.

Dimethylaminoethanol

Dimethylaminoethanol (DMAE), also known as deanol, is a naturally occurring substance that has been studied as a possible anti-aging therapy that can also improve cognitive function. DMAE is the precursor to choline and may increase acetylcholine levels.[58] DMAE inhibits production of the age-related pigment lipofuscin, which accumulates in all aging tissues. This

is significant because cells with increased lipofuscin cause lysosomes to perform poorly, which leads to increased accumulation of poorly functioning mitochondria and increased ROS production.[59] Evidence also suggests that DMAE decreases the extent of cross-linking of proteins possibly by acting as a free-radical scavenger.[60]

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a steroid hormone produced primarily in the adrenal cortex as well as in the liver, brain, and testes. DHEA is the precursor to androstenedione, which is then converted to androgens and estrogen. DHEA peaks at approximately age 20 and declines steadily with age.[61] DHEA levels have been studied relative to numerous age-related diseases. Research has suggested that low DHEA levels may be correlated with cardiovascular disease (CVD), cancer, obesity, immune deficiency, insulin resistance, and depression.[62] Evidence has shown that DHEA supplementation of 50 mg per day for one year improved bone mineral density in both men and women over age 60.[63] DHEA supplementation has been shown to decrease visceral and subcutaneous fat and insulin levels in elderly men and women.[64] Studies have also revealed the antiatherogenic effects of short-term supplementation when 50 mg of DHEA per day was given to elderly individuals. In addition, this research has shown increased platelet cGMP production, signifying nitric oxide (NO) production, decreased levels of plasminogen activator inhibitor, decreased levels of low-density lipoprotein (LDL) cholesterol, and increased levels of testosterone and estradiol.[65] Data obtained in a study indicate that DHEA sulfate (DHEAS) is decreased in elderly patients with congestive heart failure (CHF) compared with age-matched controls. This study also showed that the decline in DHEAS is proportionate to the severity of CHF and is associated with oxidative stress.[66] Recent evidence also indicates that DHEA improves muscle mass and strength in elderly individuals when combined with weight-lifting exercise compared with weight lifting alone.[67] A study of DHEA supplementation with individuals ages 45–65 with midlife-onset minor or major depression showed a significant improvement in the participants' Hamilton Depression Rating Scale scores compared with baseline after six weeks of treatment.[68]

> It might be reasonable to encourage aging patients to take small amounts of melatonin to improve their antioxidant potential.

Growth Hormone

Growth hormone (GH) is secreted by the pituitary gland and exerts its effects either directly or indirectly via insulin-like growth factor-1 (IGF-1). GH and IGF-1 decrease significantly with age. Low IGF-1 levels have been associated with numerous age-related diseases, such as atherosclerosis, CVD, dementia, and sarcopenia.[69] IGF-1 can stimulate NO production from endothelial and vascular smooth-muscle cells, indicating a vascular protective function.[70] IGF-1 also has antiapoptotic and neuroprotective effects.[71] In addition, increased serum IGF-1 levels are positively correlated with increased muscle strength and physical performance.[72]

Melatonin

Melatonin is a hormone secreted from the pineal gland primarily at night and regulates circadian rhythms. Both total output and rhythmicity of melatonin decrease with age.[73] Melatonin provides protection from oxidative damage by functioning as a free-radical scavenger and regulates the expression of antioxidant enzymes.[74] This hormone also exhibits immune-stimulating benefits. Age-related decline of humoral, innate, and cellular immunity is implicated in the increase in disease, physical degeneration, and cancer in elderly patients. Studies indicate that melatonin enhances cellular and innate immunity. The hormone stimulates progenitor cells of granulocytes, natural-killer cells, macrophages, and several cytokines.[75] Melatonin also increases the production of T-helper cells.[76] In addition, melatonin affects mitochondrial function directly. The free-radical activity of melatonin limits decline in intra-mitochondrial glutathione and decreases mitochondrial protein and DNA damage, allowing for more efficient electron transport chain function and increased ATP production. This activity blocks the decline in mitochondrial-membrane potential, which would cause opening of the mitochondrial transition pore and possibly induce the apoptotic cascade.[77] Studies indicate that melatonin has neuroprotective qualities and can slow the progression of Alzheimer's disease.[78] Melatonin also produces anti-cancer activity and has been shown to inhibit tumor-cell proliferation, stimulate tumor-cell differentiation and apoptosis, and inhibit tumor-cell uptake of linoleic acid at both physiologic and pharmacologic doses.[79] Decreased melatonin synthesis caused by increased light during the night has been shown to increase cancer-cell proliferation.[80]

Carnosine

Carnosine is a dipeptide composed of beta-alanine and L-histidine. It is found in high concentrations in skeletal muscle, cardiac muscle, and the brain.[81] Human studies indicate that muscle carnosine levels decrease significantly with age, demonstrating a 63% decrease from age 10 to age 70.[82] Studies have shown several biochemical functions of carnosine suggesting anti-aging properties. Carnosine acts as an antioxidant decreasing lipid oxidation and protecting membranes from free-radical damage as well as chelating reactive metals.[83] Carnosine has been shown to extend the life span of human fibroblasts, possibly because of the dipeptide's ability to slow telomere attrition and decrease damage to telomere DNA.[84] Studies indicate that carnosine can prevent cross-linking, glycation, protein carbonyl group formation, and the formation of AGEs, which play a role in aging and age-related disease.[85] Carnosine has also been shown to inhibit toxic effects of amyloid peptide, malondialdehyde, and hypochlorite to cells.[86]

Niacinamide

Niacinamide (vitamin B_3), also known as nicotinamide, is the amide form of niacin and is necessary for numerous biochemical reactions. Niacin is the precursor to nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). NAD and NADP are essential for oxidation-reduction reactions and ATP synthesis. Niacinamide is necessary for modulating cell metabolism, cell longevity, and mitochondrial-membrane potential.[87] Research shows that nicotinamide can reverse aging phenotypes in aging human fibroblasts. This study revealed that aging cells exposed to nicotinamide showed increased replicative potential and histone acetyltransferase activity, suggesting restoration of altered gene expression.[88] There is supportive evidence that niacin may be protective against

age-related cognitive decline and Alzheimer's disease, and that higher niacin intake from the diet produces a slower annual rate of cognitive decline.[89] Niacin supplementation has also been shown to provide benefit for patients with age-related CVDs, such as atherosclerosis, hyperlipidemia, and coronary artery disease.[90,91]

Coenzyme Q10

Coenzyme Q10 (CoQ10), or ubiquinone, is a compound made by the body and primarily functions as an antioxidant, membrane stabilizer, and a cofactor in cellular respiration. CoQ10 supplementation has been shown to ameliorate cardiovascular diseases, neurologic disorders, and possibly cancer. Studies indicate that CoQ10 supplementation in individuals with CHF improved ejection fraction, stroke volume, and cardiac output.[92] CoQ10 has also been shown to decrease systolic hypertension, with 12 weeks of supplementation producing a mean decrease in systolic blood pressure of 17.8 mmHg.[93] Additional research showed that 120 mg of CoQ10, given for 28 days after acute myocardial infarction, decreased angina, arrhythmias, poor left ventricular function, total cardiac events, and oxidative free radicals.[94] CoQ10 appears to be promising for slowing functional decline in individuals with neurodegenerative diseases caused by mitochondrial dysfunction or oxidative damage, such as Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, and Friedreich's ataxia.[95] CoQ10 supplementation is also effective as a migraine prophylactic therapy.[96] In addition, some evidence supports CoQ10 as having immunomodulating and anti-cancer actions.[97]

Resveratrol

Resveratrol is a natural polyphenol found in high concentrations in red-grape skins and berries. It is widely studied because of its antioxidant, anti-inflammatory, anti-cancer, and possibly anti-aging properties. Evidence suggests that resveratrol increases life span in simple organisms and mimics calorie restriction by activating sirtuin.[98] Additional studies indicate that resveratrol may provide chemoprotective action by inhibiting tumor initiation, promotion, and progression by possibly down-regulating pro-inflammatory mediators.[99] Resveratrol has also been shown to be cardioprotective, suppressing platelet aggregation, inhibiting LDL oxidation, and reducing myocardial damage during ischemia-reperfusion.[100] Research suggests that age-related neurologic diseases, such as stroke, ischemia, Huntington's disease, and possibly Alzheimer's disease may be ameliorated with resveratrol.[101]

Glutathione

Glutathione is a tripeptide made in the cytosol of all cells with increased production and storage in the liver. This tripeptide acts as a free-radical scavenger, modulates DNA synthesis and immune function, and detoxifies xenobiotics and their metabolites.[102] Plasma glutathione levels are significantly decreased in elderly people, and the glutathione in this population is in a more oxidized state, implying increased oxidative stress.[103] Evidence suggests that oxidative stress and glutathione deficiency play a role in neurodegenerative diseases, such as amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease.[104] Increased oxidation of glutathione is found with cigarette smoking, chemotherapy, and age-related diseases, such as cardiovascular disease and type 2 diabetes.[105] In one study, which involved 169 healthy subjects, blood glutathione levels had decreased significantly (17%) in the 60–79 age group versus the 20–39 age group.[106] Another study sought a correlation between blood glutathione

levels and the occurrence of conditions such as arthritis, glaucoma, asthma, emphysema, heart disease, diabetes, and others, which were lumped into a morbidity index. The results of the study showed that, while other factors, such as repressed anger, also correlate with higher morbidity, the strongest correlation factor, by far, was with low blood glutathione levels.[107]

Other Antioxidants

Numerous additional antioxidants have shown anti-aging benefits such as vitamin E, vitamin C, beta-carotene, and alpha-lipoic acid. Almost all age-related diseases are caused or exacerbated by oxidation and free-radical damage. Evidence suggests that, although antioxidants may not be able to prolong life, they may improve quality of life as they provide benefit for patients who have age-related diseases, such as cancer, atherosclerosis, neurodegenerative, and ocular diseases.[108] Studies have also shown that supplementation, using antioxidants, such as vitamins C and E, zinc, selenium, and beta-carotene, improves leukocyte function and restores redox balance in prematurely aging animals.[109] In addition, antioxidants such as vitamins C and E and carotenoids decrease DNA damage and malignant transformation in cells, and are associated with lower risks of cancer, ischemic heart disease, and cataracts.[110]

Antioxidant enzyme systems work together in the cytosol and mitochondria to change the superoxide anion to hydrogen peroxide and then to water or water and oxygen. There are several forms of the enzyme superoxide dismutase (SOD), which some forms require zinc and copper as cofactors.[111] SOD catalyzes the reaction to convert superoxide to oxygen and hydrogen peroxide. There are also three forms of glutathione peroxidase, an enzyme that converts glutathione and hydrogen peroxide to disulfide glutathione and water. Glutathione peroxidase requires selenium as a cofactor.[112] Glutathione reductase then converts the disulfide glutathione back to reduced glutathione. Good fueling with regard to biochemical cofactors along the steps of the biologic pathway is needed so that the process is not stalled. This is also vital between the first and second parts of the process because hydrogen peroxide can react additionally with metals, such as iron, to create the very reactive hydroxyl radical.

Table 3–2. Some Key Nutrients for Antioxidant Support During Aging

Nutrient	Adult Dosage Range	Rationale
Zinc	15–30 mg per day	Needed for antioxidant enzymes in the endothelial cells lining the blood vessels
Selenium	200 mg per day	Needed for antioxidant enzymes
Vitamin C	500–1,000 mg per day	Water-soluble antioxidant
Vitamin E	400–1,200 IU per day	Fat-soluble antioxidant
Coenzyme Q10	30–150 mg per day	Fat-soluble antioxidant, protects heart mitochondria
Virgin olive oil	As needed for food preparation	Increases the concentration of monounsaturated fatty acids in cell membranes and decreases free-radical targets
N–acetylcysteine	500–1,500 mg per day	Supports production of glutathione
Carotenes	25,000–300,000 IU per day	Increased tissue and blood levels correlate with increased lifespan
Trans-Resveratrol	100–300 mg per day	Antioxidant, activates sirtuin (SIRT-1 gene)

Vitamin E also modulates the interaction between immune-system cells and the endothelial cells that line blood-vessel walls,[113] and this action may well account for the cardiovascular benefit of vitamin E supplementation. Recent research suggests that vitamin E's prevention of low-density lipoprotein oxidation is clearly dose-dependent, with 1,200 international units (IU) per day offering significantly more protection than 400 IU per day.[114] In a preliminary study that examined the effects of supplementation with CoQ10 and virgin olive oil, researchers found that both substances protect mitochondrial membranes from free-radical damage.[115] It appears that, while CoQ10 successfully scavenges free radicals directly, the addition of virgin olive oil prevents damage by increasing cell-membrane concentration of monounsaturated fatty acids, which are not as prone to free-radical damage as fatty acids with many unsaturated bonds. Additionally, virgin olive oil is a rich source of polyphenols, which have direct free-radical scavenging activity.

Tocotrienols, a particular form of vitamin E, have been shown to effectively reduce elevated cholesterol levels. Tocotrienols have also been shown in humans to significantly reduce aortic systolic blood pressure and induce a 9.2% improvement in total antioxidant status as well.[116] One study showed that hypercholesterolemic subjects supplemented with 200 mg gamma-tocotrienol per day showed decreased serum cholesterol by 31% during a four-week period.[117] The delta and gamma isomers found in tocotrienols are effective at lowering cholesterol due to the substitution and location of methyl groups at the head region of the molecule. Tocotrienols positively affect lipid levels by suppressing the activity of HMG-CoA reductase.[118]

A recent case-control study of 317 patients with prostate cancer and 480 controls examined the effects of monounsaturated fatty acid intake. The study found that participants who reported the highest consumption of monounsaturated fatty acids, such as fish oil, cut their relative risk of prostate cancer by half.[119] An additional consideration in men's risk of prostate cancer is a recent study that examined the risk of prostate cancer and alcohol consumption and found that men who drank more than 96 g of alcohol per week had a threefold increased risk of prostate cancer.[120] Moreover, the same research showed an increased relative risk for obese men.

Other antioxidants that may be important in helping patients to achieve the maximum life span are carotenoids. In one study that examined levels of total carotenoids (carotenes plus xanthophylls), there was a positive correlation between carotenoid levels in serum and the brain and the maximum life spans of eight mammal species, including humans.[121] The correlation did not exist, however, for retinol. While this work did not show cause and effect between longevity and total carotenoid level, it did reveal a trend that held up across several mammalian species.

Study participants who reported the highest consumption of monounsaturated fatty acids cut their relative risk of prostate cancer by half.

In addition, the carotenoid xanthophylls, lutein and zeaxanthin, may have an important role in eye health as humans age.[122] The retina is very susceptible to free-radical damage because of its high oxygen consumption, high amount of polyunsaturated fatty acids, and exposure to

visible light.[123] And, while lutein supplementation is not probably a "magic bullet" for preventing free-radical damage in aging eyes completely, a cohort study of 1,354 people found that persons in the highest quintile of lutein intake were only half as likely to develop cataracts as those persons in the lowest quintile of lutein consumption.[124] (See Chapter 13 on ocular diseases.)

BOTANICAL ANTI-AGING INTERVENTIONS

Astragalus

Astragalus membranaceus (astragalus) is a botanical frequently used because of its antioxidant activity. Research suggests that this herb inhibits free radicals, decreases lipid peroxidation, and increases antioxidant enzymes.[125] Studies also suggest that astragalus provides cardioprotective and immune-stimulatory effects.[126,127] Evidence indicates that astragalosides exert anti-aging effects on mice by delaying senility, improving brain function, and improving cellular immunity.[128]

Ginkgo

Ginkgo biloba (ginkgo) leaf has antioxidant, anti-cancer, and free-radical scavenging actions as well as improving microcirculation and protecting neurons from oxidative damage. The herb also decreases platelet aggregation and induces NO.[129] Evidence suggests that ginkgo has cardioprotective activity and may provide benefit for patients who have arterial and venous insufficiency as well as preventing thrombosis.[130] In addition, ginkgo is well known for its ability to slow age-related cognitive functional decline and Alzheimer's disease.[131] In a study of 309 patients with mild dementia, patients were given either 120 mg of ginkgo biloba extract or a placebo every day for up to a year.[132] At six months, 27% of those using ginkgo experienced moderate improvement on a variety of cognitive tests. In subjects taking the placebo, by contrast, only 14% experienced an improvement on the cognitive tests. In addition, scientists have explored ginkgo's effects in conditions that may lead to dementia. In 112 patients with chronic cerebral insufficiency taking 120 mg per day of ginkgo, significant improvements occurred in blood and oxygen flow.[133] Impaired blood and oxygen flow to the brain may be an important factor in the development of Alzheimer's disease.

Huperzia serrata

One herbal medicine frequently used as a cognitive enhancer is huperzine-A, derived from a particular type of club moss (Huperzia serrata). Three double-blind trials enrolling a total of more than 450 people indicated that huperzine-A can significantly improve symptoms of Alzheimer's disease and other forms of dementia.[134–136]

Vinpocetine

Vinpocetine is another cognitive enhancer. It is derived from vincamine, a constituent of common periwinkle (Vinca minor). In a 16-week, double-blind, placebo-controlled trial of 203 people with mild to moderate dementia, vinpocetine produced significant benefit in the treated group.[137]

CONCLUSIONS

Much research is underway to understand the aging process and study potential anti-aging interventions. As the population ages, it is important to investigate potential therapeutics to slow aging and improve quality of life. According to research, interventions that produce antioxidant activity seem to be a common denominator in anti-aging treatment.

REFERENCES

[1]Centers for Disease Control Fast Stats. Online document at: www.cdc.gov=nchs=fastats=older_americans .htm. Accessed August 18, 2006.

[2]U.S. Bureau of the Census. Statistical Abstract of the United States: 1994, 114th Edition. Washington, DC: U.S. Government Printing Office, 1994.

[3]Crastes de Paulet, A. Free radicals and ageing: Review. Ann Biol Clin (Paris). 1990;48(5):323–330.

[4]Kregel KC, Zhang HJ. An integrated view of oxidative stress in aging: Basic mechanisms, functional effects and pathological considerations. Am J Physiol Regul Integr Comp Physiol. 2006 Aug 17;[Epub ahead of print].

[5]Martin I, Grotewiel MS. Oxidative damage and age-related functional declines. Mech Ageing Dev. 2006;127:411–423.

[6]Chung HY, Sung B, Jung KJ, et al. The molecular inflammatory process in aging. Antioxid Redox Signal. 2006;8(3–4):572–581.

[7]Lesnefsky EJ, Hoppel CL. Oxidative phosphorylation and aging. Ageing Res Rev. 2006;5:402–433.

[8]Dirks AJ, Hofer T, Marzetti E, et al. Mitochondrial DNA mutations, energy metabolism and apoptosis in aging muscle. Ageing Res Rev. 2006;5:179–195.

[9]Sato T, Tauchi H. The formation of enlarged and giant mitochondria in the aging process of human hepatic cells. Acta Pathol Jpn. 1975;25:403–412.

[10]Felty Q, Xiong WC, Sun D, et al. Estrogen-induced mitochondrial reactive oxygen species as signal-transducing messengers. Biochemistry. 2005;44:6900–6909.

[11]Cortopassi GA, Wong A. Mitochondria in organismal aging and degeneration. Biochim Biophys Acta. 1999;1410:183–193.

[12]Richter C. Oxidative damage to mitochondrial DNA and its relationship to ageing. Int J Biochem Cell Biol. 1995;27:647–653.

[13]Fahn HJ, Wang LS, Hsieh RH, et al. Age-related 4977 bp deletion in human lung mitochondrial DNA. Am J Respir Crit Care Med. 1996;154(4pt1):1141–1145.

[14]Wei YH, Lee HC. Oxidative stress, mitochondrial DNA mutation, and impairment of antioxidant enzymes in aging. Exp Biol Med (Maywood). 2002;227:671–682.

[15]Harper ME, Monemdjou S, Ramsey JJ, Weindruch R. Age-related increase in mitochondrial proton leak and decrease in ATP turnover reactions in mouse hepatocytes. Am J Physiol. 1998;275(2pt1):E197–E206.

[16]Mather M, Rottenberg H. Aging enhances the activation of the permeability transition pore in mitochondria. Biochem Biophys Res Commun. 2000;273:603–608.

[17]Shin JS, Hong A, Solomon MJ, Lee CS. The role of telomeres and telomerase in the pathology of human cancer and aging. Pathology. 2006;38:103–113.

[18]Blasco MA. Telomeres and human disease: Ageing, cancer and beyond. Nat Rev Genet. 2005;6:611–622.

[19]Ahmed A, Tollefsbol TO. Telomerase, telomerase inhibition, and cancer. J Anti-Aging Med. 2003;6: 315–325.

[20]von Zglinicki T. Oxidative stress shortens telomeres. Trends Biochem Sci. 2002;27:339–344.

[21]Aviv A. Telomeres, sex, reactive oxygen species, and human cardiovascular aging. J Mol Med. 2002;80: 689–695.

[22]Valdes AM, Andrew T, Gardner JP, et al. Obesity, cigarette smoking, and telomere length in women. Lancet. 2005;366:662–664.

[23]Lee DC, Im JA, Kim JH, et al. Effect of long-term hormone therapy on telomere length in postmenopausal women. Yonsei Med J. 2005;46:471–479.

[24]Simon NM, Smoller JW, McNamara KL, et al. Telomere shortening and mood disorders: Preliminary support for a chronic stress model of accelerated aging. Biol Psychiatry. 2006;60:432–435.

[25]Epel ES, Blackburn EH, Lin J, et al. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci USA. 2004;101:17312–17315.

[26]Minamino T, Komuro I. Role of telomere in endothelial dysfunction in atherosclerosis. Curr Opin Lipidol. 2002;13:537–543.
[27]Mooradian AD. Mechanisms of age-related endocrine alterations: Part I. Drugs Aging. 1993;3:81–97.
[28]Nair NP, Hariharasubramanian N, Pilapil C, et al. Plasma melatonin—an index of brain aging in humans? Biol Psychiatry. 1986;21:141–150.
[29]Blackman MR. Age-related alterations in sleep quality and neuroendocrine function: Interrelationships and implications. JAMA. 2000; 284:879–881.
[30]Noth RH, Mazzaferri EL. Age and the endocrine system. Clin Geriatr Med. 1985;1:223–250.
[31]Sato R, Maesawa C, Fujisawa K, et al. Prevention of critical telomere shortening by oestradiol in human normal hepatic cultured cells and carbon tetrachloride induced rat liver fibrosis. Gut. 2004;53:1001–1009.
[32]Meeker AK, Sommerfeld HJ, Coffey DS. Telomerase is activated in the prostate and seminal vesicles of the castrated rat. Endocrinology. 1996; 137:5743–5746.
[33]Wautier JL, Guillausseau PJ. Advanced glycation end products, their receptors and diabetic angiopathy. Diabetes Metab. 2001;27(5pt1):535–542.
[34]Verzijl N, DeGroot J, Ben ZC, et al. Cross-linking by advanced glycation end products increases the stiffness of the collagen network in human articular cartilage: A possible mechanism through which age is a risk factor for osteoarthritis. Arthritis Rheum. 2002;46:114–123.
[35]Zieman SJ, Kass DA. Advanced glycation endproduct cross-linking in the cardiovascular system: Potential therapeutic target for cardiovascular disease. Drugs. 2004;64:459–470.
[36]Munch G, Thome J, Foley P, et al. Advanced glycation endproducts in ageing and Alzheimer's disease. Brain Res Brain Res Rev. 1997;23(1–2):134–143.
[37]Bellows JG, Bellows RT. Cross-linkage theory of senile cataracts. Ann Ophthalmol. 1976;8:129–135.
[38]Heilbronn LK, de Jonge L, Frisard MI, et al., and the Pennington CALERIE Team. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: A randomized controlled trial. JAMA. 2006;295:1539–1548.
[39]Lane MA, Baer DJ, Rumpler WV, et al. Calorie restriction lowers body temperature in rhesus monkeys, consistent with a postulated anti-aging mechanism in rodents. Proc Natl Acad Sci USA. 1996;93:4159–4164.
[40]Hallows WC, Lee S, Denu JM. Sirtuins deacetylate and activate mammalian acetyl-CoA synthetases. Proc Natl Acad Sci USA. 2006;103: 10230–10235.
[41]Chen WY, Wang DH, Yen RC. Tumor suppressor HIC1 directly regulates SIRT1 to modulate p53-dependent DNA-damage responses. Cell. 2005;123:437–448.
[42]Bevilacqua L, Ramsey JJ, Hagopian K, et al. Effects of short- and medium-term calorie restriction on muscle mitochondrial proton leak and reactive oxygen species production. Am J Physiol Endocrinol Metab. 2004;286:E852–E861.
[43]Merry BJ. Molecular mechanisms linking calorie restriction and longevity. Int J Biochem Cell Biol. 2002;34:1340–1354.
[44]Lambert AJ, Wang B, Merry BJ. Exogenous insulin can reverse the effects of caloric restriction on mitochondria. Biochem Biophys Res Commun. 2004;316:1196–1201.
[45]Cho CG, Kim HJ, Chung SW, et al. Modulation of glutathione and thioredoxin systems by calorie restriction during the aging process. Exp Gerontol. 2003;38:539–548.
[46]Srivastava VK, Miller SD, Busbee DL. Aging and DNA polymerase alpha: Modulation by dietary restriction. J Nutr Health Aging. 1999; 3:111–120.
[47]Raffoul JJ, Guo Z, Soofi A, Heydari AR. Caloric restriction and genomic stability. J Nutr Health Aging. 1999;3:102–110.
[48]Shimokawa I, Higami Y. Leptin signaling and aging: Insight from caloric restriction. Mech Ageing Dev. 2001;122:1511–1519.
[49]Colotti C, Cavallini G, Vitale RL, et al. Effects of aging and anti-aging caloric restrictions on carbonyl and heat shock protein levels and expression. Biogerontology. 2005;6:397–406.
[50]Baulieu EE, et al. Dehydroepiandrosterone (DHEA), DHEA sulfate, and aging: Contribution of the DHEAge study to a sociobiomedical issue. Proc Natl Acad Sci. 97(8):4279–4284, 2000.
[51]Brewer GJ. Effect of intragastric pH on the absorption of oral zinc acetate and zinc oxide in young health volunteers. J Parent Ent Nutr. 1995;19:393–397.
[52]Jacobs A, Rhodes J. Gastric factors influencing iron absorption in anaemic patients. Scan J Hemat. 1967;4:105–110.
[53]Mahoney AW, Hendricks DG. Role of gastric acid in the utilization of dietary calcium by the rat. Nutr Metab. 1974;16:375–382.
[54]Saltzman JR, Kemp JA, Golner BB, Pedrosa MC, Dallal GE, Russell RM. Effect of hypochlorhydria due to omeprazole treatment or atrophic gastritis on protein-bound vitamin B12 absorption. J Am Coll Nutr. 1994; 13(6):584–591.

[55]Garry PJ, Goodwin JS, Hunt WC, et al. Nutritional status in a healthy elderly population: Dietary and supplemental intakes. Am J Clin Nutr. 1982;36:319–331.
[56]Selhub J, Jacques PF, Bostom AG, et al. Association between plasma homocysteine concentrations and extracranial carotid–artery stenosis. N Eng J Med. 1995;332:286–291.
[57]Selhub J, Jacques PF, Wilson PW, et al. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. JAMA. 1993;270(22):2693–2698.
[58]Grossman R. The role of dimethylaminoethanol in cosmetic dermatology. Am J Clin Dermatol. 2005; 6:39– 47.
[59]Terman A, Brunk UT. Oxidative stress, accumulation of biological ''garbage,'' and aging. Antioxid Redox Signal. 2006;8(1–2):197–204.
[60]Nagy I, Nagy K. On the role of cross-linking of cellular proteins in aging. Mech Ageing Dev. 1980;14(1–2):245–251.
[61]Orentreich N, Brind JL, Rizer RL, Vogelman JH. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. J Clin Endocrinol Metab. 1984;59:551–555.
[62]Tchernof A, Labrie F. Dehydroepiandrosterone, obesity and cardiovascular disease risk: A review of human studies. Eur J Endocrinol. 2004;151:1–14.
[63]Jankowski CM, Gozansky WS, Schwartz RS, et al. Effects of dehydroepiandrosterone replacement therapy on bone mineral density in older adults: A randomized, controlled trial. J Clin Endocrinol Metab. 2006;91:2986–2993.
[64]Villareal DT, Holloszy JO. Effect of DHEA on abdominal fat and insulin action in elderly women and men: A randomized controlled trial. JAMA. 2004;292:2243–2248.
[65]Martina V, Benso A, Gigliardi VR, et al. Short-term dehydroepiandrosterone treatment increases platelet cGMP production in elderly male subjects. Clin Endocrinol (Oxf). 2006;64:260–264.
[66]Moriyama Y, Yasue H, Yoshimura M. The plasma levels of dehydroepiandrosterone sulfate are decreased in patients with chronic heart failure in proportion to the severity. J Clin Endocrinol Metab. 2000; 85:1834–1840.
[67]Villareal D, Holloszy JO. DHEA enhances effects of weight training on muscle mass and strength in elderly women and men. Am J Physiol Endocrinol Metab. 2006;291:E1003–E1008.
[68]Schmidt PJ, Daly RC, Bloch M, et al. Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression. Arch Gen Psychiatry. 2005;62:154–162.
[69]Ceda GP, Dall'Aglio E, Maggio M, et al. Clinical implications of the reduced activity of the GH-IGF-I axis in older men [proceedings]. J Endocrinol Invest. 2005;28(11suppl):96–100.
[70]Yang AL, Chao JI, Lee SD. Altered insulin-mediated and insulin-like growth factor–1-mediated vasorelaxation in aortas of obese Zucker rats. Int J Obes (Lond). 2006 May 9;[Epub ahead of print].
[71]Aberg ND, Brywe KG, Isgaard J. Aspects of growth hormone an insulin-like growth factor-I related to neuroprotection, regeneration, and functional plasticity in the adult brain. Sci World J. 2006;6:53–80.
[72]Onder G, Liperoti R, Russo A, et al. Body mass index, free insulin growth factor 1 and physical function among older adults: Results from the ilSIRENTE study. Am J Physiol Endocrinol Metab. 2006;291:E829–E834.
[73]Zhou JN, Liu RY, van Heerikhuize J, et al. Alterations in the circadian rhythm of salivary melatonin begin during middle-age. J Pineal Res. 2003;34:11–16.
[74]Suzen S. Recent developments of melatonin related antioxidant compounds. Comb Chem High Throughput Screen. 2006;9:409– 419.
[75]Srinivasan V, Maestroni G, Cardinali D, et al. Melatonin, immune function and aging. Immun Ageing. 2005;2:17.
[76]Currier NL, Sun LZ, Miller SC. Exogenous melatonin: Quantitative enhancement in vivo of cells mediating non-specific immunity. J Neuroimmunol. 2000;104:101–108.
[77]Leon J, Acuna-Castroviejo D, Escames G, et al. Melatonin mitigates mitochondrial malfunction. J Pineal Res. 2005;38:1–9.
[78]Srinivasan V, Pandi-Perumal SR, Maestroni GJ. Role of melatonin in neurodegenerative diseases. Neurotox Res. 2005;7:293–318.
[79]Blask DE, Dauchy RT, Sauer LA. Putting cancer to sleep at night: The neuroendocrine=circadian melatonin signal. Endocrine. 2005;27:179–188.
[80]Blask DE, Dauchy RT, Sauer LA, Krause JA, et al. Light during darkness, melatonin suppression and cancer progression. Neuro Endocrinol Lett. 2002 Jul;23(suppl2):52–56.
[81]Jackson MC, Lenney JF. The distribution of carnosine and related dipeptides in rat and human tissues. Inflamm Res. 1996;45:132–135.
[82]Stuerenburg HJ. The roles of carnosine in aging of skeletal muscle and in neuromuscular diseases. Biochemistry (Mosc). 2000;65:862–865.

[83]Guiotto A, Calderan A, Ruzza P, Borin G. Carnosine and carnosinerelated antioxidants: A review. Curr Med Chem. 2005;12:2293–2315.
[84]Shao L, Li QH, Tan Z. L-carnosine reduces telomere damage and shortening rate in cultured normal fibroblasts. Biochem Biophys Res Commun. 2004 Nov 12;324:931–936.
[85]Hipkiss AR. Would carnosine or a carnivorous diet help suppress aging and associated pathologies? Ann NY Acad Sci. 2006;1067:369–374.
[86]Wang AM, Ma C, Xie ZH, Shen F. Use of carnosine as a natural antisenescence drug for human beings. Biochemistry (Mosc). 2000;65:869–871.
[87]Li F, Chong ZZ, Maiese K. Cell life versus cell longevity: The mysteries surrounding the NAD precursor nicotinamide. Curr Med Chem. 2006;13:883–895.
[88]Matuoka K, Chen KY, Takenawa T. Rapid reversion of aging phenotypes by nicotinamide through possible modulation of histone acetylation. Cell Mol Life Sci. 2001;58:2108–2116.
[89]Morris MC, Evans DA, Bienias JL, et al. Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. J Neurol Neurosurg Psychiatry. 2004;75:1093–1099.
[90]Guyton JR. Effect of niacin on atherosclerotic cardiovascular disease. Am J Cardiol. 1998;82(12A):18U–23U;discussion 39U–41U.
[91]Wieneke H, Schmermund A, Erbel R. Niacin—an additive therapeutic approach for optimizing lipid profile [in German]. Med Klin (Munich). 2005;100:186–192.
[92]Soja AM, Mortensen SA. Treatment of congestive heart failure with coenzyme Q10 illuminated by meta-analyses of clinical trials. Mol Aspects Med. 1997;18(suppl):S159–S168.
[93]Burke BE, Neuenschwander R, Olson RD. Randomized, double-blind, placebo-controlled trial of co-enzyme Q10 in isolated systolic hypertension. South Med J. 2001;94:1112–1117.
[94]Singh RB, Wander GS, Rastogi A, et al. Randomized, double-blind placebo-controlled trial of coenzyme Q10 in patients with acute myocardial infarction. Cardiovasc Drugs Ther. 1998;12:347–353.
[95]Shults CW. Coenzyme Q10 in neurodegenerative diseases. Curr Med Chem. 2003;10:1917–1921.
[96]Sandor PS, Di Clemente L, Coppola G, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: A randomized controlled trial. Neurology. 2005;64:713–715.
[97]Folkers K, Brown R, Judy WV, Morita M. Survival of cancer patients on therapy with coenzyme Q10. Biochem Biophys Res Commun. 1993;192:241–245.
[98]Labinskyy N, Csiszar A, Veress G, et al. Vascular dysfunction in aging: Potential effects of resveratrol, an anti-inflammatory phytoestrogen. Curr Med Chem. 2006;13:989–996.
[99]de la Lastra CA, Villegas I. Resveratrol as an anti-inflammatory and anti-aging agent: Mechanisms and clinical implications. Mol Nutr Food Res. 2005;49:405–430.
[100]Bradamante S, Barenghi L, Villa A. Cardiovascular protective effects of resveratrol. Cardiovasc Drug Rev. 2004;22:169–188.
[101]Anekonda TS. Resveratrol—A boon for treating Alzheimer's disease? Brain Res Brain Res Rev. 2006; 52:316–326.
[102]Lu SC. Regulation of hepatic glutathione synthesis: Current concepts and controversies. FASEB J. 1999;13:1169–1183.
[103]Samiec PS, Drews-Botsch C, Flagg EW, et al. Glutathione in human plasma: Decline in association with aging, age-related macular degeneration, and diabetes. Free Radic Biol Med. 1998;24:699–704.
[104]Bains JS, Shaw CA. Neurodegenerative disorders in humans: The role of glutathione in oxidative stress-mediated neuronal death. Brain Res Brain Res Rev. 1997;25:335–358.
[105]Jones DP. Extracellular redox state: Refining the definition of oxidative stress in aging. Rejuvenation Res. 2006;9:169–181.
[106]Lang CA, Naryshkin S, Schneider DL, Mills BJ, Lindeman RD. Low blood glutathione levels in healthy aging adults. J Lab Clin Med. 1992;120(5):720–725.
[107]Julius M, Lang CA, Gleiberman L, Harburg E, DiFranceisco W, Schork A. Glutathione and morbidity in a community-based sample of elderly. J Clin Epidemiol. 1994;47(9):1021–1026.
[108]Bonnefoy M, Drai J, Kostka T. Antioxidants to slow aging, facts and perspectives [in French]. Presse Med. 2002;31:1174–1184.
[109]Alvarado C, Alvarez P, Puerto M, et al. Dietary supplementation with antioxidants improves functions and decreases oxidative stress of leukocytes from prematurely aging mice. Nutrition. 2006;22(7–8): 767–777.
[110]Sies H, Stahl W, Sundquist AR. Antioxidant functions of vitamins: Vitamins E and C, beta-carotene, and other carotenoids. Ann NY Acad Sci. 1992;669:7–20.
[111]Parge HE, Getzoff ED, Scandella CS, Hallewell RA, Tainer JA. Crystallographic characterization of recombinant human CuZn superoxide dismutase. J Biol Chem. 1986;261:1615–1618.
[112]Marks DB, Marks AD, Smith CM. Basic Medical Biochemistry: A Clinical Approach. Baltimore: Williams & Wilkins, 1996, 337.

[113]Meydani M. Dietary antioxidants modulation of ageing and immune-endothelial cell interaction. Mech Ageing Dev. 1999;111(2–3):123–132.
[114]Fuller CJ, Huet BA, Jiala I. Effects of increasing doses of alpha-tocopherol in providing protection of low-density lipoprotein from oxidation. Am J Cardiol. 1998;81(2):231–233.
[115]Huertas JR, et al. Virgin olive oil and coenzyme Q10 protect heart mitochondria from peroxidative damage during aging. Biofactors. 1999;9(2–4):337–343.
[116]Rasool A.h.g, Yuen KH, Yusoff K, Wong AR, Rahman AR. Dose dependent elevation of plasma tocotrienol levels and its effect on arterial compliance, plasma total antioxidant status, and lipid profile in healthy humans supplemented with tocotrienol rich vitamin E. J Nutr Sci Vitaminol. 2006;52:473–478.
[117]Qureshi AA, Qureshi N, Wright JJ, Shen Z, Kramer G, Gapor A, Chong YH, DeWitt G, Ong A, Peterson DM, et al. Lowering of serum cholesterol in hypercholesterolemic humans by tocotrienols (palmvitee). Am J Clin Nutr. 1991 Apr;53(4 suppl):1021S–1026S.
[118]Parker RA, Pearce BC, Clark RW, Gordon DA, Wright JJ. Tocotrienols regulate cholesterol production in mammalian cells by post-transcriptional suppression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. J Biol Chem. 1993;268:11230–11238.
[119]Norrish AE, Jackson RT, Sharpe SJ, Skeaff CM. Men who consume vegetable oils rich in monounsaturated fat: Their dietary patterns and risk of prostate cancer. Cancer Causes Control. 2000;11(7):609–615.
[120]Putnam SD, et al. Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men. Ann Epidemiol. 2000;10(6):361–369.
[121]Cutler RG. Carotenoids and retinol: Their possible importance in determining longevity o f primate species. Proc Natl Acad Sci. 1984;81:7627–7631.
[122]Moeller SM, Jacques PF, Blumberg JB. The potential role of dietary xanthophylls in cataract and age–related macular degeneration: Review. J Am Coll Nutr. 2000;19(5 suppl.):522S–527S.
[123]Beatty S, Koh H, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. Surv Ophthalmol. 2000;45(2):115–134.
[124]Lyle BJ, Mares-Perlman JA, Klein BE, Klein R, Greger JL. Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam Eye Study. Am J Epidemiol. 1999;149(9):801–809.
[125]Ko JK, Lam FY, Cheung AP. Amelioration of experimental colitis by Astragalus membranaceus through anti-oxidation and inhibition of adhesion molecule synthesis. World J Gastroenterol. 2005;11:5787–5794.
[126]Zhang WD, Chen H, Zhang C, et al. Astragaloside IV from Astragalus membranaceus shows cardioprotection during myocardial ischemia in vivo and in vitro. Planta Med. 2006;72:4–8.
[127]Shao BM, Xu W, Dai H, et al. A study on the immune receptors for polysaccharides from the roots of Astragalus membranaceus, a Chinese medicinal herb. Biochem Biophys Res Commun. 2004;320:1103–1111.
[128]Lei H, Wang B, Li WP, et al. Anti-aging effect of astragalosides and its mechanism of action. Acta Pharmacol Sin. 2003;24:230–234.
[129]Dubey AK, Shankar PR, Upadhyaya D, Deshpande VY. Ginkgo biloba—an appraisal. Kathmandu Univ Med J (KUMJ). 2004;2:225–229.
[130]Zhou W, Chai H, Lin PH, et al. Clinical use and molecular mechanisms of action of extract of Ginkgo biloba leaves in cardiovascular diseases. Cardiovasc Drug Rev. 2004;22:309–319.
[131]Bidzan L, Biliekiewicz A, Turczynski J. Preliminary assessment of Ginkgo biloba (Ginkofar) in patients with dementia [in Polish]. Psychiatr Pol. 2005;39:559–566.
[132]Kanowski S, Hoerr R. Proof of the efficacy of the Ginkgo biloba special extract egb76 1 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type of multi-infarct dementia. Phytomedicine. 1997;4: 215–222.
[133]Le Bars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. North American EGb Study Group. JAMA. 1997;278:1327–1332.
[134]Xu SS, Gao ZX, Weng Z. Efficacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease. Zhongguo Yao Li XueBao. 1995;16:391–395.
[135]Zhang RW, Tang XC, Han YY. Drug evaluation of huperzine A in the treatment of senile memory disorders [in Chinese; English abstract]. Zhongguo Yao Li XueBao. 1991;12:250–252.
[136]Zhang Z, Wang X, Chen Q. Clinical efficacy and safety of huperzine alpha in treatment of mild to moderate Alzheimer disease: A placebo-controlled, double-blind, randomized trial. Zhonghua Yi XueZaZhi. 2002;82:941–944.
[137]Szatmari SZ, Whitehouse PJ. Vinpocetine for cognitive impairment and dementia. Cochrane Database Syst Rev. 2003;CD003119.

4

NATURE'S TRUE APHRODISIACS

Better Sex Naturally

It is estimated that more than 52% of men over age 40 have some type of erectile dysfunction, affecting nearly 150 million men.[1,2] Such statistics are not as readily available for women, probably because of the previous lack of research into the field of female sexual response and the lack of an easily quantified external response. Yet, it would seem that, because the same physiologic, biochemical, and psychologic responses are principally at play in both genders, a certain amount of expected crossover in terms of therapeutic application could be assumed. Indeed, this proves to be true in clinical practice with the same concepts of enhanced blood supply and neurologic support proving to be helpful. Thus, when treating male or female sexual response, healthy cardiovascular, neurologic, and psychologic states required for optimal sexuality should be the primary long-term focus.

In clinical practice, all too often, one finds that both men and women resign themselves to being less sexually active as they age. This is unfortunate, because, within reason, there is no true age limit to the enjoyment of a rewarding sex life. From a natural-medicine perspective, the ability to have good sex is merely the barometer of overall health. One of the first things that needs to occur in the evaluation of lowered libido or performance is a full evaluation of mental well-being, neurological health, cardiac health with a focus on circulatory health, and the ever important hormonal well-being. It is estimated that as many as one in four men over the age of 20 are measurably low in testosterone. Clinically low levels of testosterone are notable in women upwards of at least a decade from expected menopause.

Traditional healers and physicians around the world have long known that there are many natural medicines that can enhance sexual desire and function in both men and women. The Chinese have used ginseng for thousands of years as a tonic and to stimulate desire and enhance endurance. Similarly, the herb known as Indian ginseng, ashwagandha (Withania somniferum), has been used to promote potency for centuries. Throughout the world, one finds an abundance of long-revered aphrodisiacs that have now gained increased acceptance as a result of clinical trials. However, from a natural medicine perspective, the best approach to enhancing bodily functions—including sexuality—is to support the underlying health of the body as a whole. It is true that the better our patients feel, the greater will be their ability to enjoy sexual satisfaction.

COMMON DENOMINATORS

Clinically speaking, there are recurring trends seen among patients who desire to bolster their sexual enjoyment. Interestingly enough, the patients who are seeking such advice are not necessarily at the point of sexual dysfunction, but rather they want to either maintain or enhance an already satisfying sex life. In addition to gender-specific contributing factors to sexual ability, there are three critical health areas that must be evaluated and, to varying degrees, addressed. It is important to remember that there is a lot of overlap when it comes to both sexes and the clinical approach. They include cardiovascular, neurologic, and overall

psychologic state. Therefore, creating an enhancement protocol from this perspective often proves to be most beneficial. This is to say that, when patient and clinician focus on the health issues or areas of less-than-optimal health, usually, the desire for enhanced sexual function is achieved passively. Thus, it is worthwhile to look more closely at the underlying health requirements for optimal sexual enjoyment.

Cardiovascular Health

The cardiovascular link to sexual satisfaction makes sense because sufficient blood flow for both men and women is critical to optimal functioning. Both male and female erectile tissues are more sensitive and responsive to stimuli when these tissues are optimally perfused. When one also considers that an estimated 43 of every 100 Americans die from cardiovascular conditions, it is not surprising that focusing on this aspect of underlying health can yield some substantial rewards in the area of sexual satisfaction. Examine this statistic more closely: If 43% of Americans have such progressive deterioration of their vascular systems that this literally kills them, one can easily extrapolate this number to an even higher percentage of people that have lesser but varying degrees of heart disease, which also affects sexual function. Thus, it is not surprising that the blood flow to the sex organs also decreases, ultimately diminishing the ability to function. This plight of the Western world, caused by the standard American diet and lifestyle, although resulting from a series of choices, is reversible. When it comes to sustaining a healthier cardiovascular system, indeed, the investment goes well beyond achieving better sex. This key lifestyle change creates the foundation for a longer and improved quality of life.

Neuromuscular Health

The prevalence of musculoskeletal and neurologic conditions is evident if one only thinks of the common complaints of one's patients, friends, and family. We all know individuals with

Table 4–1. Gender-Based Differences in the Effects of Natural Supports for Good Sexual Functioning

	Male	Female
Arginine	D	D
Black cohosh (Cimicifuga racemosa)	—	|
Dong quai (Angelica sinensis)	—	|
Essential fatty acids	|	|
Flower pollen	|	—
g-oryzanol	—	|
Ginkgo (Ginkgo biloba)	D	D
Ginseng (Panax ginseng)	D=|	D=|
Muira puama (Ptychopetalum guyanna)	D	D
Saw palmetto (Serenoa repens)	|	—
Stinging nettle (Urtica dioica)	|	—
Wild yam (Dioscorea spp.)	—	|
Zinc	|	—

Key: D direct supportive effect; | indirect supportive effect; — not.

low-back pain, muscular pain, and, in many cases, neuropathy. Without optimal nervous-system health, both afferent and efferent nerve impulses are less than efficient in impulse transmission. Thus, supporting the nervous system is of paramount importance with nutrients such as vitamins B_1, B_2, B_6, and B_{12}.[3]

> No single nutrient is more important than zinc for maintaining a man's overall reproductive and sexual functioning.

Psychologic Health

Mental health is another large issue, with some 10% of sexual dysfunction in men alone being attributed to psychologic conditions, as a result of psychiatric illness, stress, anxiety, depression, or performance anxiety. Once again, one might reasonably assume that similar numbers of women are affected by these factors, because neither gender is immune to such powerful factors affecting one's overall life experience, let alone one's sexual satisfaction. By addressing these areas of psychologic health, one can help patients to improve daily functioning and sexual experience. There are numerous natural-medicine interventions to help patients who have anxiety and stress, in general. Appropriate natural medicines include ginseng (Panax ginseng), kava (Piper methysticum), St. John's wort (Hypericum perforatum), B complex vitamins, licorice (Glycyrrhiza glabra), and many others.[4]

MEDICATIONS

Certain medications can also inadvertently dampen a patient's sex life. Although many of these medications affect men more severely than such agents affect women, from a total satisfaction perspective, these medications are worth keeping in mind when patients report changes in their sexual function while taking such drugs. The cost benefit ratio must be considered. Some of the more common culprits include antipsychotics, antidepressants, anticholinergics, antihypertensives, and antihistamines.

MALE-SPECIFIC HEALTH CONSIDERATIONS

Often, men lose sight of the fact that prostate health can play a vital role in sexual functioning. Some researchers believe that the sensations in this walnut-sized organ can actually increase sexual excitation. It is never too early to address prostate health; by the age of 30, approximately 5%–10% of men are affected by an enlarged prostate; by age 85, 90% of men are affected. Early warning signs of prostate enlargement often include an altered urinary stream. Classically, there might be dribbling after urination, hesitancy at the onset, a sense of incomplete voiding, and the classic forked stream. It is best to pursue prevention of prostate problems before they happen. Thus, ensuring that your patients maintain optimal sexual functioning includes advising strongly that they should pamper their prostates. Numerous multivitamins designed for specific male health problems include such herbs as saw palmetto (Serenoa repens), and pygeum (Pygeum africanus), as well as therapeutic doses of zinc to help maintain prostate health.

Lifestyle choices can also affect prostate health. One large study[5] showed that consumption of alcohol can dampen a man's sex life in more than one way. A study of more than 6,500 men revealed a strong correlation between the consumption of 25 ounces or more of alcohol per month and prostate enlargement. Beyond the prostate effect, alcohol is a sedative that can dampen sexual function in a direct fashion, even when consumed in relatively small quantities.

No single nutrient is more important than zinc for maintaining a man's overall reproductive and sexual functioning. In fact, the prostate is the richest reservoir of zinc within the body. Zinc helps to ensure overall virility, including erectile function and sperm quality.[6,7] Diet also can play a critical role in prostate health. Eating a diet high in protein can inhibit the enzyme, 5-alpha reductase. This enzyme converts testosterone into the more potent hormone dihydrotestosterone (DHT), which when levels are elevated, causes the increased growth of the prostate, leading to pelvic congestion and an obstructed flow of urine. In contrast, a diet that is high in carbohydrates can actually contribute to a buildup of DHT. Recommendations for maintaining a healthy prostate call for a dietary balance of protein, 44%; complex carbohydrates, 35%; and mostly unsaturated fats, 21%.[8]

A combination of a specifically targeted diet as described previously, avoidance of alcohol, and the possible addition of one or more of the following natural medicines can help to prevent prostate-induced urinary and sexual difficulties. Among the most popular supplements for enhancing prostate and reproductive health are zinc, saw palmetto, stinging nettles (Urtica dioica), pygeum, essential fatty acids, and flower pollen. It would also make sense to advise men to stop smoking, to exercise, and to diet.

FEMALE-SPECIFIC HEALTH CONSIDERATIONS

When considering which natural substances to use for nourishing a woman's sexual vitality, the traditional focus is on herbal products that help to modulate female hormones. Yet, there are natural medicines that enhance blood flow, and these are also critical to a woman's optimal sexual satisfaction. These latter substances are discussed in the section about nutrients that are supportive for both genders. Female-specific herbs include dong quai (Angelica sinensis), black cohosh (Cimicifuga racemosa), chaste tree (Vitex agnus castus), and wild yam (Dioscorea villosa). Each of these herbs has the ability to modulate and amplify, as needed, the body's hormonal balance. They have all been used traditionally to address the signs and symptoms associated with premenstrual syndrome and menopause. (See Chapter 16 on female hormones.) Beyond herbal medicine, some good holistic approaches can maximize well-being and optimize sexual functioning. Some common lifestyle-improvement tips include avoidance of smoking, regular exercise, a limit on drinking alcohol, and eating the right foods. Smoking can lead to hormonal imbalance, thus, increasing the likelihood of early menopause. Menopause is believed to lower estrogen levels, which are critical for maintaining healthy reproductive tissues.[9] In turn, exercise can not only help keep one fit but, according to the results of studies, middle-aged women who are active, on average exercise 3.5 times per week, have experienced fewer and less substantial hot flashes than women who do not exercise.[10] So, in short, the better your patients feel, the more likely they will enjoy optimal sexual activity.

Foods that have pro-hormonal effects have been shown to help modulate hormonal function. These foods include soybean products, celery, fennel, parsley, and various nuts and seeds including flax seeds.[11] It is the high intake of these foods in other cultures that has been

Table 4–2. Natural Agents that Support Good Sexual Function

Agents	Recommended Doses	Contraindications
Black cohosh (Cimicifuga racemosa)	500 mg, 2–3 times per day	Contraindicated during pregnancy or breast feeding; may also alter menstrual cycle
Dong quai (Angelica sinensis)	500 mg, 3–4 times per day	Contraindicated during pregnancy or breast feeding; may also alter menstrual cycle
Essential fatty acids	2000 mg, 3 times per day	—[a]
Flower pollen	120 mg, 3 times per day	—
g-oryzanol	300 mg, 1–2 times per day	—
Ginkgo (Ginkgo biloba)	60–120 mg, 3 times per day	Because of blood-thinning effect, should not be taken prior to surgery (at least 2–3 days); if taken with other blood thinners, patient should be monitored closely
Ginseng (Panax ginseng)	100–200 mg, 2 times per day	Should not be used for patients with high blood pressure or heart or kidney disease; may also interact with antidepressants, heart medications, insulin, and other medications
Muira puama (Ptychopetalum guyanna)	250 mg, 3 times per day	—
Pygeum africanum (Pygeum africanus)	100 mg 2–3 times per day (standardized)	—
Saw palmetto (Serenoa repens)	160 mg, 2–3 times per day (standardized)	—
Stinging nettle (Urtica dioica)	450 mg, 2–3 times per day (freeze-dried)	Contraindicated during pregnancy or breast feeding; may also alter menstrual cycle
Wild yam (Dioscorea spp.)	500 mg, 3 times per day	Contraindicated during pregnancy or breast feeding; may also alter menstrual cycle
Chaste tree (Vitex agnus castus)	175–225 mg per day (standardized)	—

Note: These dosages need to be individualized for each patient, taking into consideration physical vitality and appropriateness of the natural medicine to the specific symptoms and signs of the patient.
[a]No literature suggesting any interactions.

attributed, in large part, to menopause and premenstrual syndrome being substantially less prevalent in non-Westernized countries. Other supplements that can also be considered for optimizing female sexual functioning include rice-bran oil, which can help to balance hormonal symptoms; magnesium, which can help cellular-energy production and decrease muscle cramps; and vitamin E suppositories, which can help to mitigate vaginal dryness or generalized hormone-dependent vaginitis.[12]

> The better your patients feel, the more likely they will enjoy optimal sexual activity.

SUPPORTING HEALTHY SEXUAL FUNCTIONING FOR BOTH GENDERS

Arginine

This amino acid is needed for nitric-oxide formation and, thus, plays a vital role in helping to sustain blood flow to erectile tissue. Arginine has been shown, in both animal and human studies, to help improve erectile response.[13,14] Thus, both penile erectile function and clitoral engorgement may be improved.[15] One might theorize that vaginal lubrication may also be improved because of the enhanced pelvic circulation. Clinically, arginine has proven itself to be effective in approximately 80% of cases in which increased circulation was needed to address optimizing sexual function. (See Chapter 35 on nitric oxide.)

Ginkgo

Ginkgo (Ginkgo biloba) has vasodilatory effects and has been shown to help men with erectile dysfunction. In two studies,[16,17] men with impotence noted meaningful benefits when they took ginkgo. Ginkgo's vasodilatory effect can help both men and women who want to achieve optimal sexual function. Like arginine, ginkgo is a natural substance that enhances circulation; yet ginkgo has potent antioxidant and vascular stabilizing effects as well. Thus, this herb not only serves as a treatment in addressing symptoms, but nourishes the body at the same time. The herb accomplishes this by facilitating microvascular circulation, vasodilation, and smooth-muscle relaxation.[18] Ginkgo and ginseng have been shown to relax smooth muscle and thereby increase circulation.[19]

Muira Puama

At a leading institution (The Institute for Sexology) for sexual studies in Paris, France,[20] a study of 262 men who were experiencing a lack of sexual desire and inability to attain or maintain an erection found that muira puama (Ptychopetalum guyanna) enhanced both erectile-tissue response and libido. After two weeks of taking this South American herb, 51% of patients with erectile dysfunction improved and 62% reported increased libido. This herb appears to increase cognitive receptiveness in addition to heightening sexual responsiveness. This effect

For Your Patients . . .

Better Sex Naturally: Herbs and Other Natural Supplements That Can Jump Start Your Sex Life

By Chris D. Meletis, N.D.

New York: HarperCollins, 2000

In one study, muira puama enhanced both erectile-tissue response and libido.

occurs consistently in clinical practice also. Clinical studies are needed on the effects of muira puama on women, but it would be reasonable to expect that the benefits would be comparable.

CONCLUSIONS

These natural medicines that have been reviewed are representative of a number of other herbs that have been used successfully to enhance sexual performance. These include wild oats (Avena sativa), yohimbe (Pausinystalia yohimbe), ashwagandha (Withania somniferum), sarsaparilla (Smilax officinalis), puncture vine (Tribulus terrestris), horny goat weed (Epimedium spp.), and damiana (Turnera diffusa). Damiana was specifically shown in an animal study to increase sexual copulatory performance as a result of phyto-progestin receptor activity but not as a result of progestin activity.[21,22] The key, however, to achieving the desired results with these and the other natural medicines discussed is appropriate prescribing, based on the underlying signs and symptoms that each individual presents with. Thus, in addressing the 43% of women and 31% of men in the United States who report sexual dysfunction,[23] it is clear that ultimate sexual functioning depends on a strong and well-nourished body that provides the foundation for increased physical endurance and enjoyment of life in all aspects.

REFERENCES

[1]Safarinejad MR, Hosseini S. Erectile dysfunction: clinical guidelines (1). Urol J. 2004 Summer;1(3): 133–147.
[2]Travison TG, Shabsigh R, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The natural progression and remission of erectile dysfunction: results from the Massachusetts Male Aging Study. J Urol. 2007 Jan;177(1):241–246; discussion 246.
[3]Jones CL, et al. Pyridoxine deficiency: A factor in diabetic neuropathy. J Am Pod Assoc. 1978;68:646–665.
[4]Bhattacharya SK, et al. Anxiolytic activity of Panax ginseng roots: An experimental study. J Ethnopharmacol. 1991;34:87–92.
[5]Chylou PH, et al. A prospective study of alcohol, diet, and other lifestyle factors in relation to obstructive uropathy. Prostate. 1993;22:253–264.
[6]Prasad AS. Zinc in growth and development and spectrum of human zinc deficiency. J Am Coll Nutr. 1988;7:377–384.
[7]Netter A, et al. Effect of zinc administration on plasma testosterone, dihydrotestosterone and sperm count. Arch Androl. 1981;7:69–73.
[8]Kappas A, et al. Nutrition-endocrine interactions: Induction of reciprocal changes in the delta-5-alpha-reduction of testosterone and the cytochrome P-450-dependent oxidation of estradiol by dietary macronutrients in man. Proc Natl Acad Sci. 1983;80:7646–7649.
[9]Midgette AS, et al. Cigarette smoking and the risk of natural menopause. Epidemiology. 1990;1:474–480.
[10]Slaven L, et al. Mood and symptom reporting among middle aged women: The relationship between menopausal status, hormone replacement therapy and exercise participation. Health Psychol. 1997;16: 203–208.
[11]Aldercreutz H, et al. Phyto-estrogens and Western diseases. Ann Med. 1997;29:95–120.
[12]Yoshino K. Effects of gamma-oryzanol on hyper lipidemic subjects. Current Ther Res. 1989;45:543–552.
[13]Jung HC, et al. Role of nitric oxide in penile erection. Yonsei Med J. 1997;38:261–269.

[14]Ito T, et al. A double blind placebo controlled study of Arginmax, a natural dietary supplement for enhancement of male sexual function. American Urological Association (AUA) Western Section Meeting, presentation 1999.

[15]Goldstein I, et al. Vasculogenic female sexual dysfunction: Vaginal engorgement and clitoral erectile insufficiency syndromes. Int J Impot Res. 1998;10(suppl.):S84–S90.

[16]Sohn M, et al. Ginkgo biloba extract in the therapy of erectile dysfunction. J Sex Educ Ther. 1991;17: 53–61.

[17]Sikora R, et al. Ginkgo biloba extract in the therapy of erectile dysfunction. J Urol. 1989;141:188.

[18]Welt K, et al. Protective effects of Ginkgo biloba EXTRACT Egb 761 on the myocardium of experimentally diabetic rats. Exp Toxicol Pathol. 1999;51:213–222.

[19]Chen X, et al. Extracts of Ginkgo biloba and ginsenoside exert cerebral vasodilation via a nitric oxide pathway. Clin Exp Pharmacol Physiol. 1997;24:958–959.

[20]Waynberg J. Aphrodisiacs: Contribution to the clinical validation of the traditional use of Ptychopetalum guyanna. First International Congress on Ethnopharmacology, Strasbourg, France, presentation June 5–9, 1990.

[21]Artletti R, et al. Stimulating properties of Turnera diffusa and Pfaffia paniculata extracts on the sexual behavior of male rats. Psychopharmacology. 1999;1:15–19.

[22]Zava DT, et al. Estrogen and progestin bioactivity of foods, herbs and spices. Proc Soc Exp Biol Med. 1998;217:369–378.

[23]Laumann EO, et al. Sexual dysfunction in the United States. JAMA. 1999;281:537–544.

5

APNEA—THE AWAKENING OF A SLEEPING AMERICA AND WORLD

To Save a Life

Sleep apnea is defined as a sleep disorder with frequent episodes of upper airway obstruction resulting in hemoglobin oxygen desaturation. The disorder is characterized by periods of breathing cessation (apnea) and periods of reduced breathing (hypopnea). Sleep apnea increases morbidity and mortality, thus making it a condition worthy of investigation.[1] Sleep apnea is typically categorized as obstructive, central, or mixed. Central sleep apnea involves complete or partial lack of respiratory drive resulting from a lack of central nervous system initiation, combined with at least 10 seconds of absent respiration. This form of the disorder affects only 10% of patients with sleep apnea.[2] Obstructive sleep apnea (OSA) is the most common type and is characterized by a cessation of airflow despite respiratory effort, which is caused by obstruction in the upper airway. Mixed sleep apnea is a combination of lack of respiratory effort and obstruction in the upper airway. Sleep disordered breathing is a general category of sleep disorders that includes snoring, upper airway resistance syndrome, and OSA.

PREVALENCE

In industrialized countries, OSA affects approximately 4% of men and 2% of women.[3] The prevalence of OSA increases with age, and studies suggest the disorder may be found in as many as 31% of elderly men and 19% of elderly women.[4] Children are also affected; studies demonstrate a prevalence of 0.7%–3%, with a peak incidence in preschool-age children.[5] Many sources state that these numbers may be low as a result of the difficulty involved with, and cost of, definitive diagnostic procedures.[6] Sleep apnea greatly affects the activities of daily living of both patients and their partners. Snoring, which may be a symptom or precursor to OSA, is common. Studies show that habitual snoring affects 29.5% of males and 8.9% of females. Snoring severity in 2.1% of females and 9.4% of males is significant enough to cause their roommates to leave the rooms shared with these patients.[7]

RISK FACTORS AND ETIOLOGY

Studies have indicated that sleep apnea is more common in men and increases with age. In addition, it is more frequent in African-Americans than in whites.[8] Males over age 40 who are obese, smoke, or use alcohol are at increased risk for snoring and OSA.[7] The strongest predictor for OSA is obesity. Studies show that the risk of OSA increases fourfold with an increase of the body mass index (BMI) by 1 standard deviation. Neck circumference is also a strong predictor, suggesting that upper body or central obesity is more predictive than generalized obesity.[9]

Hypothyroidism and menopause have also been associated with increased risk of OSA.[10,11] There are a number of anatomical abnormalities and pathologies that can also lead to sleep apnea. Studies show that obese patients with OSA have an increase in the concavity of the posterior epiglottis. This change in shape is correlated with an increased BMI and with the severity of the airway collapse and OSA.[12]

Common symptoms of sleep apnea include fatigue, excessive daytime sleepiness, headache, and impaired thinking. Other symptoms are chronic snoring, depression, and personality changes.[2] Children frequently present with attention deficit, decreased intelligence, hyperactivity, and aggressiveness. Children rarely present with daytime sleepiness because apnea in children causes less awakening.[5] In addition, women tend to present more frequently than men with depression, insomnia, and hypothyroidism.[13]

PATHOPHYSIOLOGY OF SLEEP APNEA

The obstruction present in OSA, the most common type of sleep apnea, can occur at multiple levels including the nasal cavity, the nasopharynx, and the tongue. A greater negative pressure is required to produce a given airflow volume when narrowing in these areas is present. Dilator muscles provide tone to the pharyngeal muscles to hold the airway open but are not sufficient to compensate for the closure of the airway in OSA. In addition, increased nasal resistance will increase the potential of collapse in the pharynx. Nasal obstruction often results from hypertrophy of the adenoids or palatine tonsils.[2] Chemoreceptors within the brain decrease in sensitivity to carbon dioxide (CO_2) levels, so that even when CO_2 is raised, these receptors do not compensate properly by altering the rate and depth of lung ventilation. This results in a decrease in respiratory effort at a time when an increase is actually needed, leading to partial or total collapse of the airway and limited gas exchange in the lungs. Ultimately, this leads to a state of hypoxia and hypercapnia, which then increases the respiratory drive. Often, however, a severe hypoxic-hypercapnic state is required to stimulate a respiratory effort that is adequate to overcome the obstruction and end that particular event. Specifically, the primary initiation for increased ventilation comes from chemoreceptors that are sensitive to the levels of CO_2 in the aortic arch, brainstem, and carotid bodies. In addition, changes in respiration cause changes in intrathoracic pressure, which have been shown to affect cardiovascular responses, such as ventricular filling, venous return, and the release of atrial natriuretic peptide.[2] Hypoxia and hypercapnia during an apneic episode also cause an increase in sympathetic nerve activity. This activation leads to many cardiovascular effects including increased peripheral resistance, vasoconstriction, and increased blood pressure. Interestingly, sympathetic nerve activity has been shown to increase in the daytime as well in patients with OSA. Studies suggest that this increase may be the cause of daytime hypertension and arrhythmias.[14]

DIAGNOSING SLEEP APNEA

The severity of sleep apnea–hypopnea is measured by various methods. The number of apneas and hypopneas per hour of sleep can be evaluated with the Apnea-Hypopnea Index (AHI). In addition, the severity of oxygen desaturation during sleep can be measured via pulse oximetry or arterial blood gasses. The severity of daytime sleepiness, the most common symptom associated with apnea, can also be evaluated as sleep latency time using the Multiple Sleep Latency Test. An average nocturnal sleep latency of less than 10 minutes indicates excessive sleepiness.

Sleep apnea is frequently underdiagnosed. It is estimated that 80%–90% of OSA cases go undiagnosed.[15] Studies suggest that 30% of patients with essential hypertension have undiagnosed—and thus untreated—OSA.[16] Diagnosis of OSA includes a thorough history and physical examination, using polysomnography to make the diagnosis definitive. The history should evaluate the occurrence of chronic snoring, excessive daytime sleepiness, and any medial condition associated with sleep apnea. There are many questionnaires for assessing daytime sleepiness; in addition, sleep latency time can be measured. A physical examination should evaluate any anatomical abnormalities that might cause airway obstruction, such as enlarged adenoids, septal deviation, and nasal polyps. A fiber-optic endoscopy may be done to assess pharyngeal narrowing. Confirmation of the diagnosis is done with overnight polysomnography. Portable home devices used for diagnosis have been developed as a less-expensive alternative, although the assessments they do are slightly less definitive.[17]

HEALTH EFFECTS OF SLEEP APNEA

Sleep apnea often leads to extreme daytime sleepiness and other symptoms of sleep deprivation. Sleep deprivation has been shown to increase accidents and accidental death. A study done using professional drivers demonstrated that the risk of automobile accidents increases significantly with frequent snoring and daytime sleepiness.[18] In addition to excessive sleepiness, sleep apnea can result in other problems.

Inflammation and Cardiovascular Disease

Sleep apnea increases the levels of many inflammatory markers, which may be one of the mechanisms by which it affects cardiovascular health. An example is C-reactive protein (CRP), an inflammatory marker correlated with atherosclerosis and coronary artery disease. A study performed on males with OSA showed a direct correlation between an increasing AHI and increasing CRP levels.[19]

In addition, pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha (TNF-a), have been shown to be elevated in patients with OSA.[20] The CD-40 ligand, which has been shown to be elevated in individuals with OSA, promotes pro-inflammatory mediators and is involved with atherosclerotic processes.[21] Treatment with nasal continuous positive airway pressure (nCPAP) decreases these inflammatory markers.[22] Studies also

Health Conditions Linked with Sleep Apnea

- Hypertension
- Atherosclerosis
- Tachycardia
- Bradycardia
- Ventricular ectopy
- Stroke
- Coronary artery disease
- Congestive heart failure
- Cor pulmonale
- Diabetes
- Gastroesophageal reflux disease
- Dementia
- Depression
- Aggressiveness
- Hyperactivity

Risk Factors for Sleep Apnea

Snoring	African-American ethnicity
Increased body mass index	Smoking
Increased neck circumference	Alcohol use
Increasing age	Menopause
Male gender	Andropause

indicate that individuals with OSA show increased platelet activity and aggregation, increased levels of fibrinogen and plasminogen activating factors, and a decrease in fibrinolytic functions.[23] Endothelial dysfunction also has been demonstrated, causing reduced endothelial-dependent vasodilation, while nCPAP therapy has been shown to improve nitric oxide release from the endothelium, improving the systemic endothelium-dependent vasodilation response.[24]

Sleep apnea is a risk factor for abnormal glucose metabolism, insulin resistance, and type 2 diabetes.

Cardiac Arrhythmias

Rates of both bradycardia and tachycardia are increased in individuals with sleep apnea. A large study performed on individuals with sleep apnea found that 48% had arrhythmias during nocturnal sleep.[25] In addition, it has been shown that there is a direct correlation between increased frequency of arrhythmias and an increasing number of apneic events as well as a higher degree of oxygen desaturation.[26] While awake, few of these individuals have cardiac arrhythmias. Tracheostomy has reduced most of these arrhythmias.[25] Other arrhythmias found more frequently in patients with sleep apnea include ventricular ectopy, ventricular tachycardia, premature ventricular contraction, atrioventricular block, and sinus arrest.[27]

Hypertension

Approximately 50% of individuals with OSA are also hypertensive, a correlation that also may be attributable to the effects of obesity on blood pressure (BP).[28] Studies indicate that severity of OSA is directly correlated with severity of both sleep apnea and daytime hypertension.[29] The increase in sympathetic activity caused by the induction of the fight-or-flight response is believed to be one contributing factor to the rise in BP. Treatment of OSA with nCPAP has been shown to decrease BP during both daytime and night-time hours.[30]

Strokes

OSA is an independent risk factor for the development of strokes or transient ischemic attacks.[31] Studies show that patients with untreated OSA experience more strokes and have higher rates of stroke morbidity and mortality than do patients who are treated with nCPAP.[32]

Diabetes

Sleep apnea is a risk factor for abnormal glucose metabolism, insulin resistance, and type 2 diabetes.[33,34] Treatment with nCPAP in individuals with OSA and type 2 diabetes has led to an increase in insulin sensitivity and a decrease in HbA1c levels.[35]

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) rates are increased in individuals with OSA. Studies show that the severity of GERD also increases with an increase in the AHI.[36] In patients with OSA, treatment of GERD has been shown to decrease the number of arousals during sleep.[37]

Psychiatric Conditions

Studies on veterans with sleep apnea showed an increase in psychiatric conditions compared to controls. A significant increase was found in mood disorders, such as depression, anxiety, dementia, psychosis, and post-traumatic stress disorder.[38] Studies indicate that treatment with nCPAP can reduce symptoms of depression.[39]

CHILDREN AND SLEEP APNEA

Children frequently present with different signs and symptoms of sleep-disordered breathing than adults. Children with OSA often have a low weight index, possibly the result of a decrease in growth hormone (GH) production. In part, this condition arises as a result of a relative failure to thrive; much as malnutrition contributes to a low weight index, a lack of oxygen to nourish the tissues limits growth of body tissues and makes a negative impact on the health of hormone-producing glands as well.

Insulin growth factor–1 and insulin growth factor–binding protein, both of which correlate with GH production, are lower in children with OSA. Other theories that explain the decrease in weight in children with OSA include anorexia or dysphagia caused by enlarged adenoids, and increased caloric use associated with increased respiratory effort. Children also tend to present with snoring, poor school performance, aggressiveness, and hyperactivity.[5] One study showed that 33% of children with attention-deficit hyperactivity disorder also had habitual nocturnal snoring.[40] The most common cause of OSA in children is adenotonsillar hypertrophy. A study showed that 28% of children with adenotonsillar hypertrophy present with behavioral changes, such as hyperactivity.[5]

CONVENTIONAL TREATMENT FOR SLEEP APNEA

Treatment of sleep apnea frequently entails use of nCPAP, bi-level positive airway pressure (BiPAP), oral appliances, or surgical procedures. The nCPAP provides positive pressure to prevent pharyngeal collapse, and is considered to be a first-line treatment for moderate to severe apnea. Studies indicate that the nCPAP decreases the AHI by 60%.[41] Side effects of the nCPAP include rhinorrhea, dryness, increased mucus production, and sneezing. Some 10%–50% or more patients find nCPAP intolerable and discontinue using it.[41] Oral appliances are used for mild sleep apnea and for individuals who are unable to tolerate or are noncompliant

with the nCPAP. These appliances function by changing the position of the mandible or tongue. They have been shown to be less efficacious than nCPAP, but have better rates of compliance. Oral devices may cause tooth movement and occlusion changes with long-term use.[42]

There are many types of surgeries with varying efficacies for treating sleep apnea. Most procedures attempt to remove blockages to the airway or increase retrolingual space. Such procedures include uvulopalatopharyngoplasty, septoplasty, turbinectomy, midline glossectomy, maxillomandibular osteotomy, and tracheotomy.[2]

ALTERNATIVE TREATMENTS AND LIFESTYLE CHANGES

Several lifestyle changes can make significant reductions in the severity of sleep apnea. Patients should be educated to sleep lying on one side. Weight loss is imperative, given the correlations of increased BMI and neck circumference with OSA. Even modest weight loss can be significant for reducing apnea symptoms; studies have shown that a 10% weight increase can cause a 32% increase in AHI, while a 10% weight loss could produce a 26% decrease in AHI.[43] Avoidance of alcohol and sedatives should also be encouraged.

Although specific studies on alternative treatments for sleep apnea are generally lacking, there are well-documented natural therapies that address the altered biochemistry and etiologic factors known to exist in sleep apnea. These therapies may prove important as adjunctive interventions, which are particularly important, given the well-documented poor compliance with nCPAP=BiPAP interventions and the invasiveness of many conventional options. Diet, nutritional supplements, and environmental modifications may improve sleep-disordered breathing. Controlling inflammation and allergies is paramount in treating OSA. Allergies can cause an increase in adenoids and tonsil size as well as an increase in mucous production, which can occlude the nasal airway.

Figure 5–1. Stinging nettle (Urtica dioica).

N-Acetyl-Cysteine

N-acetyl-cysteine (NAC) is an acetylated ester of the amino acid L-cysteine. NAC has a significant ability to raise glutathione levels in the body, important for its potent antioxidant activity. NAC is also used to treat lung conditions as an expectorant and mucous thinner, and to produce anti-inflammatory effects.[44] Studies suggest that NAC decreases production of pro-inflammatory cytokines, such as TNF-alpha, which have been shown to be elevated in individuals with OSA.[45]

Essential Fatty Acids

Essential fatty acids (EFAs) cannot be made in the body and need to be consumed in the diet. Omega-3 fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and omega-6 fatty acids,

such as gamma-linolenic acid (GLA), are often taken as supplements to utilize their potent anti-inflammatory properties. EPA and DHA are found in high levels in fish oils and provide both anti-inflammatory and anti-thrombotic effects. Specifically, EPA's cardioprotective effects include decreasing triglycerides, increasing high-density lipoprotein, and preventing arrhythmias.[46] EPA and DHA decrease inflammatory eicosanoids by competing with arachidonic acid (AA) in the lipo-oxygenase and cyclo-oxygenase pathways. Fish oils have been shown to decrease several pro-inflammatory cytokines as well.[47] GLA is commonly found in borage (Borago officinalis) seed oil, evening primrose (Oenothera biennis) oil, and black currant (Ribes nigrum) oil. GLA decreases the inflammatory response by inhibiting the production of inflammatory leukotrienes from AA.[48]

Figure 5–2. Basil (Ocimum spp.).

Vitamin C

Vitamin C has many functions, including acting as both an antioxidant and an antihistamine. In a study performed on patients with OSA the theory was tested that the endothelial dysfunction in this group is linked to oxidative stress. The results showed that treatment with vitamin C improved endothelium-dependent vasodilation. This study suggests that antioxidant therapy should be considered for treatment of the cardiovascular dysfunction associated with OSA.[49]

Quercitin

Quercitin is a bioflavonoid frequently used to treat allergies because of its antihistamine, anti-inflammatory, and antioxidant effects. It is found in foods such as berries, brassica vegetables, apples, green tea (Camellia sinensis), onions, and red wine. Studies have demonstrated that quercitin inhibits the release of histamine from mast cells and basophils.[50] (Histamine is a chemical mediator responsible for allergy symptoms, such as constriction in the lungs, congestion, and sneezing.) Absorption of quercitin is variable and may be improved by combining it with papain or bromelain.

Bromelain

Bromelain is a proteolytic enzyme derived from pineapples. This enzyme produces anti-inflammatory, fibrinolytic, and anti-platelet-aggregation activities.[51] Studies show that bromelain interferes with the AA pathway, causing a decrease in inflammatory eicosanoid production.[52]

Figure 5–3. Eucalyptus (Eucalyptus globulus).

Eucalyptus

Historically, eucalyptus (Eucalyptus globulus) has been used for addressing many inflammatory respiratory complaints, including asthma and bronchitis.[53] Eucalyptus oil derived from the leaves and branches contains 60%–90% of the constituent eucalyptol. Studies on eucalyptol show that it exerts strong anti-inflammatory, mucolytic, and analgesic effects. It inhibits the production of AA metabolites and such pro-inflammatory cytokines as TNF-alpha[54]

Stinging Nettle

Stinging nettle (Urtica dioica) leaf contains vitamin C, vitamin E, carotenoids, calcium, potassium, and flavonoids, such as quercitin and rutin. This herb has significant anti-inflammatory effects, and studies suggest that it may be beneficial for treating allergic rhinitis.[55] Researchers believe this may be the result of the nettles' quercitin content, which stabilizes mast cells and inhibits histamine release.[50]

Beefsteak Plant

The beefsteak plant (Perilla frutescens) contains several active ingredients such as rosmarinic acid and luteolin. Rosmarinic acid is a plant polyphenol found in the Lamiaceae genus of plants, which includes basil (Ocimum spp.), sage (Salvia officinalis), mint (Mentha spp.), rosemary (Rosmarinus officinalis), and perilla leaf.[56] Oral supplementation using perilla leaves or extracts of rosmarinic acid has been shown to suppress allergic reactions.[57,58] A study confirmed that oral administration of perilla leaf extract inhibits production of TNF-alpha and decreases the allergic response and inflammation in mice.[59] Another study demonstrated

Figure 5–4. Rosemary (Rosmarinus officinalis).

that perilla leaf extract enriched with rosmarinic acid is an effective treatment for patients who have seasonal allergic rhinoconjunctivitis.[58] Like rosmarinic acid, luteolin—found in various species of the perilla plant—is another plant flavonoid that has potent antiallergic properties.[59]

Licorice Root

Licorice (Glycyrrhiza glabra) is often used for gastrointestinal conditions such as GERD and ulcers. The finding that deglycyrrhizinated licorice (DGL) stimulates and=or accelerates the differentiation of glandular cells in the stomach—as well as stimulating mucous secretion—is of particular interest. This increased mucous secretion in the stomach is believed to account for at least part of licorice's beneficial properties. DGL also contains flavonoids that produce antimicrobial activity, including working against the ulcer-causing bacterium Helicobacter pylori. It is important to treat GERD in individuals with sleep apnea as GERD can cause increased pharyngitis and sinusitis, exacerbating the apnea. Avoidance of caffeine, mints, chocolate, fatty or spicy foods, tomatoes, and alcohol is another way to decrease acid reflux. In addition, studies have shown that raising the head at night by raising the top of the bed may decrease nocturnal reflux.[60]

Methylsulfonylmethane and Hyaluronic Acid

Both methylsulfonylmethane (MSM) and hyaluronic acid are essential for maintaining connective tissue integrity, and thus for ensuring the rigidity and firmness of the underlying cellular matrix of the airway walls. MSM has been shown to have anti-inflammatory and antioxidant properties. Anecdotal evidence suggests that MSM may be effective for addressing many conditions, including snoring and allergic rhinitis.[61] Hyaluronic acid, a glycosaminoglycan, could be considered for treatment of snoring and augmentation of airway connective tissue integrity.[62] Because of hyaluronic acid's visco-elastic quality, this substance may work to strengthen the connective tissue surrounding the airway and decrease obstructions.

Diet

Diet can affect inflammation and mucous production. Diets high in fruits and vegetables provide the vitamins and bioflavonoids that reduce allergy symptoms. Diets high in EFAs and low in animal products (such as dairy foods and meat) will decrease inflammation. (Animal products are high in AA and lead to an increase in inflammatory eicosanoids.) In addition, members of the nightshade family—such as potatoes, tomatoes, eggplants, and peppers—may also be pro-inflammatory in some individuals. Clinical observation suggests avoidance of mucous-forming foods, such as dairy foods, bananas, and citrus fruits, can be beneficial, although that line of thought is controversial. Food allergies should also be considered when modifying the diet to decrease apneic episodes. Many individuals have latent food allergies that increase the inflammatory response and cause additional overall stress on the body. Many forms of testing are readily available to measure immunoglobulin IgE and IgG antibodies to common foods.

Environment

Environmental allergies are important airway irritants. It is important to control allergies in order to minimize the nasal and pharyngeal congestion that can help compromise airway

patency. The best way to treat allergies is to advise patients to avoid the substances that trigger symptoms. The environment should be kept as free of potential allergens as possible. Pillows and mattresses should be covered with dust- and mite-proof covers. Bedding should be washed frequently in very hot water. Removal of carpets and items that collect dust in the bedroom may also help avoid dust and dust mites. Bathing and washing hair before bed also is suggested. Mold anywhere in the home should be treated aggressively. Pets should be kept away from the sleeping areas and should be bathed regularly. High-efficiency particulate absorbing filters at home and work can improve air quality and decrease pollen exposure. Avoidance of cigarette smoke is recommended.

Anecdotal literature suggests other possible—though unproven—treatments for sleep apnea. Nasal sprays, nasal dilators, and magnetic mattresses and pillows are available.[63] Essential oil sprays and gargles to treat snoring have shown efficacy.[64] A case report also suggests hypnosis as an effective treatment for snoring.[65] Snoring has also been reduced by singing exercises in nonobese patients when done correctly and regularly.[66] Biofeedback training to control abnormal breathing while sleeping also has shown promising results. In at least one study, biofeedback reduced the duration of apneic episodes, resulting in higher oxygen saturation levels.[67]

CONCLUSIONS

Sleep apnea is a medical condition that warrants thorough study because of the increase in morbidity and mortality in patients who have the condition. It also affects quality of life greatly in many patients and frequently goes undiagnosed. If a patient complains of fatigue, excess sleepiness, lack of restorative sleep, or other unexplained systemic symptoms, a close review of the potential existence of apnea is a must. Although there are many treatments that have been proposed to help with sleep apnea, the best approaches remain weight loss and use of positive airflow therapy. Nonetheless, adjunctive therapies can help control the severity of apnea and snoring.

REFERENCES

[1]Fletcher EC. Obstructive sleep apnoea and cardiovascular morbidity. Monaldi Arch Chest Dis. 1996;51: 77–80.

[2]Cutler MJ, Hamden AL, et al. Sleep apnea: From the nose to the heart. J Am Board Fam Pract. 2002;15: 128–141.

[3]Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328:1230–1235.

[4]Ancoli-Israel S, Kripke DF, Mason W. Characteristics of obstructive and central sleep apnea in the elderly: An interim report. Biol Psychiatry. 1987;22:741–750.

[5]Balbani AP, Weber SA, Montovani JC. Update in obstructive sleep apnea syndrome in children. Rev Bras Otorrinolaryngol (Engl Ed). 2005;71:74–80.

[6]Pang KP, Terris DJ. Screening for obstructive sleep apnea: An evidence-based analysis. Am J Otolaryngol. 2006;27:112–118.

[7]Kara CO, Zencir M, Topuz B, et al. The prevalence of snoring in the adult population. Kulak Burun Bogaz Ihtis Derg. 2005;14(1–2):18–24.

[8]Ancoli-Israel S, Klauber MR, Stepnowsky C, et al. Sleep-disordered breathing in African-American elderly. Am J Respir Crit Care Med. 1995;152(6pt1):1946–1949.

[9]Schafer H, Pauleit D, Sudhop T, et al. Body fat distribution, serum leptin, and cardiovascular risk factors in men with obstructive sleep apnea. Chest. 2002;122:829–839.

[10]Resta O, Pannacciulli N, Di Gioia G, et al. High prevalence of previously unknown subclinical hypothyroidism in obese patients referred to a sleep clinic for sleep disordered breathing. Nutr Metab Cardiovasc Dis. 2004;14:248–253.
[11]Resta O, Bonfitto P, Sabato R, et al. Prevalence of obstructive sleep apnoea in a sample of obese women: Effect of menopause. Diabetes Nutr Metab. 2004;17:296–303.
[12]Gazayerli M, Bleibel W, Elhorr A, et al. A correlation between the shape of the epiglottis and obstructive sleep apnea. Surg Endosc. 2006 Mar 16;[Epub ahead of print].
[13]Shepertycky MR, Banno K, Kryger MH. Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. Sleep. 2005;28:309–314.
[14]Sin DD, Fitzgerald F, Parker JD, et al. Relationship of systolic BP to obstructive sleep apnea in patients with heart failure. Chest. 2003;123:1536–1543.
[15]Silverberg DS, Iaina A, Oksenberg A. Treating obstructive sleep apnea improves essential hypertension and quality of life. Am Fam Physician. 2002;65(2):229–236.
[16]Fletcher EC. The relationship between systemic hypertension and obstructive sleep apnea: Facts and theory. Am J Med. 1995;98:118–128.
[17]Yin M, Miyazaki S, Ishikawa K. Evaluation of type 3 portable monitoring in unattended home setting for suspected sleep apnea: Factors that may affect its accuracy. Otolaryngol Head Neck Surg. 2006;134:204–209.
[18]Perez-Chada D, Videla AJ, O'Flaherty ME, et al. Sleep habits and accident risk among truck drivers: A cross-sectional study in Argentina. Sleep. 2005;28:1103–1108.
[19]Kokturk O, Ciftci TU, Mollarecep E, Ciftci B. Elevated C-reactive protein levels and increased cardiovascular risk in patients with obstructive sleep apnea syndrome. Int Heart J. 2005;46:801–809.
[20]Teramoto S, Yamamoto H, Yamaguchi Y, et al. Obstructive sleep apnea causes systemic inflammation and metabolic syndrome. Chest. 2005;127:1074–1075.
[21]Dyugovskaya L, Lavie P, Lavie L. Lymphocyte activation as a possible measure of atherosclerotic risk in patients with sleep apnea. Ann NY Acad Sci. 2005;1051:340–350.
[22]Hatipoglu U, Rubinstein I. Inflammation and obstructive sleep apnea syndrome: How many ways do I look at thee? Chest. 2004;126:1–2.
[23]Kasasbeh E, Chi DS, Krishnaswamy G. Inflammatory aspects of sleep apnea and their cardiovascular consequences. South Med J. 2006;99:58–67;quiz:68–99,81.
[24]Lattimore JD, Wilcox I, Skilton M, et al. Treatment of obstructive sleep apnoea leads to improved microvascular endothelial function in the systemic circulation. Thorax. 2006;Mar 14;[Epub ahead of print].
[25]Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol. 1983;52:490–494.
[26]Harbison J, O'Reilly P, McNicholas WT. Cardiac rhythm disturbances in the obstructive sleep apnea syndrome: Effects of nasal continuous positive airway pressure therapy. Chest. 2000;118:591–595.
[27]Flemons WW, Remmers JE, Gillis AM. Sleep apnea and cardiac arrhythmias: Is there a relationship? Am Rev Respir Dis. 1993;148:618–621.
[28]Millman RP, Redline S, Carlisle CC, et al. Daytime hypertension in obstructive sleep apnea: Prevalence and contributing risk factors. Chest. 1991;99:861–866.
[29]Carlson JT, Hedner JA, Ejnell H, et al. High prevalence of hypertension in sleep apnea patients independent of obesity. Am J Respir Crit Care Med. 1994;150:72–77.
[30]Suzuki M, Otsuka K, Guilleminault C. Long-term nasal continuous positive airway pressure administration can normalize hypertension in obstructive sleep apnea patients. Sleep. 1993;16:545–549.
[31]Yaggi HK, Concato J, Kernan WN, et al. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med. 2005;353:2034–2041.
[32]Grigg-Damberger M. Why a polysomnogram should become part of the diagnostic evaluation of stroke and transient ischemic attack. J Clin Neurophysiol. 2006;23:21–38.
[33]Punjabi NM, Polotsky VY. Disorders of glucose metabolism in sleep apnea. J Appl Physiol. 2005;99:1998–2007.
[34]Harsch IA, Hahn EG, Konturek PC. Insulin resistance and other metabolic aspects of the obstructive sleep apnea syndrome. Med Sci Monitor. 2005;11:RA70–RA75.
[35]Hassaballa HA, Tulaimat A, Herdegen JJ, Mokhlesi B. The effect of continuous positive airway pressure on glucose control in diabetic patients with severe obstructive sleep apnea. Sleep Breath. 2005;9:176–180.
[36]Demeter P, Visy KV, Magyar P. Correlation between severity of endoscopic findings and apnea-hypopnea index in patients with gastroesophageal reflux disease and obstructive sleep apnea. World J Gastroenterol. 2005;11:839–841.
[37]Zanation AM, Senior BA. The relationship between extraesophageal reflux (EER) and obstructive sleep apnea (OSA). Sleep Med Rev. 2005;9:453–458.
[38]Sharafkhaneh A, Giray N, Richardson P, et al. Association of psychiatric disorders and sleep apnea in a large cohort. Sleep. 2005;28:1405–1411.

[39]Schwartz DJ, Kohler WC, Karatinos G. Symptoms of depression in individuals with obstructive sleep apnea may be amenable to treatment with continuous positive airway pressure. Chest. 2005;128: 1304–1309.
[40]Chervin RD, Dillon JE, Bassetti C, et al. Symptoms of sleep disorders, inattention, and hyperactivity in children. Sleep. 1997;20:1185–1192.
[41]Clark GT, Blumenfeld I, Yoffe N, et al. A crossover study comparing the efficacy of continuous positive airway pressure with anterior mandibular positioning devices on patients with obstructive sleep apnea. Chest. 1996;109:1478–1483.
[42]Almeida FR, Lowe AA, Otsuka R, et al. Long-term sequelae of oral appliance therapy in obstructive sleep apnea patients: Part 2. Study-model analysis. Am J Orthod Dentofacial Orthop. 2006;129:205–213.
[43]Peppard PE, Young T, Palta M, et al. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA. 2000;284:3015–3021.
[44]Kelly GS. Clinical applications of N-acetylcysteine. Altern Med Rev. 1998;3:114–127.
[45]Gillissen A, Nowak D. Characterization of N-acetylcysteine and ambroxol in anti-oxidant therapy. Respir Med. 1998;92:609–623.
[46]Erkkila AT, Lehto S, Pyorala K, Uusitupa MI. n-3 Fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease. Am J Clin Nutr. 2003;78:65–71.
[47]Connor WE. N-3 Fatty acids from fish and fish oil: Panacea or nostrum? Am J Clin Nutr. 2001;74; 415–416.
[48]Fan YY, Chapkin RS. Importance of dietary gamma-linolenic acid in human health and nutrition. J Nutr. 1998;128:1411–1414.
[49]Grebe M, Eisele HJ, Weissmann N, et al. Antioxidant vitamin C improves endothelial function in obstructive sleep apnea. Am J Respir Crit Care Med. 2006;Jan 26;[Epub ahead of print].
[50]Anonymous. Quercetin. Alt Med Rev. 1998;3:140–143.
[51]Taussig SJ, Batkin S. Bromelain, the enzyme complex of pineapple (Ananas comosus) and its clinical application: An update. J Ethnopharmacol. 1988;22:191–203.
[52]Vellini M, Desideri D, Milanese A, et al. Possible involvement of eicosanoids in the pharmacological action of bromelain. Arzneimittelforschung. 1986;36:110–112.
[53]Silva J, Abebe W, Sousa SM, et al. Analgesic and anti-inflammatory effects of essential oils of eucalyptus. J Ethnopharmacol. 2003;89(2–3):277–283.
[54]Juergens UR, Dethlefsen U, Steinkamp G, et al. Anti-inflammatory activity of 1.8-cineol (eucalyptol) in bronchial asthma: A double-blind placebo-controlled trial. Respir Med. 2003;97:250–256.
[55]Mittman P. Randomized, double-blind study of freeze-dried Urtica dioica in the treatment of allergic rhinitis. Planta Med. 1990;56:44–47.
[56]al-Sereiti MR, Abu-Amer KM, Sen P. Pharmacology of rosemary (Rosmarinus officinalis Linn.) and its therapeutic potentials. Indian J Exp Biol. 1999;37:124–130.
[57]Makino T, Furuta A, Fujii H, et al. Effect of oral treatment of Perilla frutescens and its constituents on type-I allergy in mice. Biol Pharm Bull. 2001;24:1206–1209.
[58]Takano H, Osakabe N, Sanbongi C, et al. Extract of Perilla frutescens enriched for rosmarinic acid, a polyphenolic phytochemical, inhibits seasonal allergic rhinoconjunctivitis in humans. Exp Biol Med (Maywood). 2004;229:247–254.
[59]Ueda H, Yamazaki C, Yamazaki M. Luteolin as an anti-inflammatory and anti-allergic constituent of Perilla frutescens. Biol Pharm Bull. 2002;25:1197–1202.
[60]Ahuja V, Yencha MW, Lassen LF. Head and neck manifestations of gastroesophageal reflux disease. Am Fam Physician. 1999;60:873–880,885–886.
[61]Anonymous. Methylsulfonylmethane (MSM) [monograph]. Altern Med Rev. 2003;8:438–441.
[62]Arrich J, Piribauer F, Mad P, et al. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: Systematic review and meta-analysis. CMAJ. 2005;172:1039–1043.
[63]Hein H. The sleep apnoea syndromes: Alternative therapies. Pneumologie. 2004;58:325–329.
[64]Prichard AJ. The use of essential oils to treat snoring. Phytother Res. 2004;18:696–699.
[65]Ewin DM. Single-visit hypnotic cure of stentorian snoring: A brief communication. Int J Clin Exp Hypnosis. 2004;52:400–403.
[66]Ojay A, Ernst E. Can singing exercises reduce snoring? A pilot study. Complement Ther Med. 2000;8: 151–156.
[67]Badia P, Harsh J, Culpepper J, Shaffer J. Behavioral control of abnormal breathing in sleep. J Behav Med. 1988;11:585–592.

6

ASTHMA

Treating the Cause and Supporting the Airway Chemistry

Statistics indicate increasing prevalence of asthma in industrialized nations, particularly in the United States in the last 20 years. The Centers for Disease Control and Prevention has reported increasing asthma prevalence since 1980, including increased mortality and racial and regional disparities in asthma-related emergency department visits, hospitalizations, and deaths.[1] In 2005, an estimated 7.7% of people (22.2 million) had asthma.[2] Various reasons for this increase in asthma cases have been identified, ranging from air pollution to faulty genetics. The mainstream focus on asthma has also changed in the last 20 years, with a shift in understanding—namely, that asthma is a chronic inflammatory condition. With this new understanding, treatment focus has changed from reactive to preventive, with chronic long-term use of inhaled corticosteroids as the mainstay of therapy. Despite this shift in treatment focus, increasingly negative statistics about asthma continue to be reported. With the advent of complementary medicine, physicians are now more prepared than ever to treat asthma effectively. Asthma is a disease process with numerous associated genetic, allergic, environmental, and nutritional components, with varying symptomatologies among individuals affected with this condition. There is a vital need for today's physician to develop an awareness of asthma's many precipitating factors and to learn about the numerous complementary therapies available for treatment, because it is obvious that mainstream asthma treatment and prevention are not capable of reversing the increasing morbidity of this disease. Factors such as air quality may appear to be outside of the physician's realm of manageable patient comorbid components, while other precipitating determinants may be addressed via nutritional and botanical supplementation and lifestyle modification allowing for greater efficacy of pharmaceutical medications, when needed (see Table 6–1 on page 71).

ASTHMA PATHOGENESIS=PATHOPHYSIOLOGY

Asthma is a chronic inflammatory disorder of the airways in which several cells and cellular elements play a role, particularly mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils, and epithelial cells. The recruitment and activation of these cells and cellular components leads to recurrent symptoms, such as wheezing, chest tightness, and coughing, more so at night and early morning. Such episodes are associated with diffuse airflow obstruction that is amenable to treatment-induced or spontaneous reversal. Predisposition to this condition causes an increase in bronchial hyperreactivity to various stimuli. Asthma symptoms that appear in childhood are often associated with atopy, a genetic susceptibility in which immunoglobulin E (IgE) is produced by B lymphocytes in response to typically benign environmental antigens (dust mite feces, animal dander proteins, fungi spores). Synthesized IgE antibodies then bind to receptors on various leukocytes. Once the offending antigen binds to the Fab fragment of

Asthma Facts

Prevalence

Asthma has been increasing since the early 1980s across all age, gender, and racial groups; asthma rates are higher among children than adults and higher among blacks than whites.

Approximately 22.2 million Americans have asthma; 5 million are under age 18. Asthma is the most common chronic childhood disease, affecting slightly more than 1 child in 20.

Deaths

11 Americans die each day from asthma.

Between 1979 and 1992, asthma death rates increased 58% overall.

Asthma death rates for children under 19 increased 80% since1980.

More females die of asthma than males; more blacks die of asthma than whites.

Costs

The total annual cost of treating asthma is estimated to be $18 billion, of which direct costs amounted to $10 billion, while indirect costs were $8 billion.

Hospitalization accounted for the single largest portion of the cost.

Among children ages 5–17, asthma is the leading cause of school absences due to a chronic illness; this adds up to an annual loss of more than 10 million school days per year and more hospitalizations than any other childhood disease.

Children with asthma spend an estimated 8 million days per year restricted to bed.

For adults, asthma is the fourth leading cause of work loss, resulting in 9 million lost workdays each year.

Asthma also accounts for about 1.8 million emergency room visits and nearly 10 million doctor office visits each year.

Asthma results in about a half million hospitalizations each year; more women are hospitalized for asthma than men, and blacks are hospitalized for asthma three and one-half times more than whites.

Ethnic Differences

Blacks are three times as likely as whites to be hospitalized for asthma and three times as likely to die from the disease.

Racial differences in asthma prevalence, morbidity, and mortality are closely related to poverty, urban air quality, indoor allergens, and inadequate patient education and medical care.

Source: Adapted from the Asthma and Allergy Foundation of America (AAFA), 1233 20th Street, NW, Suite 402, Washington, D.C., 20036.

several IgE antibodies, pro-inflammatory cytokines are released. Mast-cell-released histamine and leukotrienes stimulate bronchial smooth-muscle constriction, usually within one hour of antigen exposure. Eosinophils, in particular, release destructive elements, such as major basic protein (MBP) that damage airway epithelial cells directly, increase bronchial responsiveness, and promote degranulation by mast cells and basophils. In addition, leukotrienes released from

eosinophils cause additional airway smooth-muscle constriction, increased vascular permeability, and further recruitment of additional eosinophils.

THE TH2:TH1 RATIO THEORY

It is a well-established fact that airway inflammation is the mainstay of asthma pathophysiology. That being said, however, inflammation is a nebulous descriptor in terms of the multiple workings of the immune system in asthma. Newer theories of pathologic inflammatory processes portray abnormally regulated CD4 T-cell responses to normally benign antigens as the instigators of asthma-related inflammatory processes. More specifically, the Th2 subset cell grouping of CD4 T cells is implicated, producing interleukins (ILs)-4, -5, -6, -9, -10, and -13. These cytokines establish the recruitment and differentiation of mast cells, basophils, eosinophils, and B cells, where they play a major role in humoral immunity and the generalized allergic response. Opposed to these functions, the Th1 subset of CD4 lymphocytes produce interferon-g and IL-2, both of which are used to create immunologic reactions that are specific to cellular defense, as in the case of bacterial and viral invasions. Ideally, the cytokines produced by Th2 and Th1 cells are mutually antagonistic, establishing a relative balance in functions. It is theorized that signature asthmatic inflammatory processes are expressed as a result of unbalanced Th1 and Th2 cytokine production, with a dominant polarization toward a Th2 phenotype, as asthma is a well-known Th2-mediated disease.[3] It is highly plausible that asthmatic inflammation is a result of Th2-mediated mechanisms or an imbalance between Th1 and Th2 cells. It has been observed that children born with a predominance of Th2 cell subsets that do not balance with Th1 over the first year are predisposed to allergic disease and asthma.[4] In addition, it is thought that administering factors that enhance Th1-mediated responses may restore the Th1:Th2 balance in susceptible individuals. One study investigated the relationship between Th subsets and their relationship to their relative cytokines, serum total IgE, eosinophil count, and ventilatory function in patients with asthma. The Th2:Th1 ratio in patients with acute or stable asthma was increased significantly compared to subjects in the control (non-asthma) group, with Th2 levels significantly and positively related to IL-4, total serum IgE, and total number of eosinophils. Forced expiratory volume 1 $(FEV)_1$ level in the study subjects had a significantly positive relation with Th1 levels and a negative relation with Th2 levels.[5]

THE HYGIENE HYPOTHESIS

Recent analyses of risk-factor patterns for allergic disease in Europe has led to a causal theory for the increasing asthma epidemic; this theory is known as the hygiene hypothesis. It stipulates that advances in hygiene have removed a protective influence against atopy and asthma that was once provided by infectious exposures in early childhood. This hypothesis has been questioned in the United States, where the largest sector of increasing asthma incidence since the 1970s occurs in the inner cities among minorities who are living in poverty with suboptimal hygienic conditions. When viewed from a historical perspective, the recent increasing trend in respiratory allergies among the less-advantaged in the United States may be explained as the consequence of several epiphenomena linked to Westernization (including declining exposure to foodborne and orofecal infections) that has moved downward from the richest socioeconomic strata to the poorest in the last 150 years.[6] In regard to this theory, it has been suggested that exposing infants to factors that increase Th1 cells (infected siblings, day care attendance

during the first six months of life, and avoidance of frequent antibiotic administration) may restore the T-helper subset balance, resulting in fewer incidences later in life of asthma and allergy. It appears that these exposures must occur prior to the first year of life to make a difference. Experimental use of mycobacterial strains has demonstrated a shift from Th2-immune responses to Th1-immune responses, thereby preventing the allergy development in mice, as well as ameliorating autoimmune diseases characterized by Th1 responses.[7] It is interesting to note that both autoimmune and allergic diseases share a parallel increasing prevalence. Rebalance of the Th1- and Th2-subset cell ratios is a highly speculative theory because it does not explain fully the complete immunologic etiology of asthma and allergies.

GASTROESOPHAGEAL REFLUX DISEASE

Various associations between asthma and gastroesophageal reflux disease (GERD) have been elucidated in recent clinical investigations: The prevalence of GERD in people with asthma is generally higher than in people without asthma. Patients who have asthma with GERD have a higher risk of hospitalization for asthma symptoms. Asthma medications such as albuterol decrease lower esophageal sphincter pressure and esophageal contraction amplitude, while oral prednisone results in increased esophageal acid contact times, and respiratory symptoms correlate with esophageal acid introduction events.[8] These findings suggest the possibility of asthma medications acting as promoting factors in the development of GERD in patients with asthma. It is estimated that incidence of GERD in children with asthma reaches nearly 50%–60% and is higher than in the general population.[9] This is not a newly discovered association; however, many studies are underway to determine the relationships between asthma and GERD because it is not clearly known which is the cause and which is the result. Several hypotheses surrounding the GERD–asthma connection focus on how GERD can lead to bronchial obstruction and how obstruction can exacerbate GERD. The esophagus and lungs interact by way of various mechanisms; esophageal acid-induced bronchospasm may be provoked by a vagally mediated reflex in which distal esophageal acid causes airway reactivity; by neural enhancement of bronchial reactivity, whereby esophageal acid augments airway hyper-responsiveness; and by microaspiration, in which miniscule amounts of esophageal acid are inhaled, leading to airway reactivity.[10] Possibilities that asthma may predispose patients to GERD include autonomic dysregulation, an increased pressure gradient between the thorax and abdomen, bronchodilator medications, hiatal hernia, and abnormalities in diaphragm function. Clinical trials utilizing antireflux medical therapy (e.g., histamine-2 receptor antagonists) have been largely inconclusive, producing no benefit to only modest reduction of only nocturnal asthma symptoms.[11] Other studies that have investigated the use of proton-pump inhibitors and antireflux surgery are currently in progress. Despite the mixed results from these studies, the medical literature is flush with studies that demonstrate a definite link between GERD and asthma. Treating asthma with H-2 blockers and proton-pump inhibitor medications brings to light the possibility of leaving patients with inadequate amounts of digestive acid to properly break food proteins down, potentially leading to increased allergenicity of foods and decreased nutrient absorption.[12]

FOOD ALLERGY

Asthma can be one of the major symptoms of chronic food allergy, which contributes to the total overall antigenic load of a patient. Food-mediated allergic reactions may become

clinically apparent immediately or even hours to days later in a patient with asthma, manifested by specific production by B lymphocytes of IgE and IgG antibodies to food proteins. From 20% to 60% of patients with bronchoconstrictive symptoms are reported to develop these symptoms as a result of food ingestion.[13] One study demonstrated that the elimination of previously determined food allergens early in life resulted in decreased asthma symptomatology as well as inhibiting the progression of allergic tendencies (represented by decreased production of total and specific IgE) compared to a control group that did not undergo such eliminations.[14] Increased gastrointestinal (GI) permeability and GI symptomatology has been found in a larger percentage of patients with asthma compared to controls without asthma symptoms; this may partially explain the origins of food-related allergy symptoms, such as asthmatic wheezing.[15] Clinically, identification and removal of known and suspected food allergens does provide some amelioration of asthma symptoms in certain individuals. (See Chapter 17 on food allergies.)

VITAMIN AND MINERAL THERAPY

Pyridoxine

The active form of pyridoxine (vitamin B_6) found in the human body, pyridoxal-5-phosphate, has long been known to be depleted by theophylline, a drug now rarely used in asthma medication. Regardless of current or past theophylline use, patients who have asthma tend to have lower circulating levels of this vitamin and, in one study, supplementation with 50 mg of pyridoxine twice per day for patients with asthma resulted in subjective reports of dramatic decreases in frequency and severity of asthma attacks while taking the supplement.[16] The study did not, however, indicate reasons for the apparent beneficial effects of pyridoxine supplementation. Another study placed 76 children with asthma on 200 mg of pyridoxine per day for five months. These patients reported significant reduction of asthma symptoms and reduced usage of asthma medications.[17] However, in another study, nine weeks of treatment with 300 mg of pyridoxine produced no difference in peak expiratory flow rate (PEFR), FEV_1, or asthma symptom scores compared to controls.[18] Examples of studies such as these demonstrate the need for increased research in the realm of vitamin B_6 supplementation for patients who have asthma.

Table 6–1. Doses of Supplements and Botanicals for Treating Asthma

Supplements=Botanicals	Doses
Pyridoxine (vitamin B6)	25–50 mg, 2 times per day
Ascorbic acid (vitamin C)	2000–3000 mg per day, in divided doses
Magnesium	250–300 mg, 3 times per day
Essential fatty acids (EPA DHA)	2000–3000 mg, in divided doses per day
Tylophora (Tylophora asthmatica)	Dried tylophora leaves: 200 mg, 2 times per day Or, alcoholic extract: 40 mg, 2 times per day
Coleus (Coleus forskohlii)	Standardized extract containing 18% forskolin: 50 mg, 3 times per day

EPA eicosapentaenoic acid; DHA docosahexaenoic acid.

Ascorbic Acid

Reactive oxygen species are implicated in the disease process of asthma, as it has been previously demonstrated that specific allergens were able to initiate a neutrophil-derived respiratory burst in some allergen-sensitized patients with asthma.[19] Excessive exposure to reactive oxygen and nitrogen species provides hallmark oxidative stress, propagating damage in proteins, lipids, and DNA structures. Oxidative stress in the lungs of patients with asthma is not only caused by intrinsic inflammatory pathways; environmental exposures, such as air pollution and cigarette smoke, also contribute. Interventions designed to augment endogenous antioxidant defenses are strongly indicated as adjuvant therapy for patients who are suffering from allergic respiratory disorders.[20]

Antioxidant supplementation, most notably vitamin C, can modulate the impact of air pollutants to reduce their effects on patients, including that of ozone on children with moderate to severe asthma.

Ascorbic acid (vitamin C) is one of the key antioxidant vitamins that are abundant in the extracellular fluid that lines the lungs, and low vitamin C intake has been associated with pulmonary dysfunction. One study reported that patients with asthma had significantly less ascorbic acid in both the cellular and fluid-phase fraction of induced sputum, suggesting that deficiency of ascorbic acid may be a result of airway inflammation or may be a contributing factor in the pathophysiology of asthma.[21] Children with asthma who live in Mexico City were given a daily supplement combination of 50 international units of vitamin E and 250 mg of vitamin C for 19 months. Pulmonary function tests were performed twice per week, with significant differences in forced expiratory flow (25–75) and peak expiratory flow between the test and control groups. These results suggest that antioxidant supplementation, most notably vitamin C, can modulate the impact of air pollutants to reduce their effects on patients, including that of ozone on children with moderate to severe asthma.[22] Consumption of antioxidants in foods as an asthma symptom preventative method has also been studied. Intake of citrus and=or kiwi fruit was a highly significant protective measure for reducing wheezing among children who ate fruit five to seven times per week compared to children who ate fruit less than once per week. This protective effect was even evident among the group whose fruit intake was only one to two times per week compared to those who consumed fruit less than one time per week, although no clear dose-response relationship was elucidated.[23] It appears that even relatively low dietary doses of vitamin C are protective against asthma symptomatology in children. Prophylactic administration of ascorbic acid for prevention of exercise-induced asthma is widely described in the medical literature, with most studies revealing that taking vitamin C produces moderately beneficial effects to reducing asthma symptoms caused by exercise but results in little change in pulmonary function tests. The main conclusions drawn from these studies are that vitamin C demonstrates a slight to moderate protective effect on airway hyperreactivity in patients with exercise-induced asthma.[24] A wide review of studies that have investigated the use of vitamin C for treating asthma and allergy found that, among the significantly positive effects of this therapy, positive effects on pulmonary function tests, methacholine, histamine, or allergen broncho-provocation challenges, lymphocyte function and motility, and decreased respiratory infection incidence were produced. No benefits were

noted in these studies regarding testing of cutaneous reactivity or more specific immunologic parameter measurements. This main study also showed that the majority of vitamin C–asthma investigations were short-term and only addressed the immediate effects of vitamin C supplementation on asthma symptoms.[25]

Magnesium

Magnesium and calcium play various roles in pulmonary structure and function. A magnesium deficiency leads to an enhanced action of calcium being that magnesium acts as a calcium antagonist. This is notable in patients with asthma as a result of an intracellular influx of calcium causing bronchial smooth-muscle contraction with magnesium deficiency.[26] Myogenically induced action potentials and autonomic neurotransmitters can alter cytosolic calcium concentration. Increased action potentials will lead to higher cytosolic calcium concentrations, causing greater cross-bridge activity. Likewise, intracellular magnesium can modulate smooth-muscle contractions and inhibit calcium uptake directly, allowing for smooth-muscle relaxation. Magnesium works as a smooth-muscle relaxant, of which the micromusculature surrounding the bronchioles is comprised.

Theoretically, inadequate magnesium levels may contribute to asthma exacerbations.[27] It is of interest to note that, while overall calcium intake in the United States has increased in the past 20 years, magnesium intake has remained unchanged, while the asthma epidemic continues to grow. Magnesium is an important contributor to prophylaxis of asthma symptoms and intravenous magnesium is an accepted form of emergency treatment for acute asthma attacks. Magnesium acts physiologically as a calcium antagonist, allowing muscle relaxation to occur.[28] Patients with chronic asthma were shown to be hypomagnesemic, and this was associated with airway hyper-reactivity, wheezing, and general impairment of lung function in one study. In addition, this investigation revealed that patients who have chronic asthma and have lower stores of magnesium are hospitalized more often than other patients with asthma who have normal levels of magnesium. Hypomagnesemia was also associated with more severe asthma symptoms.[29] Erythrocyte magnesium concentration shared a significant inverse relationship with bronchial reactivity after inhaled methacholine challenge, and hypomagnesemia was prevalent in 40% of the patients with asthma in this study compared to 11% of controls who did not have asthma.[30] Based on this information, correction and stabilization of magnesium levels in patients with asthma seems indicated. As a medical therapy, magnesium has a good safety record. Because magnesium is almost exclusively excreted by the kidneys, overdose levels of magnesium can only be anticipated in patients with renal disease, intestinal hypomotility, and chronic constipation.

Omega-3 Fatty Acids

The end-product metabolism of arachidonic acid (AA), a component of cellular membranes, produces pro-inflammatory 2-series prostaglandins and 4-series leukotrienes, which are highly active mediators of inflammation. AA is derived from the phospholipids layer of immune-cell membranes via phospholipase A-2 in response to immunologic stimuli. The cysteinyl leukotrienes C4, D4, and E4 are important mediators in asthma and are modulators of cytokine function, and they have been implicated in the pathophysiology of asthma via multiple mechanisms such as bronchial smooth muscle, vessels, and mucus secretory cells, while leukotriene B4 promotes leukocyte chemotaxis and less-potent bronchoconstriction.[31] Immune cells that drive the inflammatory process contain high proportions of the n-6 polyunsaturated

fatty acid (PUFA) AA in relation to low amounts of n-3 PUFA; the two fatty acids are structurally and functionally distinct. The n-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), found in high proportions in oily fish and fish oils, produce anti-inflammatory activity and are indicated for preventing asthma symptoms throughout the medical literature. Supplementation with fish oil results in partial replacement of AA in inflammatory-cell membranes with EPA, resulting in decreased production of AA-derived inflammatory mediators. However, this response alone is not totally indicative of the beneficial anti-inflammatory effects of n-3 PUFAs. Both animal and human studies have indicated that other anti-inflammatory effects of n-3 PUFAs may occur downstream from cell-membrane composition alteration, such as suppressed production of pro-inflammatory cytokines and inhibited adhesion molecule expression occurring at the level of altered gene expression.[32] In one study, dietary supplementation with fish oil for 10 months in 29 children with bronchial asthma resulted in decreased asthma symptom scores and response to an acetylcholine challenge in the treatment group with no changes in the control group.[33] Subjects in the treatment group received fish-oil capsules that contained 84 mg of EPA and 36 mg of DHA. The daily dosages of EPA and DHA were, respectively, 17.0–26.8 and 7.3–11.5 mg per kg of body weight (–1), while control subjects received capsules containing 300 mg of olive oil. No side effects were noted. Studies on fish oil consumption have revealed decreased lymphocyte proliferation, T-cell mediated cytotoxicity, natural-killer cell activity, macrophage-mediated cytotoxicity, monocyte and neutrophil chemotaxis, major histocompatibility (class II expression) and antigen presentation, production of pro-inflammatory cytokines (ILs -1 and -6, tumor necrosis factor), and adhesion molecule expression.[34] The studies described previously demonstrate the ability of fish oil supplementation to inhibit the inflammatory process of asthma. Based on these findings, one would expect to see decreased asthma symptomatology and improved lung function with addition of fish oils to the diet. The majority of studies do not indicate an optimal dose; however, most doses of fish oils both EPA and DHA range from 500 mg to 3 g per day.

BOTANICAL MEDICINES

Coleus

Coleus (Coleus forskohlii) is a member of the mint family that has been used traditionally on the Indian subcontinent for treating asthma. The active component of the plant, forskolin, has hypotensive and spasmolytic properties.[35] Forskolin's mechanism of action involves its ability to activate the enzyme adenylate cyclase. This action increases the amount of cyclic adenosine monophosphate (cAMP) in cells, which produces various physiologic and biochemical effects, including inhibition of mast-cell degranulation and histamine release as well as relaxing smooth muscle.[36] Some pharmaceutical approaches to asthma are designed to increase cAMP levels by using an agent that binds to receptors that stimulate adenylate cyclase (corticosteroids) and inhibits the enzyme phosphodiesterase, which is responsible for the breakdown of cAMP. One example is the methylxanthine-derived drug, theophylline, which has fallen out of favor as an asthma therapy because of its narrow therapeutic window. Forskolin's effects on cAMP result in bronchial dilatation and asthma symptom relief.[37] In addition, forskolin may be of benefit to patients with allergic asthma because this compound's antiallergy qualities also include histamine release inhibition.[38] Forskolin is poorly absorbed orally, and many studies use inhaled forskolin for asthma treatment.

Tylophora

Tylophora (Tylophora asthmatica), another botanical medicine that is native to India, has been shown to have anti-asthmatic, anti-inflammatory, and anti-anaphylactic properties.[39] These effects have been attributed to the plant's alkaloid constituents, tylophorine and tylophorinine.[40] For one study, 110 patients with asthma were instructed to chew and swallow one tylophora leaf each day for one week. At the end of the week, 62% of the test subjects reported moderate to complete relief of symptomatology and experienced a continued reduction of symptoms for several weeks following the study.[41] Another study revealed improvements in lung function and decreased nocturnal symptoms in patients with asthma, an effect that, again, persisted past the seven-day trial duration.[42]

Butterbur

The primary active constituents of butterbur (Petasites hybridus) are the sesquiterpene compounds, petasin, and isopetasin. Numerous studies have shown the efficacy of Butterbur in allergic rhinitis. These studies have shown that butterbur supplementation significantly reduced the levels of histamine and leukotrienes.[43] A prospective open trial with 64 adults and 16 children with asthma evaluated the effects of butterbur supplementation for two months. In this study, the number, duration, and severity of asthma attacks decreased. Peak flow, forced expiratory volume (FEV_1), and all measured symptoms also improved. In addition, more than 40% of patients using asthma medications at baseline reduced intake of these medications by the end of the study.[44] In a randomized, crossover, placebo-controlled study, 16 atopic asthmatic patients on a constant dose of inhaled corticosteroids were supplemented with 25 mg butterbur twice daily for one week. Exhaled nitric oxide was significantly reduced and both serum eosinophil cationic protein and peripheral blood eosinophil count were also significantly suppressed.[45]

Quercetin

Quercetin is an abundant flavonoid used medicinally for its antioxidant and anti-inflammatory activity. Quercetin inhibits cyclooxygenase and lipooxygenase enzymes, as well as inflammatory mediators such as leukotrienes and prostaglandins.[46] Quercetin also inhibits the release of histamine from mast cells and basophils.[47] Mast cells induce production of pro-inflammatory cytokines with immune regulatory properties. One study examined the effect of quercetin on the expression of pro-inflammatory cytokines in a human mast-cell line. The results showed that quercetin decreased the gene expression and production of tumor necrosis factor (TNF)-alpha, IL-1beta, IL-6, and IL-8 suggesting that quercetin may be suitable for the treatment of mast-cell-derived allergic inflammatory diseases, such as asthma.[48] In vitro, quercetin was shown to inhibit histamine released from rat peritoneal mast cells. Chemically induced histamine release was inhibited by 95% and immunologically induced histamine release was inhibited by 97%.[49] Although direct evidence of quercetin in asthma patients is lacking, the potent antihistamine and anti-inflammatory activity makes it likely to benefit this condition.

Pycnogenol

Pycnogenol (Pinus pinaster), a trademarked pine bark extract, has anti-inflammatory and antioxidant activity. In a randomized, placebo-controlled, double-blind study involving 60 sub-

jects aged 6–18 years old, pycnogenol supplementation was evaluated in patients with mild to moderate asthma over a three-month period. The results showed that the group taking pycnogenol had significantly more improvement in pulmonary functions and asthma symptoms, was able to reduce or discontinue their use of rescue inhalers, and there was a significant reduction of urinary leukotrienes compared to the placebo.[50] In another randomized, double-blind, placebo-controlled crossover study, 26 patients with varying asthma severity were supplemented with 1 mg=lb per day (maximum 200 mg per day) pycnogenol. Almost all of the patients responded favorably to pycnogenol supplementation with no adverse effects reported. There was also as significant reduction in serum leukotrienes in the pycnogenol group compared with the placebo.[51]

CONCLUSIONS

Asthma, like other chronic disease conditions, has increased in incidence over the last 20 years. Mainstream therapy includes the use of beta-adrenergic agonists to maintain bronchial patency, while corticosteroids are used to prevent the now well-addressed inflammatory component of asthma. Relatively new outlooks on asthma pathogenesis, such as Th2:Th1 balance theory and the hygiene hypothesis, provide exciting new opportunities from which to base new approaches to asthma therapy. Table 2 summarizes some of these approaches. Continued investigations of complementary therapies for asthma are well-recommended, because many therapies are offering promising outcomes, based on preliminary research. Addressing asthma in a preventative manner, using common supplemental interventions such as ascorbic acid, magnesium, and fish oils, as well as botanical medicines, offers significant benefits for preventing bronchial hyper-reactivity and inhibition of the damaging inflammatory response.

Recommendations for patients that are serious about battling allergies include minimizing allergen exposure and supporting the body in controlling the allergic response. The goal is simple—minimize the total burden of allergic exposure by:

- Checking the pollen count (with local media)
- Staying indoors when it is high, such as early evening when pollen counts peak
- Sleeping with the windows closed
- Driving with the vehicle car windows closed
- Wearing a mask when mowing the lawn or better yet hire out the job
- Protecting the eyes with glasses=sunglasses to stop pollen from entering the eyes
- Washing hair prior to bed (to rinse out allergens collected throughout the day)
- Staying well hydrated—moist mucous membranes are more resistant to irritation
- Testing for food allergies
- Minimizing mold and mildew in the house
- Using air filters=HEPA in the bedroom
- Cleaning central ventilation system in the home or office
- Remembering indoor=outdoor pets carry pollen and allergens on their fur
- Cleaning carpets regularly with a HEPA vacuum

REFERENCES

[1]Mannino DM, Homa DM, Pertowski CA. Surveillance for asthma: United States, 1960–1995. CDC Surveillance Summaries, April 24, 1998. MMWR 1998;47(SS-1)1–28.

[2]National Center for Health Statisitics. Asthma Prevalence, Health Care Use and Mortality: United States, 2003-05. Available at: www.cdc.gov=nchs=products=pubs=pubd=hestats=ashtma03-05=asthma03-05.htm. Accessed November 15, 2007.

[3]Matsuda H, Suda T, Hashizume H, Yokomura K, Asada K, Suzuki K, Chida K, Nakamura H. Alteration of balance between myeloid dendritic cells and plasmacytoid dendritic cells in peripheral blood of patients with asthma. Am J Respir Crit Care Med. 2002;166:1050–1054.

[4]Busse WW, Lemanske Jr RF. Asthma. N Engl J Med. 2001;344:350–362.

[5]Wang Q, Lin J, Sun H. The study of T helper cell subsets and relationship to relative cytokines and ventilatory function in asthmatic patients [in Chinese]. Zhonghua Jie He He Hu Xi Za Zhi. 2000;23(3): 147–150.

[6]Matricardi PM, Bouygue GR, Tripodi S. Inner-city asthma and the hygiene hypothesis. Ann Allergy Asthma Immunol. 2002;89(6[suppl 1]):69–74.

[7]Zuany-Amorim C, Sawicka E, Manlius C, Le Moine A, Brunet LR, Kemeny DM, Bowen G, Rook G, Walker C. Suppression of airway eosinophilia by killed Mycobacterium vaccae–induced allergen-specific regulatory T-cells. Nat Med. 2002;8:625–629.

[8]Harding SM. Acid reflux and asthma. Curr Opin Pulm Med. 2003;9:42–45.

[9]Wasowska-Krolikowska K, Toporowska-Kowalska E, Krogulska A. Asthma and gastroesophageal reflux in children. Med Sci Monit. 2002;8:RA64–RA71.

[10]Harding SM. Gastroesophageal reflux, asthma, and mechanisms of interaction. Am J Med. 2001; 111(suppl 8A):8S–12S.

[11]Sontag SJ. Gastroesophageal reflux and asthma. Am J Med. 1997;103(5A[suppl]):84S–90S.

[12]Wright JV. Treatment of childhood asthma with parenteral vitamin B12, gastric re-acidification, and attention to food allergy, magnesium, and pyridoxine: Three case reports with background and an integrated hypothesis. J Nutr Med. 1990;1:277–282.

[13]Baker JC, Duncanson RC, Tunnicliffe WS, Ayres JG. Development of a standardized methodology for double-blind, placebo-controlled food challenge in patients with brittle asthma and perceived food intolerance. J Am Diet Assoc. 2000;100:1361–1367.

[14]Ito S, Mikawa H. Immunological aspects of asthma (prophylaxis). Acta Paediatr Jpn. 1990;32: 192–196.

[15]Benard A, Desreumeaux P, Huglo D, et al. Clinical aspects of allergic disease: Increased intestinal permeability in bronchial asthma. J Allergy Clin Immunol. 1996;97:1173–1178.

[16]Reynolds RD, Natta CL. Depressed plasma pyridoxal phosphate concentrations in adult asthmatics. Am J Clin Nutr. 1985;41:684–688.

[17]Collipp PJ, Goldzier 3rd S, Weiss N, Soleymani Y, Snyder R. Pyridoxine treatment of childhood bronchial asthma. Ann Allergy. 1975;35:93–97.

[18]Sur S, Camara M, Buchmeier A, Morgan S, Nelson HS. Double-blind trial of pyridoxine (vitamin B6) in the treatment of steroid-dependent asthma. Ann Allergy. 1993;70:147–152.

[19]Monteseirin J, Camacho MJ, Bonilla I, De la Calle A, Guardia P, Conde J, Sobrino F. Respiratory burst in neutrophils from asthmatic patients. J Asthma. 2002;39:619–624.

[20]Bowler RP, Crapo JD. Oxidative stress in allergic respiratory diseases. J Allergy Clin Immunol. 2002; 110:349–356.

[21]Kongerud J, Crissman K, Hatch G, Alexis N. Ascorbic acid is decreased in induced sputum of mild asthmatics. Inhal Toxicol. 2003;15:101–109.

[22]Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, Tellez-Rojo MM, Moreno-Macias H, Reyes-Ruiz NI, del Rio-Navarro BE, Ruiz-Navarro MX, Hatch G, Slade R, Hernandez-Avila M. Antioxidant supplementation and lung functions among children with asthma exposed to high levels of air pollutants. Am J Respir Crit Care Med. 2002;166:703–709.

[23]Forastiere F, Pistelli R, Sestini P, Fortes C, Renzoni E, Rusconi F, Dell'Orco V, Ciccone G, Bisanti L. Consumption of fresh fruit rich in vitamin C and wheezing symptoms in children. SIDRIA Collaborative Group, Italy [Italian Studies on Respiratory Disorders in Children and the Environment]. Thorax. 2000; 55(4):283–238.

[24]Cohen HA, Neuman I, Nahum H. Blocking effect of vitamin C in exercise-induced asthma. Arch Pediatr Adolesc Med. 1997;151:367–370.

[25]Bielory L, Gandhi R. Asthma and vitamin C. Ann Allergy. 1994;73:89–96.

[26]Landon RA, Young EA. Role of magnesium in regulation of lung function. J Am Diet Assoc. 1993; 93:674–677.

[27]Skotnicki AB, Jablonski MJ, Musial J, Swadzba J. The role of magnesium in the pathogenesis and therapy of bronchial asthma [in Polish]. Przegl Lek. 1997;54:630–633.
[28]Gulhas N, Durmus M, Demirbilek S, Togal T, Ozturk E, Ersoy MO. The use of magnesium to prevent laryngospasm after tonsillectomy and adenoidectomy: A preliminary study. Paediatr Anaesth. 2003;13: 43–47.
[29]Alamoudi OS. Hypomagnesaemia in chronic, stable asthmatics: Prevalence, correlation with severity and hospitalization. Eur Respir J. 2000;16:427–431.
[30]Hashimoto Y, Nishimura Y, Maeda H, Yokoyama M. Assessment of magnesium status in patients with bronchial asthma. J Asthma. 2000;37:489–496.
[31]Hamid Q, Tulic MK, Liu MC, Moqbel R. Inflammatory cells in asthma: Mechanisms and implications for therapy. J Allergy Clin Immunol. 2003;111(1[suppl]):S5–S12; discussion S12–S17.
[32]Calder PC. Dietary modification of inflammation with lipids. Proc Nutr Soc. 2002;61:345–358.
[33]Nagakura T, Matsuda S, Shichijyo K, Sugimoto H, Hata K. Dietary supplementation with fish oil rich in omega-3 polyunsaturated fatty acids in children with bronchial asthma. Eur Respir J. 2000;16:861–865.
[34]Calder PC. Immunoregulatory and anti-inflammatory effects of n-3 polyunsaturated fatty acids. Braz J Med Biol Res. 1998;31:467–490.
[35]Ammon HPT, Muller, AB: Forskolin: From Ayurvedic remedy to a modern agent. Planta Medica. 1985; 51;473–477.
[36]Seamon KB, Daly JW: Forskolin: A unique diterpene activator of cAMP-generating systems. J Cyclic Nucleotide Res. 1981;7:201–224.
[37]Kreutner W. Bronchodilatory and antiallergy activity of forskolin. Eur J Pharmacol. 1985;111:1–8.
[38]Lichey I, Friedrich T, Priesnitz M, Biamino G, Usinger P, Huckauf H. Effect of forskolin on methacholine-induced bronchoconstriction in extrinsic asthmatics. Lancet. 1984;21:167.
[39]Shivpuri DN, Menon MPS, Prakash D. A crossover double-blind study on Tylophora indica in the treatment of asthma and allergic rhinitis. J Allergy. 1969;43:145–150.
[40]Miller AL. The etiologies, pathophysiology, and alternative=complementary treatment of asthma. Altern Med Rev. 2001;6:20–47.
[41]Thiruvengadam KV, Haranath K, Sudarsan S, et al. Tylophora indica in bronchial asthma: A controlled comparison with a standard anti-asthmatic drug. J Indian Med Assoc. 1978;71:172–176.
[42]Ganguly T, Sainis KB. Inhibition of cellular immune responses by Tylophora indica in experimental models. Phytomedicine. 2001;8:348–355.
[43]Thomet OA, Schapowal A, Heinisch IV, Wiesmann UN, Simon HU. Anti-inflammatory activity of an extract of Petasites hybridus in allergic rhinitis. Int Immunopharmacol. 2002 Jun;2(7):997–1006.
[44]Danesch UC. Petasites hybridus (Butterbur root) extract in the treatment of asthma—an open trial. Altern Med Rev. 2004 Mar;9(1):54–62.
[45]Lee DK, Haggart K, Robb FM, Lipworth BJ. Butterbur, a herbal remedy, confers complementary anti-inflammatory activity in asthmatic patients receiving inhaled corticosteroids. Clin Exp Allergy. 2004 Jan; 34(1):110–114.
[46]Anon. Quercetin. Altern Med Rev. 1998 Apr;3(2):140–143.
[47]Fox CC, Wolf EJ, Kagey-Sobotka A, Lichtenstein LM. Comparison of human lung and intestinal mast cells. J Allergy Clin Immunol. 1988 Jan;81(1):89–94.
[48]Min YD, Choi CH, Bark H, Son HY, Park HH, Lee S, Park JW, Park EK, Shin HI, Kim SH. Quercetin inhibits expression of inflammatory cytokines through attenuation of NF-kappaB and p38 MAPK in HMC-1 human mast cell line. Inflamm Res. 2007 May;56(5):210–215.
[49]Haggag EG, Abou-Moustafa MA, Boucher W, Theoharides TC. The effect of a herbal water-extract on histamine release from mast cells and on allergic asthma. J Herb Pharmacother. 2003;3(4):41–54.
[50]Lau BH, Riesen SK, Truong KP, Lau EW, Rohdewald P, Barreta RA. Pycnogenol as an adjunct in the management of childhood asthma. J Asthma. 2004;41(8):825–832.
[51]Hosseini S, Pishnamazi S, Sadrzadeh SM, Farid F, Farid R, Watson RR. Pycnogenol in the management of asthma. J Med Food. 2001 Winter;4(4):201–209.

7

IS AUTISM THE COAL MINER'S CANARY OF AMERICA'S HEALTH STATUS?

Possibly because of the reported 556% increase in the pediatric prevalence of autism between 1991 and 1997,[1] the classical presentation of autistic spectrum disorders (ASD) is currently an area of widespread study. In addition to autistic disorder or classic autism, ASD comprises five categories of pervasive developmental disorder (PDD) described in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association, of which the remaining four are Asperger's disorder; disintegrative disorder; PDD not otherwise specified, or atypical autism; and Rett's disorder, a genetic disorder of postnatal brain development caused by a defect in a single gene.[2]

ASD is characterized by impairments in three behavioral domains. The first is social interaction, often marked by deficits in reciprocal social interaction; a developmentally delayed or absent ability to communicate verbally; and difficulty with nonverbal cues, such as facial expression, body posture, and eye-to-eye contact. The second is communication. Deficits are also typically present in communication, imaginative play, and the normal range of childhood interests and activities. The third is that individuals with ASD often exhibit repetitive, stereotyped behavior, have restricted areas of interest, exhibit repetitive motor mannerisms, and require strict routines or rituals in order to accord with appropriate social standards and have their needs met.

PREVALENCE

According to data for 2000–2002 published by the Autism and Developmental Disabilities Monitoring Network of the Centers for Disease Control and Prevention (CDC), about 1 in 150 eight-year-old children in several areas of the United States have ASD.[3] The CDC data demonstrated some geographic variation, with a significantly lower prevalence in Alabama, of 3.3 per 1,000 eight-year-olds, and a higher prevalence in New Jersey, of 10.6 per 1,000 eight-year-olds.[3] These figures stand out against the estimated prevalence for ASD of 1 per 1,000 population in the early 1990s. It is estimated that as many as 560,000 American youngsters between birth and age 21 have ASD.[4] The condition affects males at a 4:1 frequency over the occurrence in females.[4]

ETIOLOGY AND PATHOPHYSIOLOGY

The etiology of ASD is currently unknown, although numerous possibilities, based on pathologic findings made in ASD, are currently under investigation. Medical conditions associated with autism include epilepsy, tuberous sclerosis, blindness, deafness, and neurofibromatosis.

Genetics

Evidence suggests that ASD is highly heritable, with some estimates of its heritability reaching 90%.[5] However, twin studies and the wide range of its phenotypic expression indicate that environmental influences also play an important role in the occurrence of ASD. Research has shown that monozygotic twins have a concordance of more than 60% for classical autism, without any concordance for dizygotic twins. When this same study included a broader range of cases with diagnoses of PDD, the concordance for monozygotic twins rose to 92% while that for dizygotic twins reached 10%.[1] Studies also show a frequency of 2%–8% of autism in siblings of autistic children, which far exceeds the frequency of the condition in the general population.[1]

> Oxidative stress from oxygen-bearing free radicals may have a causal role in autistic spectrum disorders.

Genetic screening studies suggest that at least 10 genes may be involved in the etiology of autism, with studies now examining numerous genes for this possibility, such as those in the speech and language region of the human genome at 7q31-q33, 15q11-q13, FOXP2, RAY1=ST7, and IMMP2L; RELN genes at 7q22-q33; a subunit of the gene for the gamma-amino-butyric acid (GABA)(A) receptor; UBE3A genes on chromosome 15q11-q13; the gene for the serotonin transporter (SERT) at 17q11-q12; and the gene for the oxytocin receptor at 3p25-p26.[1] Chromosome 15 duplications are frequently examined owing to their correlation with variable degrees of language delay, ataxia, epilepsy, mental retardation, and facial abnormalities. Studies also indicate that a low level of melatonin, as the result of a primary deficit in ASMT, the gene that encodes the last enzyme in the metabolic pathway leading to melatonin synthesis, is a risk factor for ASD.[6]

Parental Influences and Perinatal Development

Studies have found a greater frequency of certain traits and characteristics among parents of autistic than of healthy children. Greater maternal and paternal age are independently associated with an increased risk for ASD in offspring.[7] Additionally, mothers who have allergies and asthma during the second trimester of pregnancy have a twofold greater than average risk of having a child with ASD. Although this same study found maternal psoriasis to be the only autoimmune disease associated with an increased risk for ASD,[8] another study found a link between both maternal ulcerative colitis and paternal type 1 diabetes and increased risk for infantile autism.[9]

It has been suggested that in many cases, the cerebral developmental abnormalities in autism occur before 30 weeks' gestation.[10] A study of perinatal risk factors and autism found that daily maternal smoking during early pregnancy, a small birth size for gestational age, maternal birth outside of Europe or North America, congenital malformations, cesarean delivery, and a 5-minute Apgar score below 7 were all associated with an increased risk of autism.[11] Another study found a link between autism and parental histories of schizophrenia-like psychosis and affective disorders,[12] while yet another study found a twofold greater risk for autism among children born to mothers with diagnosed psychiatric disorders.[13] The risk for autism has also been found to increase with an increasingly urban location of birth.[13]

Neurologic Dysfunction

Research indicates a significant generalized increase in cerebral cortical volumes of both white and gray matter in autism. This is accompanied by a normal head circumference at birth followed by an abnormally increased growth rate beginning at 12 months of age.[14] Other studies have found an increased cerebellar volume and bilateral enlargement of the amygdala and hippocampus in children with ASD.[15] Recent work with functional magnetic resonance imaging has demonstrated cortical neural under-connectivity in individuals with autism, as well as a smaller corpus callosum—a structure through which many bilaterally activated cortical areas communicate—in individuals with autism as compared to controls.[16] Although the relevance of this is unknown, another study found greater frequencies of left-handedness and preferential left-eye use in children with autism as compared with normal groups, as well as left nasal dominance in most children with autism.[17]

Gastrointestinal Dysfunction

Gastrointestinal (GI) symptoms are common in children with ASD. One study found that 70% of children with ASD had histories of such symptoms, as compared to only 28% of children showing normal development.[18] The most common GI symptom in this study was an abnormal stool pattern.[18] Another study of GI complaints in children with ASD found that the most common complaints were chronic diarrhea, gas, and abdominal discomfort and distension.[19] Reflux esophagitis was evident in over 69% of the children, chronic gastritis in 41%, and chronic duodenitis in 66%. Additionally, 58% of the children had decreased intestinal digestive enzyme activity for carbohydrate, and 75% showed increased pancreaticobiliary fluid output after intravenous administration of secretin.[19] Abnormalities of the gut flora have also been seen in children with ASD, with one study finding an increased incidence of Clostridium histolyticum, a known toxin-producing organism.[20]

Endocrine and Metabolic Dysfunction

Numerous studies indicate endocrine and metabolic abnormalities in children with ASD. Researchers have shown that some of these children have levels of serum=plasma dehydro-epiandrosterone and serum total testosterone that are significantly above age- and gender-appropriate values.[21] The children with ASD were also found to have significantly subnormal levels of serum follicle-stimulating hormone, plasma-reduced glutathione, plasma cysteine, plasma methionine, and serum cystathionine. The investigators who conducted this study suggested that these findings indicate that in some children with ASD, there is an interaction between the mechanisms for trans-sulfuration in the methionine cycle that is important for detoxification and androgen pathways, causing hyper-androgenic behavior and developmental abnormalities.[21] Another study found significantly lower levels of free and total carnitine and pyruvate and elevated levels of ammonia and alanine in children with ASD, possibly reflecting mild mitochondrial dysfunction.[22]

Oxidative Stress

Oxidative stress from oxygen-bearing free radicals may have a causal role in ASD. Individuals with autism have shown increased nitric oxide in their red blood cells and increased activity of the antioxidant enzyme glutathione peroxidase in these individuals' plasma.[23] Other studies

have shown increased levels of such antioxidant enzymes as superoxide dismutase and xanthine oxidase in autism.[24]

Increased lipid peroxidation has also been observed in individuals with autism. Transferrin, an iron-binding protein, and ceruloplasmin, a copper-binding protein, which exhibit antioxidant activity, have been found to be significantly decreased in autistic children, a finding that has been linked to a loss of language skills.[25] Some children with autism show elevated levels of total homocysteine, a finding strongly correlated with decreased erythrocyte glutathione peroxidase activity and diminished levels of vitamin B_{12}.[26]

Immunologic Dysfunction

Studies have indicated that children with ASD have numerous abnormalities in immune function. Studies have shown that these children have significantly increased proportion of CD4 and CD8 lymphocytes making IL-4, with a relative decrease of CD4 and CD8 cells making IL-2 and interferon-gamma indicating impaired cellular immunity and an imbalance of Th1=Th2 cytokines.[27] Studies of immunoglobin (Ig) levels in children with ASD have found a significant increase in total serum protein, and serum IgG, IgG2, and IgG4, and have demonstrated a positive correlation between total serum protein and serum gamma globulin and social problems.[28] Recent studies have identified serum antibodies specific for prenatally expressed brain antigens in mothers of autistic children, suggesting that these auto-antibodies could cross the placental barrier and affect fetal brain development.[29] Other immunologic findings are that children with autism have significantly higher levels of antibodies to measles virus than do controls, with these antibodies present in 83% of the autistic children in one study, but not in healthy children or in the siblings of the autistic children.[30] Antibodies to mumps and rubella are not elevated.[30]

Some autistic children exhibit auto-antibodies to brain proteins such as myelin basic protein (anti-MBP) and neuron-axon filament protein (anti-NAFP). One study found a correlation between these auto-antibodies and antibodies directed against measles virus (measles-IgG) and human herpes virus-6 (HHV-6-IgG). This study found that serum that was positive for measles-IgG and HHV-6-IgG also contained anti-MBP and anti-NAFP antibodies, suggesting virus-induced autoimmunity as a possible etiology for autism.[31] Congenital rubella infection has also been linked to autism, behavioral disorders, and mental retardation.[32]

It is highly controversial whether measles-mumps-rubella (MMR) vaccine is a causal factor in autism, and the vast majority of studies do not support such a link.[33] The possibility is based on the correlation of a type of regressive autism with concomitant GI symptoms soon after administration of the MMR vaccine.[34] The finding of measles virus persistent in the intestines of some autistic children, as well as in individuals with Crohn's disease and ulcerative colitis, implies an autoimmune component in autism.[34]

Studies support the theory that children with autism have an impaired ability to excrete heavy metals.

Mercury, Heavy Metals, and Vaccines

Disputed epidemiologic evidence has correlated neurodevelopmental disorders with increasing doses of mercury from the ethylmercury-containing preservative thimerosal in vaccines.[35] On

the basis of the mercury content of the respective vaccines, children who received diphtheria-tetanus-pertussis vaccine (DTP) and Haemophilus influenza type b (Hib) vaccine at the standard vaccination schedule of 2, 4, 6, and 15–18 months of age may be exposed to 100 mg of mercury more than children given the combined DTP=Hib (DTPH) vaccine. According to the Vaccine Adverse Event Reporting System, this may indicate that children given the DTP and Hib vaccines as separate entities are at significantly greater risk for autism and related disorders than those given the combined vaccine.[36] Thimerosal has since been removed from most vaccines.

Several studies support the theory that children with autism have an impaired ability to excrete heavy metals.[37–39] One such study found significantly lower concentrations of arsenic, cadmium, and lead in the hair of such children than in controls, suggesting lower excretion rates for these three metals.[37] It has also been found that children with ASD have a 2.1-fold greater than average concentration of mercury in their baby teeth, which is a good measure of cumulative exposure to toxic metals during fetal development and infancy.[38] In this study, it was noted that these children had also received significantly more oral antibiotics than average during their first 12 months of life, which may have reduced the children's ability to excrete mercury, since studies with rats have found that antibiotics can almost completely inhibit the excretion of mercury by altering the gut flora.[38] A study in which the levels of mercury in first childhood haircut samples from children with autism were much lower than those of controls also found that the mothers of the autistic children had had significantly greater exposure to mercury from amalgam fillings and thimerosal-containing Rho D immunoglobulin injections than did a control group.[39] A Texas study found a 43% increase in the frequency of special education services and a 61% increase in the rate of autism for every 1,000 lb of environmentally released mercury.[40]

Serotonin

Numerous cursory studies indicate abnormalities in the metabolism of serotonin and measurable levels of this amine in autistic individuals. Among findings in this area are that platelet levels of serotonin are significantly higher in autistic than in control subjects, and that a correlation exists between platelet levels of this amine and abnormal speech development.[41] Significantly lower plasma levels of serotonin have been found in mothers of autistic children than in mothers of children with normal development.[42] Another finding has been that that supplementation with 5-hydroxytryptophan (5-HT), a metabolic precursor of serotonin, raised serotonin levels to a significantly greater degree in subjects with autism than in a control group.[43] Abnormalities in the genes encoding the serotonin transporter and enzymes required for serotonin synthesis are subjects of current study in connection with autism.

DIAGNOSIS OF ASD

The diagnosis of ASD is usually made between the ages of two and three, with tools such as the Checklist for Autism in Toddlers (CHAT), Modified Checklist for Autism in Toddlers (M-CHAT), Pervasive Developmental Disorders Screening Test (PDDST), Screening Tool for Autism in Two-year-olds (STAT), and Checklist for Autism in Toddlers-23 (CHAT-23).

TREATMENT

The wide range in presentations of ASD has led to numerous treatments for it. These include behavioral and psychosocial interventions; occupational, speech, music, and sensory-integration

therapy; immunotherapy; and several alternative and complementary therapies including nutritional therapy, chelation, and vitamin and other nutritional supplementation. The following sections describe a number of treatments investigated for autism, and their effects.

Immunotherapy

A small study of the effect of encapsulated human Ig in males with autism, conducted to test the theory that GI symptoms in the condition may stem from a deficiency in mucosal immunity, found reductions in GI signs and symptoms, as well as improvement in behavioral measures, in half of the treated individuals.[44]

Ascorbic Acid

A 30-week, double-blind, placebo-controlled study demonstrated a reduction in symptom severity in autistic children treated with ascorbic acid, supporting the hypothesis from animal models that this vitamin has a dopaminergic mechanism of action correlating with research suggesting a hyperdopaminergic state in autistic individuals.[45–47] The antioxidant activity of ascorbic acid may also be of benefit in autism.

Carnosine

Carnosine, a dipeptide of alanine and histidine, exhibits antioxidant and antiglycating activity, in addition to binding heavy metals. A controlled study involving children with ASD found that an eight-week trial of l-carnosine at 800 mg per day produced a significant improvement in autistic traits as measured with the Receptive One-Word Picture Vocabulary test and the total score and the Behavior, Socialization, and Communication subscales of the Gilliam Autism Rating Scale.[48]

Hyperactivity and stereotypic behavior declined in children with ASD who were given supplemental omega-3 fatty acids at 1.5 g per day.

Vitamin Supplementation

A study has indicated that children with ASD show significant improvement in sleep and reduction of GI symptoms when given nutritional supplementation with a multivitamin=mineral preparation.[48] The pretreatment baseline finding of vitamin B_6 levels that were 75% higher in these children than in a control group supported previous reports of deficient conversion of pyridoxal to the active pyridoxal-5-phosphate (P5P) by pyridoxal kinase in autistic children, and pointed to an indication for supplementation with vitamin B_6 or P5P in autism.[49,50]

Lower red-blood-cell levels of magnesium have also been found in children with PDD than in controls, with nearly 70% of the affected children showing significant improvement, unaccompanied by adverse effects, upon supplementation with magnesium at a dose of 6 mg=kg per day and 0.6 mg=kg per day of vitamin B_6.[51]

Other nutrient deficiencies and abnormalities have also been found in children with autism. Hair analyses have found lower concentrations of lithium as well as iodine levels 45% below those of controls, as well as a 38% lower level of chromium in autistic children with pica. A 31% greater level of zinc and a 66% lower level of potassium were found in autistic children with diminished muscle tone, suggesting possible avenues for additional vitamin treatment.[52]

Omega-3 Fatty Acids

In a controlled six-week trial, hyperactivity and stereotypic behavior declined in children with ASD who were given supplemental omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) at 1.5 g per day.[53]

Diet

Limited evidence suggests that dietary restriction of gluten and casein may be beneficial in children with autism. A small controlled study found that such children showed significantly better development with a gluten- and casein-restricted diet than did controls.[54] Food allergy may play a role in autistic symptomatology, as suggested by significantly increased levels of antibodies to casein, beta-lactoglobulin, and lactalbumin in autistic children than in controls, followed by reductions in behavioral symptoms with an eight-week elimination diet for these three food components.[55] However, a small, double-blind, placebo-controlled study failed to find any significant changes in autistic children with a gluten- and casein-restricted diet, although the children's parents did report improvements in the children's conditions.[56] Another study found behavioral improvement after six months in 60% of autistic children given a ketogenic diet.[57]

Chelation

A small trial of meso-2, 3-dimercaptosuccinic acid combined with leuprolide acetate was conducted to test the concept that ASD may result from interactions between trans-sulfuration in the methionine cycle and androgen pathways as noted earlier, and in accord with a previous finding of abnormal detoxification associated with the methionine and trans-sulfuration pathways in children with autism.[58] The results showed a dramatic reduction in severity of symptoms, from the 70th–79th percentile of severity to the 40th–49th percentile of severity. Behavior, sociability, and cognitive awareness were notably improved. In another study with autistic children, involving anti-androgen and anti-heavy-metal therapy, urinary levels of heavy metals increased and blood levels of androgens decreased.[59]

Pharmaceutical Treatment

The antipsychotic drug risperidone has been approved by the Food and Drug Administration for treating ASD marked by self-injurious behavior, severe tantrums, and aggression in children ages 5–16. Risperidone has been found to improve social responsiveness and nonverbal communication, and to decrease hyperactivity and aggression in these children.[60] Treatment with selective serotonin reuptake inhibitors (SSRIs) also modifies some symptoms of ASD, including anxiety and repetitive behavior, and improves global functioning.[61]

Behavioral Interventions

Intensive interventions provide better outcomes than less-intensive treatments for ASD. Several behavioral interventions have shown benefit. Early applied behavioral therapy given at home for 30 hours a week can produce gains in behavior.[62] A small study of long-term follow-up of preschool children who had undergone intensive behavioral intervention showed long-lasting gains at a mean age of 11.5 years as compared to controls.[63]

Secretin

Secretin, a peptide that functions in both the GI system and the brain, is being investigated on the basis of anecdotal evidence that this peptide may be effective in easing autistic traits, but most studies have not shown it to be significantly beneficial.[64]

CONCLUSIONS

A vast amount of research is currently focused on identifying the etiology of autism. The large variation in phenotypes of this condition indicates that its etiology is most likely to be multifactorial, with both genetic and environmental components. Complementary and alternative therapies provide treatment options that can support conventional behavioral modification therapies for autism. Like the coal miner's canary, with its sensitivity to silent danger, the dramatic increase in ASD over the past decade warns that something may be amiss in our culture.

REFERENCES

[1]Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics. 2004;113:e472–e486.

[2]American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. Arlington, VA: American Psychiatric Association, 1994.

[3]Autism and Developmental Disabilities Monitoring Network Surveillance, Centers for Disease Control and Prevention. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002: Prevalence of autism spectrum disorders—autism and developmental disabilities monitoring network, 14 sites, United States, 2002. MMWR Surveill Summ. 2007;56:12–28.

[4]Autism Information Center, Centers for Disease Control and Prevention. Online document at: www.cdc.gov=ncbddd=autism=faq_prevalence.htm. Accessed May 20, 2007.

[5]Santangelo SL, Tsatsanis K. What is known about autism: Genes, brain, and behavior. Am J Pharmacogenomics. 2005;5:71–92.

[6]Melke J, Goubran Botros H, Chaste P, et al. Abnormal melatonin synthesis in autism spectrum disorders. Mol Psychiatry. 2007;May 15;[Epub ahead of print].

[7]Croen LA, Najjar DV, Fireman B, Grether JK. Maternal and paternal age and risk of autism spectrum disorders. Arch Pediatr Adolesc Med. 2007;161:334–340.

[8]Croen LA, Grether JK, Yoshida CK, et al. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: A case-control study. Arch Pediatr Adolesc Med. 2005;159:151–157.

[9]Mouridsen SE, Rich B, Isager T, Nedergaard NJ. Autoimmune diseases in parents of children with infantile autism: A case-control study. Dev Med Child Neurol. 2007;49:429–432.

[10]Halsey NA, Hyman SL; Conference Writing Panel. Measles–mumps–rubella vaccine and autistic spectrum disorder: Report from the New Challenges in Childhood Immunizations Conference convened in Oak Brook, Illinois, June 12–13, 2000. Pediatrics. 2001;107:E84.

[11]Hultman CM, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. Epidemiology. 2002;13:417–423.

[12]Larsson HJ, Eaton WW, Madsen KM, et al. Risk factors for autism: Perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol. 2005;161:916–925;discussion:926–928.

[13]Lauritsen MB, Pedersen CB, Mortensen PB. Effects of familial risk factors and place of birth on the risk of autism: A nationwide register-based study. J Child Psychol Psychiatry. 2005;46:963–971.
[14]Hazlett HC, Poe M, Gerig G, et al. Magnetic resonance imaging and head circumference study of brain size in autism: Birth through age 2 years. Arch Gen Psychiatry. 2005;62:1366–1376.
[15]Sparks BF, Friedman SD, Shaw DW, et al. Brain structural abnormalities in young children with autism spectrum disorder. Neurology. 2002;59:184–192.
[16]Just MA, Cherkassky VL, Keller TA, et al. Functional and anatomical cortical underconnectivity in autism: Evidence from an fMRI study of an executive function task and corpus callosum morphometry. Cereb Cortex. 2007;17:951–961.
[17]Dane S, Balci N. Handedness, eyedness and nasal cycle in children with autism. Int J Dev Neurosci. 2007;25:223–226.
[18]Valicenti-McDermott M, McVicar K, Rapin I, et al. Frequency of gastrointestinal symptoms in children with autistic spectrum disorders and association with family history of autoimmune disease. J Dev Behav Pediatr. 2006;27(2suppl):S128–S136.
[19]Horvath K, Papadimitriou JC, Rabsztyn A, et al. Gastrointestinal abnormalities in children with autistic disorder. J Pediatr. 1999;135:559–563.
[20]Parracho HM, Bingham MO, Gibson GR, McCartney AL. Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. J Med Microbiol. 2005;54(pt10): 987–991.
[21]Geier DA, Geier MR. A clinical and laboratory evaluation of methionine cycle-transsulfuration and androgen pathway markers in children with autistic disorders. Horm Res. 2006;66:182–188.
[22]Filipek PA, Juranek J, Nguyen MT, et al. Relative carnitine deficiency in autism. J Autism Dev Disord. 2004;34:615–623.
[23]Sogut S, Zoroglu SS, Ozyurt H, et al. Changes in nitric oxide levels and antioxidant enzyme activities may have a role in the pathophysiological mechanisms involved in autism. Clin Chim Acta. 2003;331(1–2): 111–117.
[24]Zoroglu SS, Armutcu F, Ozen S, et al. Increased oxidative stress and altered activities of erythrocyte free radical scavenging enzymes in autism. Eur Arch Psychiatry Clin Neurosci. 2004;254:143–147.
[25]Chauhan A, Chauhan V, Brown WT, Cohen I. Oxidative stress in autism: Increased lipid peroxidation and reduced serum levels of ceruloplasmin and transferrin—the antioxidant proteins. Life Sci. 2004; 75:2539–2549.
[26]Pasca SP, Nemes B, Vlase L, et al. High levels of homocysteine and low serum paraoxonase 1 arylesterase activity in children with autism. Life Sci. 2006;78:2244–2248.
[27]Gupta S, Aggarwal S, Rashanravan B, Lee T. Th1- and Th2-like cytokines in CD4 and CD8 T cells in autism. J Neuroimmunol. 1998;85:106–109.
[28]Croonenberghs J, Wauters A, Devreese K, et al. Increased serum albumin, gamma globulin, immunoglobulin IgG, and IgG2 and IgG4 in autism. Psychol Med. 2002;32:1457–1463.
[29]Zimmerman AW, Connors SL, Matteson KJ, et al. Maternal antibrain antibodies in autism. Brain Behav Immunol. 2007;21:351–357.
[30]Singh VK, Jensen RL. Elevated levels of measles antibodies in children with autism. Pediatr Neurol. 2003;28:292–294.
[31]Singh VK, Lin SX, Yang VC. Serological association of measles virus and human herpes virus-6 with brain autoantibodies in autism. Clin Immunol Immunopathol. 1998;89:105–108.
[32]Chess S, Fernandez P, Korn S. Behavioral consequences of congenital rubella. J Pediatr. 1978;93:699–703.
[33]Wilson K, Mills E, Ross C, et al. Association of autistic spectrum disorder and the measles, mumps, and rubella vaccine: A systematic review of current epidemiological evidence. Arch Pediatr Adolesc Med. 2003;157:628–634.
[34]Kawashima H, Mori T, Kashiwagi Y, et al. Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism. Dig Dis Sci. 2000;45:723–729.
[35]Geier DA, Geier MR. A comparative evaluation of the effects of MMR immunization and mercury doses from thimerosal-containing childhood vaccines on the population prevalence of autism. Med Sci Monit. 2004;10:PI33–P139.
[36]Geier DA, Geier MR. An evaluation of the effects of thimerosal on neurodevelopmental disorders reported following DTP and Hib vaccines in comparison to DTPH vaccine in the United States. J Toxicol Environ Health [A]. 2006;69:1481–1495.
[37]Kern JK, Grannemann BD, Trivedi MH, Adams JB. Sulfhydryl-reactive metals in autism. J Toxicol Environ Health [A]. 2007;70:715–721.
[38]Adams JB, Romdalvik J, Ramanujam VM, Legator MS. Mercury, lead, and zinc in baby teeth of children with autism versus controls. J Toxicol Environ Health [A]. 2007;70:1046–1051.

[39]Holmes AS, Blaxill MF, Haley BE. Reduced levels of mercury in first baby haircuts of autistic children. Int J Toxicol. 2003;22:277–285.

[40]Palmer RF, Blanchard S, Stein Z, et al. Environmental mercury release, special education rates, and autism disorder: An ecological study of Texas. Health Place. 2006;12:203–209.

[41]Hranilovic D, Bujas-Petkovic Z, Vragovic R, et al. Hyperserotonemia in adults with autistic disorder. J Autism Dev Disord. 2006;December 13;[Epub ahead of print].

[42]Connors SL, Matteson KJ, Sega GA, et al. Plasma serotonin in autism. Pediatr Neurol. 2006;35:182–186.

[43]Croonenberghs J, Verkerk R, Scharpe S, et al. Serotonergic disturbances in autistic disorder: L-5-hydroxytryptophan administration to autistic youngsters increases the blood concentrations of serotonin in patients but not in controls. Life Sci. 2005;76:2171–2183.

[44]Schneider CK, Melmed RD, Barstow LE, et al. Oral human immunoglobulin for children with autism and gastrointestinal dysfunction: A prospective, open-label study. J Autism Dev Disord. 2006;36:1053–1064.

[45]Dolske MC, Spollen J, McKay S, et al. A preliminary trial of ascorbic acid as supplemental therapy for autism. Prog Neuropsychopharmacol Biol Psychiatry. 1993;17:765–774.

[46]Previc FH. Prenatal influences on brain dopamine and their relevance to the rising incidence of autism. Med Hypoth. 2007;68:46–60.

[47]Kimura K, Sidhu A. Ascorbic acid inhibits 125I-SCH 23982 binding but increases the affinity of dopamine for D1 dopamine receptors. J Neurochem. 1994 Dec;63(6):2093–2098.

[48]Chez MG, Buchanan CP, Aimonovitch MC, et al. Double-blind, placebo-controlled study of L-carnosine supplementation in children with autistic spectrum disorders. J Child Neurol. 2002;17:833–837.

[49]Adams JB, Holloway C. Pilot study of a moderate dose multivitamin=mineral supplement for children with autistic spectrum disorder. J Altern Complement Med. 2004;10:1033–1039.

[50]Adams JB, George F, Audhya T. Abnormally high plasma levels of vitamin B6 in children with autism not taking supplements compared to controls not taking supplements. J Altern Complement Med. 2006;12: 59–63.

[51]Mousain-Bosc M, Roche M, Polge A, Pradal-Prat D, et al. Improvement of neurobehavioral disorders in children supplemented with magnesium–vitamin B6: II. Pervasive developmental disorder-autism. Magnes Res. 2006;19:53–62.

[52]Adams JB, Holloway CE, George F, Quig D. Analyses of toxic metals and essential minerals in the hair of Arizona children with autism and associated conditions, and their mothers. Biol Trace Elem Res. 2006; 110:193–209.

[53]Amminger GP, Berger GE, Schafer MR, et al. Omega-3 fatty acids supplementation in children with autism: A double-blind randomized, placebo-controlled pilot study. Biol Psychiatry. 2007;61:551–553.

[54]Knivsberg AM, Reichelt KL, Hoien T, Nodland M. A randomised, controlled study of dietary intervention in autistic syndromes. Nutr Neurosci. 2002;5:251–261.

[55]Lucarelli S, Frediani T, Zingoni AM, et al. Food allergy and infantile autism. Panminerva Med. 1995;37:137–141.

[56]Elder JH, Shankar M, Shuster J, et al. The gluten-free, casein-free diet in autism: Results of a preliminary double blind clinical trial. J Autism Dev Disord. 2006;36:413– 420.

[57]Evangeliou A, Vlachonikolis I, Mihailidou H, et al. Application of a ketogenic diet in children with autistic behavior: Pilot study. J Child Neurol. 2003;18:113–118.

[58]James SJ, Cutler P, Melnyk S, et al. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. Am J Clin Nutr. 2004;80:1611–1617.

[59]Geier DA, Geier MR. A clinical trial of combined anti-androgen and anti–heavy metal therapy in autistic disorders. Neurol Endocrinol Lett. 2006;27:833–838.

[60]Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: Randomized, placebo-controlled, double-blind study. J Child Neurol. 2006;21:450– 455.

[61]Kolevzon A, Mathewson KA, Hollander E. Selective serotonin reuptake inhibitors in autism: A review of efficacy and tolerability. J Clin Psychiatry. 2006;67:407– 414.

[62]Reed P, Osborne LA, Corness M. Brief report: Relative effectiveness of different home-based behavioral approaches to early teaching intervention. J Autism Dev Disord. 2006;December 19;[Epub ahead of print].

[63]McEachin JJ, Smith T, Lovaas OI. Long-term outcome for children with autism who received early intensive behavioral treatment. Am J Ment Retard. 1993;97:359–372;discussion:373–391.

[64]Pallanti S, Lassi S, La Malfa G, et al. Short report: Autistic gastrointestinal and eating symptoms treated with secretin: A subtype of autism. Clin Pract Epidemiol Ment Health. 2005;1:24.

8

CARDIOVASCULAR DISEASE

Phytochemical and Nutritional Prevention and Treatment

According to the American Heart Association 2004 data, it is estimated that 79,400,000 American adults, approximately 1 in 3, had some form of cardiovascular disease (CVD). These CVDs include hypertension, stroke, and coronary heart disease, including angina pectoris and myocardial infarction. Individually, 72,000,000 people had hypertension; 7,900,000 suffered from acute myocardial infarction; 8,900,000 people experienced angina pectoris; 5,200,000 had heart failure, and 5,600,000 had strokes.[1] In 2004, CVD was the underlying cause of death in 36.3% of deaths, or 1 in every 2.8 deaths, with over 147,000 deaths in Americans under age 65.[2]

It is not only an equal-opportunity killer for both men and women, it also decreases quality of life. The heart beats 103,680 times a day for a person with a pulse of 72 beats per minute. Even more amazing is the fact that the human body is comprised of 75 trillion cells that are nourished by 60,000 miles of blood vessels. Indeed, any given cell in the body is no further than 1=500 of an inch from its own personal blood supply. Cardiovascular diseases represent one of the greatest health concerns in modern history. Death from cardiovascular-related disease is estimated to kill 1 person every 33 seconds in the United States. Not limited in prevalence to the United States, diseases of the cardiovascular system affect people across the world, mainly in modernized countries.

The American Heart Association (AHA) identifies increasing age, male gender, and heredity as uncontrollable risk factors for heart disease. Tobacco smoking, high blood cholesterol, high blood pressure, physical inactivity, obesity=overweight, and diabetes are modifiable risk factors for heart disease. Other negative risk factors identified by the AHA as contributory to heart disease include stress levels and responses, sex hormones, birth control pills, and excessive alcohol intake.[3] Despite the acknowledgment of this problem and intense educational efforts in this country to make people aware of CVD, large numbers of people are continually diagnosed each year in this country and the in rest of the world.

New insights into CVD reveal foci for testing and prevention, other than standard lipid profiles. Testing for homocysteine, C-reactive protein (CRP), and fibrinogen place new emphasis on cardiovascular risk parameters while research into naturally derived medicines provides viable preventative and treatment options for CVD.

LIPID LEVELS

The standard lipid panel provides information about plasma concentrations of total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and very low-density lipoprotein (VLDL) cholesterol. However, a patient who scores within the ''average'' ranges for these parameters should take little comfort because being average, in this case, means a greater than 50% likelihood of dying of heart disease.

Other lipids and lipid-related cardiovascular risk factors include Apolipoprotein A-1, Apolipoprotein B, and lipoprotein(a). Apolipoprotein A-1 is the major protein constituent of HDL cholesterol and is responsible for the activation of two enzymes that are necessary for the formation of HDL. This may be an important factor in the relationship between HDL levels and the incidence of atherosclerosis. Apolipoprotein B is the major protein found in LDL cholesterol. Studies suggest that this protein plays an important role in targeting the selective uptake of LDL by the liver. In a study examining lipids, lipoproteins, and apolipoproteins in individuals with angiographic evidence of coronary artery disease (CAD) and healthy patients, the strongest association with coronary artery disease was the ratio of apolipoptotein B:apolipoprotein A-1 (apo B=apo A-I).[4] In a similar study, lipid parameters were evaluated in a lower-risk population with and without coronary artery stenosis to investigate the risk factors associated with increased risk of CAD. Total cholesterol and apo B=apo A-I ratio were significantly different between groups with and without CAD in men. In women, triglyceride, HDL, and apo B=apo A-I ratio were significantly different between the two groups. In the lowest quartile of total cholesterol, triglycerides and LDL, and the highest quartile of HDL, only apo B=apo A-I ratio was associated with CAD in both men and women; thus the only variable showing a significant difference between patients in men and women with and without CAD was the apo B=apo A-I ratio.[5] Lipoprotein(a) is a complex of Apolipoprotein A and LDL, and elevated levels are associated with an increased risk for atherosclerosis and cardiovascular disease. Lipoprotein(a) is similar to that of LDL in the development of atherosclerosis; it is localized in the blood vessel walls, then oxidized, and forms foam cells associated with atherosclerotic plaques. Lipoprotein(a) is also pro-thrombotic, a result of its inhibition of plasminogen activation along with its ability to stimulate secretion of plasminogen activator inhibitor-1 (PAI-1).

According to the recommendations of the National Cholesterol Education Program, these laboratory tests provide useful parameters for evaluating risk status for coronary heart disease (CHD). Both individual and stand-alone values and comparison ratios between individual components of the lipid panel provide information for classifying patients into low, medium, and high-risk categories. With regard to risk, so-called ''normal'' levels are derived from groups of patients with no obvious evidence of CVD and this, in itself, is inaccurate because such patients may have preclinical CVD and therefore do not reflect a true ''no-risk'' population. Cholesterol levels undergo considerable variation among individuals, with day-to-day values fluctuating by as much as 15%, while an 8% difference can be identified within the same day. Even positional changes can alter these values; recumbency can decrease cholesterol values by 15%.[6] Although cholesterol is no longer considered to be such a significant culprit in CVD as much as in the past, great emphasis is still directed at reducing cholesterol blood levels. However, current research is aimed at examining the increased risk of having small LDL particles and a greater number of LDL particles, rather than look at the total weight of LDL, HDL, and total cholesterol. Also, examining the role of oxidized LDL has also taken on increased significance in assessing overall cardiovascular risk.

Alternative and complementary (ACM) practitioners utilize the lipid panel in much the same way as standard medical practitioners, but ACM practitioners utilize natural-based medicines with minimal side effects that are effective for lowering cholesterol, LDL, and VLDL, while elevating HDL over time. In addition, ACM practitioners have a larger arsenal for treating and preventing heart disease, which provides even greater benefit when combined with traditional statin drug therapy. The following plant-derived medicines are used to treat suboptimal cholesterol, HDL, LDL, VLDL, and triglyceride levels. It is essential from a clinical perspective to remember that cholesterol serves many essential purposes in the body as a pro-hormone building

block for estrogen, progesterone, testosterone, corticosteroids, and vitamin D, and is incorporated in each of the cells within the human body. Cholesterol is certainly a risk factor yet, it should not be made the sole culprit since it is guilty in large part through association with other risk factors.

Myrrh

Also known as guggulipid, Commiphora mukul is the standardized extract of the myrrh tree, native to India. This botanical medicine contains two main active compounds: Z-guggulsterone and E-guggulsterone, both of which lower total cholesterol and triglycerides and raise HDL cholesterol.[7] These phytosteroids act as antagonist ligands for the bile acid receptor farnesoid X receptor, an important regulator of cholesterol homeostasis.[8] More specifically, this regulation involves increasing the liver's metabolism of LDL cholesterol.[9] Guggulipid, administered two times per day, containing a standardized dose of 50 mg of guggulsterones per day, for 24 weeks to 31 patients was found to reduce total cholesterol by 11.7%, LDL by 12.5%, triglycerides by 12%, and total cholesterol=high density lipoprotein (HDL) cholesterol ratio by 11.1%.[10] HDL cholesterol itself was not affected in this study. In a multicenter clinical trial, 205 patients took 500 mg of guggulipid two times per day. On average, cholesterol levels fell 11%, while triglycerides decreased by 16.8%, and HDL levels increased by 60% in cases that responded to the guggul therapy.[11] Although these studies show benefit from guggulipid, more recent studies have not been able to verify these findings. In one double-blind, randomized, placebo-controlled trial, a standardized guggul extract (guggulipid, containing 2.5% guggulsterones, average 21 mg guggulsterone per 1,000 mg capsule) of 1,000 mg or 2,000 mg was given three times daily to hypercholesteremic patients who ate a standard Western diet for eight weeks. The results showed no significant changes in levels of total cholesterol, HDL, triglycerides, or VLDL with guggulipid supplementation.[12] Crude guggul extracts have been associated with occasional side effects such as skin rashes and diarrhea.[13]

Garlic

Garlic (Allium sativum) and its derivatives are popularly known as effective preventives and treatment options for atherosclerosis, hyperlipidemia, thrombosis, hypertension, diabetes, and other metabolic diseases, with numerous clinical trials demonstrating its efficacy for treating these conditions.[14] The pharmacologic effects of garlic are attributed to allicin, ajoene, and other organosulfur constituents in the herb.[15] Efficacy of garlic compounds is determined by the ability of the product to produce allicin, the keystone constituent that yields the production of other active garlic components.

The hypocholesterolemic properties of garlic are not well understood, and the mechanism of action is not entirely clear at this time. A large portion of the research on garlic has yielded positive results, showing that garlic can modestly improve total cholesterol, LDL, and triglyceride levels.[16] Garlic preparations, used from 4 to 25 weeks, will typically lower serum cholesterol by 4%–12%, while conventional statin drugs lower serum cholesterol by 17%–32%. In a placebo-controlled, double-blind study, 800 mg garlic powder (standardized to 1.3% of allicin content) was given daily for 16 weeks in individuals with hypercholesteremia. Mean serum cholesterol levels dropped from 266 to 235 mg=dl (12%) and mean triglyceride levels decreased from 226 to 188 mg=dl (17%). This study also concluded that the best cholesterol-lowering effects were in the patients with initial total cholesterol values between 250–300 mg=dl.[17] Other research has not validated these findings. In a recent study, adults with moderate hypercholesterolemia were given either raw garlic, powdered garlic supplement, or an aged

Figure 8–1. Garlic (Allium satiuum).

Figure 8–2. Artichoke (Cynara scolymus).

garlic extract supplement for six months. The results showed no statistically significant effects on levels of LDL, HDL, triglycerides, or total cholesterol:HDL ratio.[18]

One recent comprehensive study of hydrophilic and hydrophobic compounds of garlic elucidated the inhibitory potency of individual water- and lipid-soluble garlic compounds effects on cholesterol synthesis. Results from this study demonstrated that the cholesterol-lowering effects of garlic extract result mainly from inhibition of hepatic cholesterol synthesis of mainly water-soluble sulfur compounds.[19] Another study probed further by examining the inhibitory effects at potential sites in the cholesterol biosynthetic pathway. Fresh garlic extract and 16 different water- and lipid-soluble garlic derivatives were studied in relation to purified recombinant human squalene monoxygenase. Squalene monooxygenase catalyzes the second step in the downstream pathway of cholesterol biosynthesis and is considered to be the rate-limiting step in this process. The results of this study indicated squalene monooxygenase as one of the target enzymes through which garlic inhibits cholesterol biosynthesis.[20] In another study oriented toward establishing the cholesterol-lowering effects of garlic, rat hepatocytes were utilized to determine the effects of garlic preparations (petroleum ether, methanol, and water-extractable fractions from fresh garlic) on [1-14C]acetate and [2-3H]glycerol incorporation into cholesterol, fatty acids, and glycerol lipids. The study results suggested that garlic lowers cholesterol by mitigating hepatic cholesteogenesis while the triglyceride-lowering effect of garlic results from inhibition of fatty-acid synthesis.[21] Garlic and garlic extracts provide a highly cost-effective therapy for hypercholesterolemia, with minimal side effects—with the most often reported ones being malodorous breath and body odor.

Artichoke

The extract of artichoke (Cynara scolymus) has the ability to reduce total serum cholesterol and LDL and to improve the LDL=HDL ratio.[22] New methods of action are continually being explained. While one study suggested a different method of action from the well-known one of lowering cholesterol by increasing its excretion in bile (and listed chemical contents that were

thought to be responsible), another study suggested that inhibiting gastric emptying may lower cholesterol. Because of botanical medicines' ability to work via several different biochemical pathways to achieve the same result, the newer research covered in this article does not negate the idea that artichoke acts as a cholagogue.

The results of a study to determine the lipid-lowering effects of artichoke suggest that this occurs via an indirect modulation of hydroxymethylglutaryl-CoA-reductase activity.[23] Furthermore, this study investigated many of artichoke's main active constituents and revealed that cynaroside and, more specifically, its aglycone luteolin were most responsible for inhibition, while chlorogenic acid was less effective and caffeic acid, cynarin, and dicaffeoylquinic acids exerted little hypocholesterolemic influences. A methanol-derived extract from artichoke leaves was able to suppress triglyceride elevation in mice that were fed large amounts of olive oil; these active compounds were determined to be both sesquiterpenes (cynaropicrin, aguerin B, and grosheimin) and three newly discovered sesquiterpene glycosides (cynarascolosides A, B, and C).[24] Inhibition of gastric emptying was also shown to contribute to the antihyperlipidemic activity in this study. The side effects of this plant are minimal, with flatulence being the most-often reported consequence.[25] No other internal side effects are mentioned in the literature but one external one—allergic contact dermatitis—did occur; this was attributed to cynaropicrin.[26] The body of research for artichoke is fairly small at this time; however, it contains positive support for use of this plant as a reliable lipid-lowering agent.

Curcumin

A yellow pigment compound derived from the spice turmeric (Curcuma longa), curcumin, and its structurally related compounds (curcuminoids) produce several pharmacologic effects including anti-inflammatory, antioxidative, hypocholesterolemic, and anti-carcinogenic activities. Precise mechanisms for the previously mentioned actions have not been elucidated fully. The anti-inflammatory and anti-carcinogenic properties are believed to be mediated, in part, to curcumins' ability to down-regulate NFkB activation and by activation of the NRF-2 receptor, which activates the antioxidant response element on DNA. Curcumin also down-regulates the expression of COX-2, a gene regulated by NFkB.[27] Curcuminoids are thought to exert a lipid-lowering effect, possibly as a result of alterations in fatty-acid metabolism.[28] Wistar rats who were fed a high-fat diet for four weeks, then placed on a diet containing curcumin (5 g=kg of body weight), had decreased serum levels of cholesterol and triglycerides, with increases in apolipoprotein A. This effect remained for an additional two weeks' post-diet alteration.[29] There are several studies demonstrating similar effects on animal lipid models, but human studies are infrequent. Based on these models, however, curcumin may be a useful tool in helping to prevent or manage atherosclerotic diseases.

Tocotrienol

Tocotrienols, a particular form of vitamin E, have been shown to effectively reduce elevated cholesterol levels. One study showed that hypercholesterolemic subjects supplemented with 200 mg gamma-tocotrienol per day showed decreased serum cholesterol by 31% during a four-week period.[30] The delta and gamma isomers found in tocotrienols are effective at lowering cholesterol due to the substitution and location of methyl groups at the head region of the molecule. Tocotrienols positively affect lipid levels by suppressing the activity of HMG-CoA reductase.[31] Tocotrienols have also been shown in humans to significantly reduce aortic systolic blood pressure and induce a 9.2% improvement in total antioxidant status as well.[32]

Red Yeast Rice

Red yeast rice is formed from the fermentation of rice with Monascus purpureus. Red yeast contains mevinic acids, which have been shown to inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, thus blocking cholesterol synthesis similarly as statin pharmaceuticals. Studies indicate that red yeast rice supplementation significantly decreases total cholesterol, LDL, and triglycerides in hyperlipidemic patients.[33] Of the mevinic acids, also known as monacolins, the highest concentration is a constituent called monacolin K (also known as mevinolin or lovastatin). Most studies use a proprietary blend red yeast rice product standardized to monocolin K. Many preparations sold in the United States have low levels of monacolin K, thus, they may not effectively reduce cholesterol. Additionally, some products contain a nephrotoxin that results from incorrect rice fermentation processes known as citrinin. Thus, patients should be advised to use only standardized products to monocolin K that have been analyzed and found to be citrinin-free. Coenzyme Q10 (CoQ10) should be supplemented in conjunction with red yeast rice as HMG-CoA reductase inhibitors also inhibit the biosynthesis of CoQ10.

Niacin and Other B Vitamins

Niacin (vitamin B_3) is a water-soluble vitamin. The FDA has approved the use of high-dose niacin for the treatment of hyperlipidemia. Numerous studies have verified the efficacy of niacin for this purpose. In one study, dyslipidemic patients were supplemented with time-released nicotinic acid (mean 1,297 mg per day) for a mean duration of 7.4 months. HDL levels increased a mean of 18%, total cholesterol concentrations decreased 9%, the ratio of total cholesterol: HDL decreased 25%, LDL cholesterol levels decreased 13%, and triglyceride levels decreased by 20%.[34] Niacin is frequently prescribed in addition to statin therapy. Studies show that adding prolonged-release nicotinic acid to statin therapy in patients at increased cardiovascular risk increased HDL cholesterol by 23%, decreased triglycerides by 15%, and decreased LDL by 4%.[35] The most common side effect reported was flushing.

When examining lipid subclasses, the most atherogenic appear to be the small, dense LDL and large VLDL subclasses, while the large HDL2 subclass, which transports esterified cholesterol from the periphery to the liver, is considered the more cardioprotective. In addition to decreasing total lipids, niacin has been shown to cause an increase in LDL particle size and a shift from small LDL to the less atherogenic, large LDL subclasses, as well as decrease concentrations of the larger VLDL subclasses.[36] In another study, niacin was added to existing therapy for three months in 54 subjects with stable coronary artery disease. The results showed an increase in total HDL by 7.5% and decreased triglycerides by 15% compared with baseline values, although total cholesterol and LDL levels remained unchanged. Addition of niacin resulted in a 32% increase in large-particle HDL, an 8% decrease in small-particle HDL, an 82% increase in large-particle LDL, and a 12% decrease in small-particle LDL. Niacin decreased inflammatory markers as well, showing a decrease in lipoprotein-associated phospholipase A2 by 20% and C-reactive protein levels (CRP) by 15%.[37] In one clinical trial, niacin at 1,000 mg per day was supplemented to patients with metabolic syndrome for 52 weeks. The results showed that the niacin-treated group had a regression in carotid intimal medial thickness, endothelial function improved by 22%, hsCRP decreased by 20%, HDL increased, and LDL and triglycerides decreased significantly.[38]

Niacinamide does not cause flushing but has not been shown to be effective for hyperlipidemia. Niacin in high doses can significantly raise homocysteine levels as research shows a

17%–55% increase;[39] thus, high-dose niacin should be supplemented with folic acid and other B vitamins.

It has been discovered that choline, long considered to be a B vitamin, is produced in very small amounts in the human body. Choline, in the form of phosphatidylcholine, can increase the solubility of cholesterol in the body, lower cholesterol levels, and inhibit platelet aggregation.[40] In one study, 32 patients with elevated cholesterol and triglycerides were treated with 3.5 g of phosphatidylcholine three times per day before meals. The results showed that phosphatidylcholine supplementation decreased cholesterol levels by 33%, triglycerides by 33%, and HDL cholesterol increased by 46% after 30 days of treatment.[41]

Fish Oil

Omega-3 fatty acids are cardioprotective mainly due to beneficial effects on arrhythmias, atherosclerosis, inflammation, and thrombosis, as well as improvement in endothelial function, and the ability to lower blood pressure and triglycerides.[42] Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are responsible for the triglyceride-lowering properties. A prescription form of omega-3 fatty acids has been approved by the United States Food and Drug Administration as an adjunct to diet for the treatment of very high triglyceride levels at a dose of 2–4 g per day. In patients with triglyceride levels above 500 mg=dl, approximately 4 g per day of EPA and DHA reduces triglyceride levels 45% and very low-density lipoprotein cholesterol levels by more than 50%.[43] In one very large clinical trial, over 11,000 patients surviving recent myocardial infarction were randomly assigned supplements of n-3 polyunsaturated fatty acids (PUFA) at a dose of 1 g per day, vitamin E 300 mg per day, both, or neither for 3.5 years. Treatment with n-3 PUFA, but not vitamin E, significantly lowered the risk of mortality. The 20% all-cause mortality benefit could be attributed to a 45% reduction in sudden death.[44,45] In another double-blind, randomized, placebo-controlled study, hypertriglyceridemic men received either 3 g DHA per day or olive oil (placebo) for three months. The group taking DHA showed significantly decreased concentrations of fasting triacylglycerol by 24%, large VLDL by 92%, and intermediate-density lipoproteins by 53% at 45 days.[46] In a prospective, randomized, double-blind trial, DHA supplementation was compared to DHA plus EPA in patients with coronary artery disease with triglycerides greater than 200 mg=dL. Patients received either 1,000 mg of DHA or 1,252 mg of DHA plus EPA for eight weeks. The results indicated that there was not a significant difference between the groups, with an average decrease in triglycerides 18.3%–21.8% in both groups.[47]

MARKERS OF INFLAMMATION

C-Reactive Protein and Fibrinogen

CRP, an emerging marker of CHD risk, is a nonspecific acute-phase reactant protein for which the concentration in serum becomes increased in response to inflammatory stimuli. Studies show that CRP is not just a marker of inflammation; it also acts as a mediator that amplifies the inflammatory cascade. High values are noted in early bacterial infections, active rheumatoid disease, Crohn's disease, acute myocardial infarction, and following trauma. In patients with ischemic chest pain, elevated CRP is associated with a negative prognosis upon hospital admission. In seemingly healthy individuals, elevated CRP indicates an increased risk of atherosclerotic disease and reflects a chronic nonspecific inflammatory process in the body,

which in turn confers an increased risk of the cardiovascular events. An elevated CRP level is normally treated with aspirin prophylaxis and hyperlipidemia medications, or ''statins.'' While obesity is, itself, a well-known risk factor for CHD, lowering CRP via lowering body fat will decrease CRP and CHD. In particular, high-sensitivity hsCRP is considered to be a promising marker for CHD and is interrelated with obesity and other risk factors, such as age, tobacco use, blood pressure, and dyslipidemia.[48] One of the most common causes of an elevated CRP has been shown to be periodontal disease.

This being said, complementary and alternative practitioners view CRP as yet another risk factor for CVD in patients who do not manifest the other pathologies that cause elevated CRP. The strong association between elevated CRP and cardiovascular disease supports the concept that cardiovascular disease is not simply a lipid-accumulation disease, but an inflammatory disorder involving the endothelium and hypercoagulability. Consequently, the most effective strategies for preventing cardiovascular disease are those that reduce systemic inflammation, and CRP then becomes a benchmark for the efficacy of those strategies. Because current medical opinion does not place CRP decidedly as a definitive cause of CVD, this marker can only be looked upon as a potential warning sign for future disease. Recent research has elucidated, however, the importance of CRP and risk of recurrent myocardial infarction or death from coronary causes. The study concluded that individuals who had lower CRP levels after therapy had better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol.[49] Additional studies show that CRP is a significant risk factor for the progression of atherosclerosis in patients with coronary artery disease.[50]

Fibrinogen

Fibrinogen is independently, consistently, and vigorously associated with risk of CVD, based on multiple prospective epidemiologic studies and clinical observations.[51] The reasons for elevation of fibrinogen in CVD are not well-elucidated yet; however, it has been speculated that cellular components involved in the atherosclerotic process produce cytokines that induce an acute-phase reaction, leading to increased fibrinogen levels. Fibrinogen plays several roles in the cardiovascular system such as forming the substrate for thrombin and represents the final step in the coagulation cascade, is essential for platelet aggregation, modulates endothelial function, promotes smooth muscle cell proliferation and migration, and interacts with the binding of plasmin with its receptor.[52] The role of fibrinogen in the etiology of CVD is yet to be completely determined. Even so, fibrinogen is an important cardiovascular disease marker.

With the knowledge that CRP and fibrinogen are signatures of inflammatory processes in the body, ACM practitioners use these markers as a sign that the body is creating inflammatory processes in the cardiovascular system, and treatments are geared toward lowering levels of these markers in the body. The inflammatory process is considered to be the premier etiologic event that initiates the development and propagation of the atherosclerotic process.[53] Elevated CRP and fibrinogen levels are indirectly treated with an overall anti-inflammatory approach, involving diet, supplementation, and botanical medicines. Fibrinogen is known to be elevated in individuals with diabetes; those who are overweight, sedentary; and in smokers. Even in healthy people, fibrinogen levels have been shown to increase by 25 mg=dL per decade.[54] Studies have also shown that increased social stress, such as lack of job control, causes an increase in fibrinogen levels, suggesting the possible pathway between elevated stress and increased risk of heart disease.[55] Another study showed that individuals with low plasma fibrinogen had a low incidence of coronary events even when serum LDL cholesterol was elevated. Individuals with

high serum LDL cholesterol levels who also had high plasma fibrinogen concentrations had a 6.1-fold increase in coronary risk.[56]

TREATMENTS FOR INFLAMMATION

Nattokinase and Serrapeptase

Nattokinase is a fibrinolytic enzyme derived from natto, a fermented soybean product. It acts by inactivating plasminogen activator inhibitor-1 (PAI-1).[57] Studies show that it has fibrinolytic activity four times more potent than plasmin.[58] Animal models demonstrate that nattokinase supplementation inhibits thickening of the intimal wall after vessel injury.[59] Research has also shown that nattokinase increases thrombolysis at the site of thrombus formation caused by endothelial injury.[60]

Serrapeptase is a proteolytic enzyme originally isolated from the silkworm. It has anti-inflammatory and fibrinolytic activity and decreases swelling. A double-blind, placebo-controlled study demonstrated that serrapeptase supplementation rapidly decreased inflammation and decreased symptoms in a group of patients suffering from ENT symptoms.[61] Although there are no current studies with serrapeptase and cardiovascular disease, it may provide benefit for decreasing inflammation associated with these conditions.

Other anti-inflammatory botanicals worth mentioning include Holy Basil (Ocimum sanctum), ginger (Zingiber officinale), Boswellia serrata, Green tea (Camellia sinensis), and Perilla frutescens. (See Chapter 20 on inflammation.)

Fish Oils

The anti-inflammatory effects of fish oils and fish oil supplementation have been widely studied with positive findings for managing chronic inflammatory diseases, such as asthma,

Natural Treatments for Preventing or Managing Coronary Heart Disease

What to Tell Your Patients

Guggulipid extract—standardized to 25 mg of guggulsterone per 500 mg tablet, three times per day
Fish oils (EPA DHA)—2–3 g per day
Garlic—4,000 mg of allicin per day
Artichoke—500 mg of a standardized extract per day
Curcumin—200–400 mg, three times per day, in between meals
Bromelain—standardized to 1,800–2,000 milk-clotting units or gelatin-digesting units, 500 mg, three times per day, in between meals
B vitamins—B_6: 10 mg per day; B_{12}: 400 mg per day; and folate: 1 mg per day
Vitamin E (mixed tocopherols)—800 international units per day

EPA eicosapentaenoic acid; DHA docosahexaenoic acid.

rheumatoid arthritis, dermatologic diseases, and antioxidant therapy. In addition, this research has demonstrated the effectiveness of fish oils on CRP levels.

A study involving 269 patients evaluated baseline levels of CRP, granulocyte membrane content of n-3-polyunsaturated fatty acids derived from fish, and angiographic findings. Subjects with lower CRP levels had significantly higher contents of docosahexaenoic acid (DHA) in granulocytes than subjects with higher CRP levels. The study hypothesized that, based on the inverse correlation between CRP and DHA, an anti-inflammatory effect of DHA suggests a novel mechanism by which fish consumption may decrease the risk of coronary artery disease.[62]

A vegetarian diet, or a diet supplemented with fish oils, provides improvement in patients with chronic inflammatory diseases, leading these oils to be useful for treating patients who have elevated CRP levels. Investigators studied the effects of an anti-inflammatory diet providing less than 90 mg of arachidonic acid (AA) per day and 30 mg of fish oil per kg of body weight on fatty-acid composition of erythrocyte lipids, eicosanoids, and inflammatory cytokines. Compared to baseline measurements, the treated subjects' erythrocyte lipids contained higher amounts of eicosapentaenoic acid (EPA) and had decreased formation of leukotriene B4, 11-dehydrothromboxane B(2), and prostaglandin metabolites.[63] A diet low in AA supplemented with EPA can decrease physiologic markers of inflammation, providing a basis for treatment in patients with elevated inflammatory cardiovascular markers such as CRP.

Vitamin E

Vitamin E is another widely researched adjunctive therapy, with various effects throughout the body and on inflammatory diseases. Vitamin E exists as eight different forms including four tocopherols and four tocotrienols. A powerful antioxidant with several antiatherogenic effects, much attention has been focused on vitamin E in the prevention and treatment of cardiovascular disease. Vitamin E exerts beneficial effects on LDL oxidation, pro-inflammatory cytokines, and CRP levels.[64] Providing patients with 1,200 international units (IU) per day of alpha-tocopherol significantly lowered interleukin-6 and hsCRP levels in a five-month study.[65] Other studies have shown a direct dose-response effect of up to 1,200 IU of vitamin E on anti-inflammatory effects and inhibition of CRP.[66] In another study, 1,200 IU of vitamin E reduced elevated CRP levels by 33% in control subjects who were nondiabetic and by 25% in patients with type 2 diabetes after three months of supplementation.[45] A similar trial with 800 IU of vitamin E reduced CRP levels by 48% in four weeks.[67] Supplementation with alpha-tocopherol is considered to be therapeutically safe, even at 1,200 IU.[68] Studies regarding the efficacy of vitamin E supplementation in cardiovascular disease have been conflicting, however. This may be due to the use of alpha-tocopherol exclusively. Studies show that supplementation with alpha-tocopherol depletes levels of serum gamma-tocopherol concentrations by a median change of 58%.[69] Some evidence suggests that gamma-tocopherol is more potent than alpha-tocopherol in regard to decreasing platelet aggregation, delaying time to occlusive thrombus, decreasing arterial superoxide anion generation, decreasing lipid peroxidation and LDL oxidation, and increasing endogenous superoxide dismutase (SOD) activity.[70] A clinical trial compared a mixed tocopherol preparation rich in gamma-tocopherol for eight weeks with alpha-tocopherol. The results showed that the mixed tocopherols were more potent in preventing platelet aggregation than alpha-tocopherol and modulating increased nitric oxide (NO) release and endothelial constitutive nitric-oxide synthase (ecNOS) activation.[71] (Also see the previous section on tocotrienols.)

Garlic

In addition to lowering lipid levels, garlic shows promise for treating platelet-function discrepancies related to CVD. An aged extract of garlic was shown to exert inhibitory effects on platelet aggregation and adhesion to fibrinogen at all levels of supplementation in the course of one study.[72] In a different study, platelet adhesion to fibrinogen was decreased by approximately 30% compared to a placebo in subjects whose blood was studied in a laminar-flow chamber.[73] Because of this herb's platelet inhibitory capabilities, its use for treating elevated fibrinogen makes garlic even more useful for prevention or treatment of CVD.

Bromelain

Bromelain includes a grouping of sulfhydryl proteolytic enzymes obtained from the pineapple plant (Ananas comosus). Bromelain is typically derived from either the fruit or stem of the plant, with most commercial sources being derived from the stem. In addition to a proteolytic portion, bromelain contains peroxidase, acid phosphatase, and protease inhibitors. It is interesting to note that the purified proteolytic fraction has been shown to be physiologically inactive whereas whole bromelain extract inhibits platelet aggregation, and also has fibrinolytic activity, anti-inflammatory activity, and cytokine modulation effects as well as producing mucolytic effects and cardiovascular and circulatory improvements.[74]

The fibrinolytic activity of bromelain is thought to be the result of the conversion of plasminogen to plasmin, limiting the coagulation cascade by degrading fibrin.[75] Bromelain acts as a more efficient fibrinolytic in vitro compared to in vivo, possibly because of the antiprotease compounds found in plasma.[52] Bromelain produces dose-dependent decrease in serum fibrinogen, and at higher concentrations, prothrombin and activated partial thromboplastin time are prolonged.[76]

HOMOCYSTEINE

Associated with increased risk of cardiovascular disease, elevated plasma levels of the amino acid homocysteine are affected by genetic, physiologic, and nutritional factors. Increased homocysteine levels are considered to be, collectively, an independent predictor for atherosclerosis and thromboembolism and are correlated with significant risk of coronary artery disease, myocardial infarction, peripheral vascular occlusive disease, cerebral vascular occlusive disease, and retinal vascular disease.[77] Research has also shown that elevated homocysteine is associated with an increase risk of developing Alzheimer's disease, cognitive impairment, pregnancy complications, and osteoporosis.[78] The association between homocysteinemia and CVD is causal, because an increase in plasma homocysteine precedes the onset of cardiovascular disease.[79] Desirable plasma levels are below 10 mmol=L. The plasma concentration ranges for mild, moderate, and severe homocysteinemia are, respectively 15–25; 25–50; and 50–500 mmol=L. Homocysteine can be elevated in the absence of an increased mean corpuscular volume (MCV), if a patient presents with a MCV above 92 (range 80–100) and there is a family or personal history of osteoporosis, Alzheimer's, or heart disease, testing is essential. In preventive medicine practice, homocysteine testing is routine screening.

B Vitamins

Nutritional factors that can mitigate elevated homocysteine levels include vitamins B_{12}, B_6, B_2, and folic acid. The presence of these vitamins has been found to be inversely related to plasma homocysteine concentration, thus, combination therapy with these vitamins is an effective way to reduce homocysteine levels.[80] In addition to supplementation, patients are encouraged to consume green leafy vegetables and fruits, all food items that are rich in B vitamins and folate.

Homocysteinemia is a standard laboratory value that is treated similarly by both allopathic and naturopathic physicians, if not more vigorously by naturopathic physicians as a result of their particular view of nutritional status as a generalized health predictor. Patients with homocysteinemia and known coronary artery disease are encouraged to take 1 mg per day of folic acid, 400 mg per day of vitamin B_{12}, and 10 mg per day vitamin of vitamin B_6, but the side effects of this therapy are relatively unknown.[81] In addition, treatment of homocysteinemia also includes a low-methionine diet because homocysteine is an intermediate product of methionine metabolism in the body. Foods that are rich in methionine include cheddar cheese, eggs, chicken, and beef.

DIETARY INTERVENTIONS

Dietary interventions can be an important modality in the treatment of cardiovascular disease. The traditional Mediterranean diet has been shown to benefit individuals with cardiovascular disease. It is characterized by moderate energy intake, low animal fat, high fish intake, high olive oil, high cereals, high legumes, nuts and vegetables, and regular and moderate wine intake. In a recent randomized, controlled, parallel-group clinical trial, 372 subjects at high cardiovascular risk were assigned to a low-fat diet, a traditional Mediterranean diet plus virgin olive oil, or traditional Mediterranean diet plus nuts. After three months, the mean oxidized LDL levels decreased in both Mediterranean diet groups, while no changes in oxidized LDL was seen in the low-fat diet group.[82] Another study examined the effect of the Mediterranean diet in individuals with a high risk of cardiovascular disease on cardiovascular inflammatory markers. The study showed that a higher consumption of fruits and cereals is associated with lower concentrations of IL-6, and the highest consumption of nuts and virgin olive oil showed the lowest concentrations of VCAM-1, ICAM-1, IL-6 and CRP.[83] The Mediterranean diet has also been shown to decrease serum glucose, systolic blood pressure, and the cholesterol:HDL ratio in individuals with high cardiovascular disease risk.[84] A three-month study showed a 15% reduction in cardiovascular disease risk with the Mediterranean diet,[85] while other studies report a 50%–70% reduction of the risk of recurrence in CHD patients after four years of follow-up.[86]

Dietary whole grains have also been associated with decreased cardiovascular risk. Whole-grain foods provide complex carbohydrates, dietary fiber, minerals, vitamins, and antioxidants. Research indicated that whole grain dietary intake decreases the risk of hypertension, myocardial infarction, and heart failure.[87] In one study to evaluate the role of whole grains and atherosclerosis, whole-grain intake was evaluated and carotid intimal medial thickness was measured. Whole-grain intake was shown to be inversely associated with common carotid artery intimal medial thickness and intimal medial thickness progression.[88] A 12-week, randomized, controlled trial compared two whole-grain oat-based cereals with two refined grain wheat-based cereals to evaluate their effects on the need for antihypertensive medications in patients with hypertension. At the end of 12 weeks, 73% of participants in the oats group versus

42% in the wheat group were able to stop their medication or reduce their medication by half. Treatment group participants whose medication was not reduced had substantial decreases in BP. The oats group experienced a 24.2 mg=dL reduction in total cholesterol levels, a 16.2 mg=dL decrease in LDL levels, and a 15.03 mg=dL drop in plasma glucose levels compared to the control group.[89]

Green tea polyphenols, particularly epigallocatechin gallate (EGCG), have been studied for their antioxidant and anti-inflammatory activity. Specific to cardiovascular disease, these catechins have been shown to reduce markers of atherosclerosis and lipid peroxidation, such as oxidized LDL.[90] One study found that green tea consumption was significantly higher in patients without CAD than in those with the disease, and showed an inverse relationship between the intake of green tea and the incidence of CAD.[91] In one double-blind study, green tea extract high in catechins was supplemented to a group of visceral fat-type obesity patients for 12 weeks, after a 2-week run-in period. The results showed a greater decrease in systolic blood pressure in the catechin group for subjects whose initial systolic BP was 130 mmHg or higher compared with the control group. LDL cholesterol was also decreased to a greater extent in the catechin-supplemented group. In addition, a decrease in body weight, body mass index, body fat ratio, body fat mass, waist circumference, hip circumference, visceral fat area, and subcutaneous fat area were found to be greater in the catechin group than in the control group as well.[92]

CONCLUSIONS

Phytochemical treatments for CVDs offer good methods for reducing unfavorable blood-related cardiovascular risk factors. Prevention, probably the best medicine for this grouping of diseases, is a major hurdle for medical practitioners of various types. Natural-based medicines may be used both prior to and following actual clinical diagnosis of heart disease and, with newer cardiovascular risk factors being identified and validated, nutritional treatments can play a major role in reducing these risk factors.

REFERENCES

[1]American Heart Association. Heart Disease and Stroke Statistics—2007 Update. Online document available at: www.americanheart.org=downloadable=heart=1166712318459HS_StatsInsideText.pdf. Accessed October 20, 2007.

[2]Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, Haase N, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell CJ, Roger V, Rumsfeld J, Sorlie P, Steinberger J, Thom T, Wasserthiel-Smoller S, Hong Y; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation. 2007 Feb 6;115(5):e69–171. Epub 2006 Dec 28.

[3]The Expert Panel. Summary of the second report of the national cholesterol education panel (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). JAMA. 1993;269:1421–1426,3015–3023.

[4]Sahi N, Pahlajani DB, Sainani GS. Apolipoproteins A-1 and B as predictors of angiographically assessed coronary artery disease. J Assoc Physicians India. 1993 Nov;41(11):713–715.

[5]Kim HK, Chang SA, Choi EK, Kim YJ, Kim HS, Sohn DW, Oh BH, Lee MM, Park YB, Choi YS. Association between plasma lipids, and apolipoproteins and coronary artery disease: A cross-sectional study in a low-risk Korean population. Int J Cardiol. 2005 Jun 8;101(3):435–440.

[6]Pagana KD, Pagana TJ. Mosby's Manual of Diagnostic and Laboratory Tests. St. Louis: Mosby, 1998.

[7]Satyavati GV. Gugulipid: A promising hypolipidaemic agent from gum guggul. Econ Med Plant Res. 1991;5:48–82.
[8]Urizar NL, Moore DD. Gugulipid: A natural cholesterol-lowering agent. Annu Rev Nutr. 2003;[Epub ahead of print].
[9]Nityanand S, Srivastava JS, Asthana OP. Clinical trials with gugulipid a new hypolipaedemic agent. J Assoc Phys India. 1989;37:321–328.
[10]Singh RB, Niaz MA, Ghosh S. Hypolipidemic and antioxidant effects of Commiphora mukul as an adjunct to dietary therapy in patients with hypercholesterolemia. Cardiovasc Drugs Ther. 1994;8:659–664.
[11]Nityanand S, Srivastava JS, Asthana OP. Clinical trials with gugulipid: A new hypolipidaemic agent. J Assoc Phys India. 1989;37:323–328.
[12]Szapary PO, Wolfe ML, Bloedon LT, Cucchiara AJ, DerMarderosian AH, Cirigliano MD, Rader DJ. Guggulipid for the treatment of hypercholesterolemia: A randomized controlled trial. JAMA. 2003 Aug 13;290(6):765–772.
[13]Pizzorno ME Jr., Murray M. Encyclopedia of Natural Medicine. Rocklin, CA: Prima Publishers, 1998.
[14]Banerjee SK, Maulik SK. Effect of garlic on cardiovascular disorders: A review. Nutr J. 2002;1:4.
[15]Ali M, Thomson M, Afzal M. Garlic and onions: Their effect on eicosanoid metabolism and its clinical relevance. Prostaglandins Leukot Essent Fatty Acids. 2000;62:55–73.
[16]Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia: A meta-analysis of randomized clinical trials. Ann Intern Med. 2000;133:420– 429.
[17]Mader FH. Treatment of hyperlipidaemia with garlic-powder tablets: Evidence from the German Association of General Practitioners' multicentric placebo-controlled double-blind study. Arzneimittelforschung. 1990;40:1111–1116.
[18]Gardner CD, Lawson LD, Block E, Chatterjee LM, Kiazand A, Balise RR, Kraemer HC. Effect of raw garlic vs commercial garlic supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia: A randomized clinical trial. Arch Intern Med. 2007 Feb 26;167(4):346–353.
[19]Yeh YY, Liu L. Cholesterol-lowering effect of garlic extracts and organosulfur compounds: Human and animal studies. J Nutr. 2001;131(suppl.3):989S–993S.
[20]Gupta N, Porter TD. Garlic and garlic-derived compounds inhibit human squalene monooxygenase. J Nutr. 2001;131:1662–1667.
[21]Yeh YY, Yeh SM. Garlic reduces plasma lipids by inhibiting hepatic cholesterol and triacylglycerol synthesis. Lipids. 1994;29:189–193.
[22]Englisch W, Beckers C, Unkauf M, et al. Efficacy of artichoke dry extract in patients with hyperlipoproteinemia. Arzneimittelforschung. 2000;50:260–265.
[23]Gebhardt R. Inhibition of cholesterol biosynthesis in primary cultured rat hepatocytes by artichoke (Cynara scolymus L.) extracts. J Pharmacol Exp Ther. 1998;386:1122–1128.
[24]Shimoda H, Ninomiya K, Nishida N, Yoshino T, Morikawa T, Matsuda H, Yoshikawa M. Anti-hyperlipidemic sesquiterpenes and new sesquiterpene glycosides from the leaves of artichoke (Cynara scolymus L.): Structure requirement and mode of action. Bioorg Med Chem Lett. 2003;13:223–228.
[25]Walker AF, Middleton RW, Petrowicz O. Artichoke leaf extract reduces symptoms of irritable bowel syndrome in a post-marketing surveillance study. Phytother Res. 2001;15:58–61.
[26]Leung AY, Foster S. Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics, 2nd Edition. New York: John Wiley & Sons, 1996.
[27]Divya CS, Pillai MR. Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFkB and AP-1 translocation, and modulation of apoptosis. Mol Carcinog. 2006 May;45(5):320–332.
[28]Asai A, Miyazawa T. Dietary curcuminoids prevent high-fat diet-induced lipid accumulation in rat liver and epididymal adipose tissue. J Nutr. 2001;131:2932–2935.
[29]Wang S, Chen B, Sun C. Regulation effect of curcumin on blood lipids and antioxidation in hyperlipidemia rats [in Chinese]. Wei Sheng Yan Jiu. 2000;29:240–242.
[30]Qureshi AA, Qureshi N, Wright JJ, Shen Z, Kramer G, Gapor A, Chong YH, DeWitt G, Ong A, Peterson DM, et al. Lowering of serum cholesterol in hypercholesterolemic humans by tocotrienols (palmvitee). Am J Clin Nutr. 1991 Apr;53(4 suppl):1021S–1026S.
[31]Parker RA, Pearce BC, Clark RW, Gordon DA, Wright JJ. Tocotrienols regulate cholesterol production in mammalian cells by post-transcriptional suppression of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. J Biol Chem. 1993;268:11230–11238.
[32]Rasool A.h.g, Yuen KH, Yusoff K, Wong AR, Rahman AR. Dose dependent elevation of plasma tocotrienol levels and its effect on arterial compliance, plasma total antioxidant status, and lipid profile in healthy humans supplemented with tocotrienol rich vitamin E. J Nutr Sci Vitaminol. 2006;52:473– 478.
[33]Heber D, Yip I, Ashley JM, Elashoff DA, Elashoff RM, Go VL. Cholesterol-lowering effects of a proprietary Chinese red-yeast-rice dietary supplement. Am J Clin Nutr. 1999 Feb;69(2):231–236.

[34]Squires RW, Allison TG, Gau GT, Miller TD, Kottke BA. Low-dose, time-release nicotinic acid: effects in selected patients with low concentrations of high-density lipoprotein cholesterol. Mayo Clin Proc. 1992 Sep;67(9):855–860.

[35]Birjmohun RS, Kastelein JJ, Poldermans D, Stroes ES, Hostalek U, Assmann G. Safety and tolerability of prolonged-release nicotinic acid in statin-treated patients. Curr Med Res Opin. 2007 Jul;23(7):1707–1713.

[36]Morgan JM, Carey CM, Lincoff A, Capuzzi DM. The effects of niacin on lipoprotein subclass distribution. Prev Cardiol. 2004 Fall;7(4):182–187.

[37]Kuvin JT, Dave DM, Sliney KA, Mooney P, Patel AR, Kimmelstiel CD, Karas RH. Effects of extended-release niacin on lipoprotein particle size, distribution, and inflammatory markers in patients with coronary artery disease. Am J Cardiol. 2006 Sep 15;98(6):743–745. Epub 2006 Jul 26.

[38]Thoenes M, Oguchi A, Nagamia S, Vaccari CS, Hammoud R, Umpierrez GE, Khan BV. The effects of extended-release niacin on carotid intimal media thickness, endothelial function and inflammatory markers in patients with the metabolic syndrome. Int J Clin Pract. 2007 Nov;61(11):1942–1948.

[39]Garg R, Malinow M, Pettinger M, Upson B, Hunninghake D. Niacin treatment increases plasma homocyst(e)ine levels. Am Heart J. 1999 Dec;138(6 Pt 1):1082–1087.

[40]Brook JG, Linn S, Aviram M. Dietary soya lecithin decreases plama triglyceride levels and inhibits collagen- and ADP- induced platelet aggregation. Biochem Med Metabol Biol. 1986;35;31–39.

[41]Wojcicki J. Clinical evaluation of lecithin as a lipid-lowering agent. Phytotherapy Res. 1995;9:597–599.

[42]Schwalfenberg G. Omega-3 fatty acids: their beneficial role in cardiovascular health. Can Fam Physician. 2006 Jun;52:734–740.

[43]McKenney JM, Sica D. Role of prescription omega-3 fatty acids in the treatment of hypertriglyceridemia. Pharmacotherapy. 2007 May;27(5):715–728.

[44]Anon. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999 Aug 7;354(9177):447–455.

[45]Verboom CN; Critical Analysis of GISSI-Prevenzione Trial. Highly purified omega-3 polyunsaturated fatty acids are effective as adjunct therapy for secondary prevention of myocardial infarction. Herz. 2006 Dec;31(suppl 3):49–59.

[46]Kelley DS, Siegel D, Vemuri M, Mackey BE. Docosahexaenoic acid supplementation improves fasting and postprandial lipid profiles in hypertriglyceridemic men. Am J Clin Nutr. 2007 Aug;86(2):324–333.

[47]Schwellenbach LJ, Olson KL, McConnell KJ, Stolcpart RS, Nash JD, Merenich JA; Clinical Pharmacy Cardiac Risk Service Study Group. The triglyceride-lowering effects of a modest dose of docosahexaenoic acid alone versus in combination with low dose eicosapentaenoic acid in patients with coronary artery disease and elevated triglycerides. J Am Coll Nutr. 2006 Dec;25(6):480–485.

[48]Saito M, Ishimitsu T, Minami J, Ono H, Ohrui M, Matsuoka H. Relations of plasma high-sensitivity C-reactive protein to traditional cardiovascular risk factors. Atherosclerosis. 2003;167:73–79.

[49]Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. N Engl J Med. 2005 Jan 6;352(1):20–28.

[50]Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, Orazem J, Magorien RD, O'Shaughnessy C, Ganz P; Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005 Jan 6;352(1):29–38.

[51]Koenig W. Fibrin(ogen) in cardiovascular disease: An update. Thromb Haemost. 2003;89:601–609.

[52]Canseco-Avila LM, Jerjes-Sánchez C, Ortiz-López R, Rojas-Martínez A, Guzmán-Ramírez D. [Fibrinogen. Cardiovascular risk factor or marker?] Arch Cardiol Mex. 2006 Oct-Dec;76(suppl 4):S158–S172.

[53]Morrow DA, Ridker PM. C-reactive protein, inflammation, and coronary risk. Med Clin North Am. 2000;84:149–161.

[54]Hager K, Felicetti M, Seefried G, Platt D. Fibrinogen and aging. Aging (Milano). 1994 Apr;6(2): 133–138.

[55]Clays E, De Bacquer D, Delanghe J, Kittel F, Van Renterghem L, De Backer G. Associations between dimensions of job stress and biomarkers of inflammation and infection. J Occup Environ Med. 2005 Sep;47(9):878–883.

[56]Heinrich J, Balleisen L, Schulte H, Assmann G, van de Loo J. Fibrinogen and factor VII in the prediction of coronary risk. Results from the PROCAM study in healthy men. Arterioscler Thromb. 1994 Jan;14(1): 54–59.

[57]Urano T, Ihara H, Umemura K, Suzuki Y, Oike M, Akita S, Tsukamoto Y, Suzuki I, Takada A. The profibrinolytic enzyme subtilisin NAT purified from Bacillus subtilis Cleaves and inactivates plasminogen activator inhibitor type 1. J Biol Chem. 2001 Jul 6;276(27):24690–24696. Epub 2001 Apr 26.

[58]Fujita M, Hong K, Ito Y, Fujii R, Kariya K, Nishimuro S. Thrombolytic effect of nattokinase on a chemically induced thrombosis model in rat. Biol Pharm Bull. 1995 Oct;18(10):1387–1391.
[59]Suzuki Y, Kondo K, Ichise H, Tsukamoto Y, Urano T, Umemura K. Dietary supplementation with fermented soybeans suppresses intimal thickening. Nutrition. 2003 Mar;19(3):261–264.
[60]Suzuki Y, Kondo K, Matsumoto Y, Zhao BQ, Otsuguro K, Maeda T, Tsukamoto Y, Urano T, Umemura K. Dietary supplementation of fermented soybean, natto, suppresses intimal thickening and modulates the lysis of mural thrombi after endothelial injury in rat femoral artery. Life Sci. 2003 Jul 25;73(10):1289–1298.
[61]Mazzone A, Catalani M, Costanzo M, Drusian A, Mandoli A, Russo S, Guarini E, Vesperini G. Evaluation of Serratia peptidase in acute or chronic inflammation of otorhinolaryngology pathology: A multicentre, double-blind, randomized trial versus placebo. J Int Med Res. 1990 Sep–Oct;18(5):379–388.
[62]Madsen T, Skou HA, Hansen VE, Fog L, Christensen JH, Toft E, Schmidt EB. C-reactive protein, dietary n-3 fatty acids, and the extent of coronary artery disease. Am J Cardiol. 2001;88:1139–1142.
[63]Adam O, Beringer C, Kless T, Lemmen C, Adam A, Wiseman M, Adam P, Klimmek R, Forth W. Anti-inflammatory effects of a low arachidonic acid diet and fish oil in patients with rheumatoid arthritis. Rheumatol Int. 2003;23:27–36.
[64]Jialal I, Devaraj S, Venugopal SK. Oxidative stress, inflammation, and diabetic vasculopathies: The role of a-tocopherol therapy. Free Radic Res. 2002;36:1331–1336.
[65]Devaraj S, Jialal I. a-Tocopherol supplementation decreases serum C-reactive protein and monocyte interleukin-6 levels in normal volunteers and type 2 diabetic patients. Free Radic Biol Med. 2000;29: 790–792.
[66]Dieber-Rotheneder M, Puhl H, Waeg G. Effect of oral supplementation with D-a-tocopherol on the vitamin E content of human low density lipoproteins and resistance to oxidation. J Lipid Res. 1991;32:1325–1332.
[67]Upritchard JE, Sutherland WH, Mann JI. Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. Diabetes Care. 2000;23:733–738.
[68]Kappus H, Diplock AT. Tolerance and safety of vitamin E: A toxicological position report. Free Radic Biol Med. 1992;13:55–74.
[69]Huang HY, Appel LJ. Supplementation of diets with alpha-tocopherol reduces serum concentrations of gamma- and delta-tocopherol in humans. J Nutr. 2003 Oct;133(10):3137–3140.
[70]Saldeen T, Li D, Mehta JL. Differential effects of alpha- and gamma-tocopherol on low-density lipoprotein oxidation, superoxide activity, platelet aggregation and arterial thrombogenesis. J Am Coll Cardiol. 1999 Oct;34(4):1208–1215.
[71]Liu M, Wallmon A, Olsson-Mortlock C, Wallin R, Saldeen T. Mixed tocopherols inhibit platelet aggregation in humans: Potential mechanisms. Am J Clin Nutr. 2003 Mar;77(3):700–706.
[72]Steiner M, Li W. Aged garlic extract, a modulator of cardiovascular risk factors: A dose-finding study on the effects of AGE on platelet functions. J Nutr. 2001;131(suppl. 3):980S–984S.
[73]Steiner M, Lin RS. Changes in platelet function and susceptibility of lipoproteins to oxidation associated with administration of aged garlic extract. J Cardiovasc Pharmacol. 1998;31:904–908.
[74]Kelly, GS. Bromelain: A literature review and discussion of [sic] its therapeutic applications. Alt Med Rev. 1996;1:243–257.
[75]De-Giuli M, Pirotta F. Bromelain: Interaction with some protease inhibitors and rabbit specific antiserum. Drugs Exp Clin Res. 1978;4:21–23.
[76]Livio M, Bertoni MP, De Gaetano G. Effect of bromelain on fibrinogen level, prothrombin complex factors and platelet aggregation in the rat—a preliminary report. Drugs Exp Clin Res. 1978;4:49–53.
[77]Miller AL, Kelly GS. Homocysteine metabolism: Nutritional modulation and impact on health and disease. Altern Med Rev. 1997;2:234–254.
[78]Herrmann W. Significance of hyperhomocysteinemia. Clin Lab. 2006;52(7–8):367–374.
[79]Graham IM, O'Callaghan P. Vitamins, homocysteine and cardiovascular risk. Cardiovasc Drugs Ther. 2002;16:383–389.
[80]Krishnaswamy K, Lakshmi AV. Role of nutritional supplementation in reducing the levels of homocysteine. J Assoc Physicians India. 2002;50(suppl.):36– 42.
[81]O'Connor JJ, Meurer LN. Should patients with coronary disease and high homocysteine take folic acid? J Fam Pract. 2003;52:16–18.
[82]Fitó M, Guxens M, Corella D, Sáez G, Estruch R, de la Torre R, Francés F, Cabezas C, López-Sabater Mdel C, Marrugat J, García-Arellano A, Arós F, Ruiz-Gutierrez V, Ros E, Salas-Salvadó J, Fiol M, Solá R, Covas MI; for the PREDIMED Study Investigators. Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. Arch Intern Med. 2007 Jun 11;167(11):1195–1203.
[83]Salas-Salvadó J, Garcia-Arellano A, Estruch R, Marquez-Sandoval F, Corella D, Fiol M, Gómez-Gracia E, Viñoles E, Arós F, Herrera C, Lahoz C, Lapetra J, Perona JS, Muñoz-Aguado D, Martínez-González MA, Ros

E. Components of the mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease. Eur J Clin Nutr. 2007 Apr 18;[Epub ahead of print].

[84]Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gómez-Gracia E, López-Sabater MC, Vinyoles E, Arós F, Conde M, Lahoz C, Lapetra J, Sáez G, Ros E; PREDIMED Study Investigators. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. Ann Intern Med. 2006 Jul 4;145(1):1–11.

[85]Vincent-Baudry S, Defoort C, Gerber M, Bernard MC, Verger P, Helal O, Portugal H, Planells R, Grolier P, Amiot-Carlin MJ, Vague P, Lairon D. The Medi-RIVAGE study: reduction of cardiovascular disease risk factors after a 3-mo intervention with a Mediterranean-type diet or a low-fat diet. Am J Clin Nutr. 2005 Nov;82(5):964–971.

[86]de Lorgeril M, Salen P. The Mediterranean-style diet for the prevention of cardiovascular diseases. Public Health Nutr. 2006 Feb;9(1A):118–123.

[87]Djoussé L, Gaziano JM. Breakfast cereals and risk of heart failure in the physicians' health study I. Arch Intern Med. 2007 Oct 22;167(19):2080–2085.

[88]Mellen PB, Liese AD, Tooze JA, Vitolins MZ, Wagenknecht LE, Herrington DM. Whole-grain intake and carotid artery atherosclerosis in a multiethnic cohort: The Insulin Resistance Atherosclerosis Study. Am J Clin Nutr. 2007 Jun;85(6):1495–1502.

[89]Pins JJ, Geleva D, Keenan JM, Frazel C, O'Connor PJ, Cherney LM. Do whole-grain oat cereals reduce the need for antihypertensive medications and improve blood pressure control? J Fam Pract. 2002 Apr;51(4): 353–359.

[90]Sung H, Min WK, Lee W, Chun S, Park H, Lee YW, Jang S, Lee DH. The effects of green tea ingestion over four weeks on atherosclerotic markers. Ann Clin Biochem. 2005 Jul;42(Pt 4):292–297.

[91]Sano J, Inami S, Seimiya K, Ohba T, Sakai S, Takano T, Mizuno K. Effects of green tea intake on the development of coronary artery disease. Circ J. 2004 Jul;68(7):665–670.

[92]Nagao T, Hase T, Tokimitsu I. A green tea extract high in catechins reduces body fat and cardiovascular risks in humans. Obesity (Silver Spring). 2007 Jun;15(6):1473–1483.

9

CLEANSING OF THE HUMAN BODY

A Daily Essential Process

Toxic exposure is a fact of modern life and a health risk that is faced on a daily basis by patients regardless of how carefully they attempt to limit environmental sources of exposure. It is important to also look within the body to understand how to control the toxic load that arises from the body's inability to process and eliminate toxic substances. This is also relevant to the body's creation of toxins resulting from metabolic processes. This chapter reviews some common toxic substances and provides an overview of detoxification processes and how they can be supported clinically to maximize the body's healthy functioning and confer optimal protection.

What, exactly, qualifies as a ''toxin''? A toxin is a substance that has a detrimental effect on the functioning or structure of a living cell, with deleterious effects ranging from minimal to fatal to a host organism. Although there are tens of thousands of toxic substances that affect the human body adversely, they can be categorized into the following five general groups: (1) toxic chemicals, (2) endotoxins and exotoxins, (3) heavy metals, (4) dietary breakdown products, and (5) products of altered metabolic homeostasis.

ENVIRONMENTAL CHEMICALS

Environmental chemicals include, but are not limited to, prescription, over-the-counter, and illegal drugs; cigarette smoke; solvents; alcohol; pesticides; herbicides; and food additives (see Table 9–1 on page 107). One needs only to visit a suburban neighborhood or home to observe the extent to which potentially toxic chemicals permeate people's lives. One finds lush green and weed-free lawns well-fertilized and pest-free gardens, which are the result of using herbicides and pesticides. There are also sparkling homes with the ''fresh scent of clean,'' thanks to the advent of cleaners, grout and tile mildew retardants. And there are shiny vinyl floors still off-gassing in the summer sun and pervasive deodorizing chemicals. These are but a small sample of the total and daily exposure that people in the Western world endure from childhood throughout life. Time spent away from home means additional exposures in classrooms, offices, grocery stores, and cars.

MICROBIAL TOXINS

Toxic amines, carcinogenic substances, and other health-damaging chemicals are produced by microbes within the human body and by pathogens in the human environment. Microbe-derived toxic loads can arise from consumption of contaminated foods or from disturbances in microflora in the gastrointestinal (GI) tract and elsewhere in the body. Besides botulism and salmonella, more subtle toxic loads can result from GI bacterial imbalances. Such disturbances may cause direct toxin production, but equally significant are disruptions of metabolic

Table 9–1. Common Environmental Chemicals

Chemical Constituents	Modern-day Environmental Sources of Toxins	Effect in Body
Phthalates	Plastics, plastic bottles, plastic wrap	Mimics hormones
Polychlorinated biphenyls (PCBs)	Contaminated fish	Cancer, negative effects in cognitive function, and thyroid disruption
Heavy metals	Dental amalgams, fish, water	Many neurological disorders and autoimmune diseases
Volatile organic compounds	Water, cleaning products, paint	Cancer, memory problems
Dioxins	Animal fat	Cancer, reproductive disorders
Chlorine	Household cleaners, contaminated air or water	Respiratory conditions, skin irritation
Parabens	Preservative in cosmetics, industrial products	Estrogenic activity
Artificial coloring, flavoring, sweeteners, preservatives	Processed foods	Cancer, nervous system disorders

processes that normally occur with the proper functioning and maintenance of ''friendly'' flora. Antibiotic use and imbalances caused by fecal-oral contamination may increase the potential toxic burden. Research indicates that bacteria found in the stomach with low stomach acid, as found with acid-blocking therapies, induces the production of N-nitroso compounds, similar to carcinogenic nitrosamines known to contribute to gastric cancer.[1] Additionally, mycotoxins, such as aflatoxin, are toxic metabolites produced by certain fungi in or on foods and feeds, and are converted to potent carcinogen metabolites via phase 1 enzymes. It is believed that supporting phase 2 detoxification may protect against the carcinogenicity of aflatoxin metabolites.

DIETARY BREAKDOWN PRODUCTS

Toxic breakdown products of protein metabolism include urea and ammonia. The old saying ''input equals output'' can be mirrored with the saying that ''output equals input.'' The breakdown processes that fuel the body by breaking down food yield toxic metabolic byproducts. Thus, it is important for patients to maintain a balanced diet and avoid excess that can strain biochemical pathways and provide extra demands on already challenged detoxification processes. Many labs are now providing testing to evaluate functional capacity of detoxification pathways as well as organic acids for cellular energy production.

Identifying and compensating for toxic exposure can minimize the detrimental effects of the exposure.

HEAVY METALS

Aluminum, arsenic, cadmium, lead, mercury, nickel, and other heavy metals abound in the human environment, where they are found in pesticides, cooking utensils, paint, tin cans, solder, cigarettes, dental fillings, contaminated fish, some cosmetics and antacids, and industrial products and by-products. Battery makers, gas station attendants, agricultural workers, printers, jewelers, and dentists, for example, face increased heavy-metal exposure risks.

Products of Altered Metabolic Homeostasis

Physiologic, psychologic, and pathologic stressors may interfere with metabolic homeostasis and cause excess toxic burdens. Numerous disease processes and stressors can result in dysfunction of normally functioning, sufficient pathways. Oxidative, physiologic, and psychologic stressors can contribute to such impairments. Such stressors can result in direct increases in free-radical production as a result of altered biochemical pathways shunted to cope with such stressors. As a consequence of these altered biochemical pathways, over the course of time, disease processes can take hold within the body. These disease processes can also have devastating consequences, such as those that arise from diabetes mellitus, including glycosylation of proteins and accumulation of sorbitol. Advanced glycosylation endproducts (AGEs) can be ingested in the diet generally in the form of foods undergoing prolonged heating, particularly fats, meat and meat-substitutes, and broiled foods.[2] Studies show that serum AGE cross-linking is significantly increased after ingestion of an AGE-containing meal.[3] Animal studies also indicate that high-fat diets are correlated with obesity, tissue damage, and increased levels of AGEs.[4] Physiological reactions involving AGEs have been implicated in the pathology of numerous diseases, such as diabetes and cardiovascular disease; they place a significant burden on detoxification pathways and contribute to the total toxic load of an individual.

CONTROLLING TOXIC RISK

Wellness is the state of existence that arises when health-sustaining homeostatic balance is gained and maintained. Individual and cumulative toxic exposures threaten this optimal homeostatic state. However, identifying and compensating for toxic exposure can minimize the detrimental effects of the exposure. General signs, symptoms, and risks that may indicate the presence of a high risk for toxic load include diabetes; congestive heart failure; obesity; history of alcohol abuse; psoriasis and other skin disorders; heavy exposure to industrial or household chemicals; frequent or recurrent use of medications; use of hormonal therapy, including hormone replacements and oral contraceptives; and disease states that alter liver, kidney, or GI functioning. Also, due to the sensitivity of the immune system, immunologic disorders may also be seen with toxic exposures such as autoimmune diseases, immune suppression, and chronic inflammation. The review below of the mechanisms of some of the most important protective and detoxifying pathways offers insights into how best to cope with and accommodate toxic burden risk factors, and how to intervene naturally.[5,6]

DETOXIFYING PROCESSES

The body processes toxic substances in two fundamental ways: (1) by excreting or eliminating them; or (2) by neutralizing them. Excretion and elimination occur primarily via

Table 9–2. Detoxification Pathway Dysfunctions

Dysfunction	Symptoms
Phase 1	Can sleep after consuming 16 ounces of caffeinated beverage
Phase 1—overactive	
Phase 1—underactive	Small amount of caffeine causes insomnia, and perfumes and chemical smells make one ill
Phase 2	
Phase 2—underactive amino acid conjugation	Toxemia in pregnancy; gastrointestinal toxicity
Glucuronidation	Yellow eyes (non-hepatitis-related)[a]; Gilbert's syndrome
Glutathione conjugation	Chronic exposure to toxins
Sulfation	Gastrointestinal toxicity, including gastroenteritis, irritable bowels, or enterocyte damage
Sulfoxidation	Poor response to sulfites, found in salads from salad bars and in commercially prepared potato salad; reactive airways upon eating out; garlic intolerance; asparagus causes urine odor

From ref. 11.

[a]Any patient who presents with yellow eyes must be evaluated to rule out more serious liver disorders.

the urine (kidneys) and feces (liver and intestines). The skin and lungs provide ancillary support for these processes. Neutralization occurs via a series of complex processes by which toxic chemicals are metabolized to either inert or more readily excreted substances until elimination occurs. When detoxification pathways fail, toxins may accumulate in body tissues, most frequently in fat tissue. This situation emphasizes the importance of nutrient support for antioxidant functioning and detoxification processes for any patient who is experiencing rapid weight loss, when that patient's fat tissues release their toxic loads.

The Liver

The liver is, without question, the leading detoxification organ. On the macroscopic level, the liver filters 2 liters of blood per minute, filtering out large toxins. The liver synthesizes bile and cholesterol that help to bind fat-soluble toxins for excretion. On the microscopic level, this organ neutralizes chemical substances metabolically.

Microscopic-level functions include:

Filtration—The liver filters blood that arrives directly from the intestines. Under ideal circumstances, the liver eliminates 99% of bacteria and other toxins successfully before the blood enters the general circulation. This filtration minimizes the passage of endotoxins, antigen-antibody complexes, certain foreign proteins, and numerous chemicals into the circulatory system.

Bile—Every day, the liver produces and secretes 1 quart of bile that serves as the vehicle by which fat-soluble toxic substances enter the bowel, become bound by dietary fiber, and are eliminated. Insufficient fiber within the bowel or elevated beta-glucuronidase from bacterial

overgrowth, however, can result in reabsorption and thus increase total toxic burden as a result of adding the reabsorbed load to the toxic load generated each day.

On the microscopic level, toxins are neutralized. The enzymes involved in the neutralizing process function in two distinctive phases. Phase 1 of the process modifies toxic substances to facilitate the conjugation reactions these chemicals undergo during phase 2 detoxification. Chemical compounds that are neutralized include drugs, pesticides, hormones, inflammatory chemicals, and toxins absorbed from the intestinal tract. Phase 1 detoxification generates more chemically active substances, which, in turn, require proper functioning of phase 2 detoxification to eliminate these metabolic intermediates.

PHASE 1 DETOXIFICATION

In general, phase 1 detoxification arises from the function of a group of some 50–100 enzymes referred to as cytochrome P450. The healthy functioning of this pathway depends upon an individual's nutritional status, genetics, and level of exposure to chemical toxins. Thus, an individual's risks of developing disease states arising from insufficient detoxification varies greatly. Indeed, this can explain the great variability in patients' susceptibility to, and manifestation of, disease processes such as cancer from environmental pollutants, such as smoking.

Clinical evaluation of a patient's risk entails a twofold consideration: (1) that of total toxin load and (2) that of his or her ability to process the exposure. Phase 1 detoxification becomes less active with aging. Complicating this decreased function is that blood flow through the liver also diminishes with age. Not surprisingly, there is an increased susceptibility to adverse drug reactions among older adults, whose detoxification capabilities have diminished. Studies have shown a fivefold variability of phase 1 functioning among healthy individuals.[7] In light of this range of activity, there is also a significant oscillating need for antioxidant protection, because each toxin that is processed via phase 1 detoxification generates a free radical that either requires quenching or neutralization by phase 2 conjugation. Thus, phase 1 and phase 2 processing must be kept in balance to prevent the accumulation of highly reactive intermediates and to minimize the requirement for antioxidants to protect against free radicals. Many drugs, foods, nutrients, and chemicals can cause phase 1 and phase 2 detoxification processes to become desynchronized. Factors that affect the efficiency of phase 1 and phase 2 detoxification processes are summarized in Table 9–3.

There are clearly numerous substances that both affect induction and inhibition of these pathways positively and negatively.

When grapefruit or grapefruit juice rich in naringenin is consumed while a patient is taking certain medications, there can be potentially serious deleterious consequences; for example, this could happen in the case of nifedipine.[8]

PHASE 2 DETOXIFICATION

Phase 2 detoxification can be broken down into well-defined detoxification pathways, each with unique abilities for addressing certain toxin categories. Phase 2 detoxification occurs principally via the pathways of acetylation, amino acid conjugation, glucuronidation, glutathione conjugation, methylation, sulfation, and sulfoxidation.

Table 9–3. Phase 1 and Phase 2 Detoxification Modulators[a]

	Phase 1 Inducers	Phase 2 Inducers	Phase 1 Inhibitors	Phase 2 Inhibitors
Drugs				
Acid blockers			X	
Alcohol	X			
Antihistamines			X	
Ascorbic acid	X			
Benzodiazepines			X	
Birth control pills		X		
Ketoconazole			X	
Nicotine=smoking	X	X		
Nonsteroidal anti-inflammatory drugs				X
Phenobarbital	X	X		
Probenecid				X
Sulfaphenazole			X	
Sulfonamides	X			
Steroids	X			
Foods=herbs=nutrients				
Betaine		X		
Broccoli	X	X		
Brussels sprouts	X	X		
Cabbage	X	X		
Caraway	X	X		
Cayenne (capsaicin)			X	
Charbroiled meat	X			
Choline		X		
Clove oil (eugenol)			X	
Cobalamin (vitamin B_{12})		X		
Cobalamin (vitamin B_{12}) deficiency				X
Curcumin (turmeric; Curcuma longa)		X	X	
Cysteine		X		
Dill	X	X		
Fish oil		X		
Folic acid		X		
Folic acid deficiency				X
Glycine		X		
Glutathione deficiency				X
Grapefruit juice			X	
Limonene (peels)	X	X		
Methionine		X		
Molybdenum deficiency				X
N-acetylcysteine			X	
Niacin (vitamin B_3)	X			
Oranges	X			
Pantothenic acid deficiency				X
Protein (high)	X			
Protein (low)				X

(continued)

Table 9–3. (continued)

	Phase 1 Inducers	Phase 2 Inducers	Phase 1 Inhibitors	Phase 2 Inhibitors
Riboflavin (vitamin B_2)	X			
Riboflavin (vitamin B_2) deficiency				X
Selenium deficiency				X
St. John's wort (Hypericum perforatum)	X			
Tangerines	X			
Taurine		X		
Vitamin C	X			
Vitamin C deficiency				X
Zinc deficiency				X
Chemical toxins				
Air pollutants	X			
Carbon tetrachloride	X			
Dioxin	X			
Endotoxins=exotoxins			X	
Herbicides	X			
Pesticides	X			
Solvent fumes	X			
Tartrazine				X

From refs. 4,13,14; and Nagabhushan M, et al. Curcumin as an inhibitor of cancer. J Am Coll Nutr. 1992;11:192–198.
[a]Note: Because of the complexity of phase 2 detoxification, the induction and inhibition substances listed above have not been broken down to the individual pathways within the phase 2 system; instead, they are reported in a generalized format.

Many disease states have been correlated with suboptimal functioning of an amino acid conjugation pathway.

ACETYLATION

Conjugation of toxins with acetyl coenzyme A promotes the elimination of sulfa drugs. Acetylation is dependent upon pantothenic acid, thiamine, and vitamin C. Consumption of B-vitamin-rich foods, such as whole grains and yeast, and of vitamin-C-abundant sources, such as citrus fruits, cabbage, and peppers, can support this pathway.[9]

AMINO ACID CONJUGATION

Numerous amino acids, including, but not limited to, arginine, glutamine, glycine, ornithine, and taurine, combine with toxins and neutralize them. Glycine is most commonly involved in phase 2 detoxification. Many disease states have been correlated with suboptimal functioning

of an amino acid conjugation pathway. These disease states include alcoholic liver disease, arthritis, cancers, hepatitis, hypothyroidism, eclampsia, and chemical overload. Low-protein diets can result in lowered efficacy of this detoxification system.

GLUCURONIDATION

Glucuronidation, involving the incorporation of glucuronic acid with toxins, helps to detoxify the body of numerous drugs, aspirin, menthol, synthetic vanilla, benzoates and other food additives, and some hormones. Gilbert's disease affects 1 in 20 individuals and results in fasting serum bilirubin levels in the range of 1.2–3.0 mg=dL. Bilirubin is metabolized by the conjugating biotransformation enzyme UDP-glucuronosyltransferase (UGT) 1A1. Consumption of S-adenylmethionine (SAMe), which fuels glucuronidation, has been shown to help support individuals with this condition.[10] Cruciferous vegetable intake has also been shown to reduce bilirubin concentrations with particular enzyme polymorphisms,[11] possibly due to the sulforaphane found in these vegetables. Also of potential clinical significance is consumption of limonene-rich foods, such as caraway oil, citrus peel, and dill weed seed, to support UDP-glucuronyl transferase, the enzyme required for glucuronidation.

GLUTATHIONE CONJUGATION

This pathway assists in making fat-soluble toxins water-soluble, allowing for excretion via the kidneys. Because this pathway is glutathione-dependent, it is indirectly dependent upon the presence of sufficient cysteine and methionine in the body. Chronic alcohol intake is also strongly associated with increased oxidative stress and decreased glutathione levels.[12] Vitamin C has also been shown to be effective in supporting the maintenance of glutathione levels.[13] Consumption of foods that stimulate glutathione conjugation, such as orange-peel oil, turmeric, artichoke, and dill and caraway seeds, can be recommended therapeutically. If phase 1 detoxification generates excess free radicals, glutathione depletion can occur, thereby preventing or stalling the glutathione-conjugation pathway.

METHYLATION

Methylation involves the conjugation of methyl groups to toxic substances. Primary methyl groups come from SAMe, which requires sufficient methionine, choline, vitamin B_{12}, and folic acid for synthesis. Foods that are rich in these nutrients include whole grains and legumes (sources of vitamin B_6), green leafy vegetables (sources of folic acid), and animal products and yeast (sources of vitamin B_{12}).

SULFATION

Binding sulfur-containing compounds can conjugate potentially toxic steroidal hormones and thyroid hormone, and promote the elimination of neurotransmitters. Diets that are low in protein, and thus low in cysteine and methionine, diminish sulfation. Evidence shows that taking

more than 100 mg per day of vitamin B_6 or consuming excess molybdenum can slow this pathway.[14] Consuming the amino acid taurine and sulfur-rich foods, such as broccoli, Brussels sprouts, egg yolks, garlic, and red peppers, can support sulfation activity.

It is believed that up to 90% of cancer cases arise from the effects of exposure to environmental chemicals.

SULFOXIDATION

The enzyme sulfite oxidase helps to metabolize toxic substances, such as transforming sulfites to sulfate. This detoxification pathway is essential for the elimination of sulfite-containing drug and food substances. Sources of sulfites include certain processed foods, such as commercial potato salad, dried fruits, salad commonly found at salad bars, and certain drugs, such as some medicines for asthma. This pathway can be supported by molybdenum because sulfite oxidase is dependent upon this trace mineral.[15] Legumes and whole grains are typically high in molybdenum as long as they are grown in soil that is replete with trace minerals.

SUPPORTING DETOXIFICATION WITHIN THE BODY

Using this overview and framework of principal mechanisms of liver detoxification, it is wise to focus on essentials for therapeutic intervention, ensuring that the proper balance between phases 1 and 2 detoxification stages is maintained. It is believed that up to 90% of cancer cases arise from the effects of exposure to environmental chemicals, such as those found in air pollution, tobacco, chemically contaminated food, and antimetabolites that deplete nutrients that are essential for proper detoxifyication.[16,17] Therefore, choosing nutrients and botanical medicines to support detoxification can improve quality of life, alleviate acute signs and symptoms of excess toxic load, and confer protection over the course of a patient's life. The next sections cover key botanicals, nutrients, and dietary constituents that represent potential clinical interventions for treating acute or chronic cases of toxicity, depending on each patient's condition.

BOTANICALS

Curcumin

This common herb, used frequently in the form of turmeric (Curcuma longa), has antioxidant and anti-inflammatory properties. Curcumin has been shown to help inhibit the carcinogenic effects of benzopyrene that arise from the consumption of charbroiled meat. This herb has been shown to modulate phase 1 detoxification while inducing phase 2 of the process. When 1.5 g of turmeric was given to 16 smokers and 6 nonsmokers (control subjects), it was shown that, after 30 days of consuming turmeric, urinary excretion of mutagens in smokers was nearly equivalent to that of nonsmokers. This study demonstrated that turmeric is an effective inhibitor of phase 1 detoxification, preventing the excess accumulation of toxic metabolite conversion of

smoke by-products, which have been linked as major contributors to increased risks of cancer development.[18]

Milk Thistle

Silymarin, an extract of milk thistle (Silybum marianum), is particularly renowned for its antioxidant and hepatoprotective effects. When toxic exposures and burdens are elevated, it is vital to pay special attention to supporting and protecting the liver as it detoxifies the body. This herb's antioxidant effects have been reported to be several times greater than those of vitamin C or vitamin E. Silymarin also helps to support detoxification by preventing glutathione depletion. Research has shown that silymarin can increase glutathione levels by more than 35%. Silymarin has increased the reduced form of glutathione (GSH) in the liver by more than 35% and by more than 50% in rats.[19]

Other Herbs

There are numerous other herbs that can provide meaningful support for liver detoxification, including:

Green tea (Camellia sinensis): enhances hepatic phase 2 detoxifying enzyme activity.[20]
Schisandra (Schisandra chinensis): increases hepatic glutathione, glucose-6-phosphate, and glutathione-reductase activity; induces phase 1 enzymes.[21,22]

DIETARY APPROACHES

Fiber, indole, ellagic acids, and limonene, found in foods, also help to support detoxification.

Fiber

Sufficient fiber consumption can support detoxification in several ways. Primarily, fiber binds excreted toxins, helps to limit initial absorption of toxins from the intestines, supports proper bowel transit times, and increases the frequency of bowel movements. The importance of sufficient daily bowel movements cannot be overemphasized; the longer fecal material is retained in the lower colon, the more toxins are absorbed, burdening the entire body. A diet rich in fiber also commonly helps to support healthy intestinal flora, assisting in controlling excess endotoxin production.

> Detoxifying the body of toxic substances
> is a continual process.

Glucosinolates

Members of the Brassica family, such as broccoli, Brussels sprouts, and cabbage, are rich in glucosinolates, including indole-3-carbinol and sulforaphane. This combination supports both phase 1 and phase 2 toxin processing.[23] Thus, these foods have both direct and indirect

anticarcinogenic properties. Sulforaphane is currently studied as a portent anticancer agent. The activity of sulforaphane includes increasing glutathione level, the induction of phase 2 detoxification enzymes, inhibition of carcinogen-activating phase 1 enzymes, induction of apoptosis and cell cycle arrest in cancer cells, and has anti-inflammatory properties as well.[24]

Ellagic Acid and Ellagitannins

Ellagic acid and ellagitannins are constituents found in raspberries, strawberries, blackberries, pomegranates, and walnuts. Ellagic acids have antioxidant, anti-inflammatory, and free-radical scavenging activity. They have also been shown in numerous studies to provide excellent support for phase 2 detoxification.[25]

Limonene

A phytochemical found in oranges, tangerines, and caraway and dill seeds,[26] limonene has anticarcinogenic properties and induces both phase 1 and phase 2 detoxification pathways.

NUTRIENTS

Copper

This ubiquitous mineral is required for phase 1 detoxification. Supplementation is not usually necessary unless a deficiency has been identified, if excess body stores of zinc have been confirmed, or if zinc supplementation has exceeded 30 mg per day for more than a few weeks. Of significance, however, is that copper, in turn, can displace zinc, which also supports detoxification.

Glutathione

This tripeptide, comprised of cysteine, glutamic acid, and glycine, is the most important antioxidant in neutralizing free radicals produced by phase 1 detoxification pathways. Glutathione is also required for phase 2 detoxification. When high toxic loads burden phase 1 detoxification and elevate production of free radicals, increased glutathione may be required to prevent depletion that can lead to a cessation of phase 2 glutathione dependent pathways. Glutathione is available via diet or supplementation. Dietary sources include fresh fruits and vegetables (e.g., asparagus, avocados, walnuts) and cooked meat and fish. Glutathione supplementation has shown variable and sometimes negligible effects in increasing blood levels of this tripeptide. However, vitamin C, alpha-lipoic acid, glycine, methionine, and N-acetyl-cysteine (NAC) support glutathione synthesis. It appears that vitamin C and NAC have maximal effects. In a case study of supplementation therapy for an individual with an inherited glutathione deficiency, either 3,000 mg of vitamin C per day or 800 mg of NAC were given to the patient for one to two weeks. Vitamin C supplementation increased GSH in red blood cells fourfold and plasma GSH eightfold. NAC increased GSH in white blood cells 3.5-fold and was increased in plasma two- to fivefold.[27] In addition, whey protein concentrate supplementation has been shown to significantly increase glutathione levels with a dose-dependent response. In one study, 45 g per day of whey protein concentrate for two weeks increased lymphocyte glutathione by 24%.[28]

Magnesium

Deficiency of magnesium prevents proper phase 1 detoxification and leads to increased toxicity risks for people who are taking numerous medications.

Methionine

Methionine plays a pivotal role in helping to ensure proper phase 2 detoxification. When toxic load increases, methionine is also converted to cysteine and glutathione to support maximal detoxification. Being that methionine can feed the pathway that results in excess homocysteine generation, other approaches should be implemented first, unless supplemented with adequate levels of methyl groups via folate, betaine, and methylcobalamin to enhance the conversion of homocysteine to cysteine. If methionine is used, monitoring homocysteine levels is warranted.

N-Acetyl-cysteine

A rich source of sulfur in the form of cysteine, NAC helps to support glutathione-dependent detoxification. (See the previous section, ''Glutathione.'')

Vitamin C

Essential for phase 1 detoxification, vitamin C, a potent water-soluble antioxidant, helps to quench free-radical damage and helps to fuel glutathione preservation. (See the previous section, ''Glutathione.'')

Zinc

Crucial for phase 1 detoxification, this multifaceted mineral has both antioxidant and immune-supportive effects. Supplementation with zinc seems to be warranted for numerous reasons, and long-term use would be particularly significant in male patients because zinc helps to inhibit the 5-alpha-reductase conversion of testosterone to dihydrotestosterone.

Other Therapeutic Supplements

The elements mentioned previously are merely representative of numerous potential interventions; others worth consideration include choline, inositol, dandelion (Taraxacum officinale), artichoke, beet greens, selenium, B vitamins, and numerous amino acids.

SYMPTOMS THAT SUGGEST DETOXIFICATION IMBALANCE

Numerous tests can be conducted to measure liver detoxification functioning. Measurement of metabolite levels before and after challenges with acetaminophen, caffeine, or other chemicals can provide detailed information about an individual's detoxification functions. Testing for phase 1 and phase 2 enzyme polymorphisms are also available and are able to predict susceptibilities to toxic overload. There are, however, a number of readily observable signs that suggest that an individual may have overactive or underactive detoxification functions. Table 9–2

on page 109 summarizes some of the more commonly noted detoxification pathway dysfunctions and their symptoms.

CONCLUSIONS

Detoxifying the body of toxic substances is a continual process. Yet, the body's detoxification mechanisms can become overwhelmed. Thus, nourishing these protective defenses properly is of paramount importance. Equally important is the active avoidance of undue exposure to minimize total toxic load. Numerous detoxification products are available for supporting a balanced approach to minimizing the likelihood of imbalances in phase 1 or phase 2 detoxification, either via induction or inhibition. Most of these products can also be used in combination with antioxidant support during a fasting routine. Whenever there is weight loss, whether or not this is intentional on the part of a given patient, the released toxins in that patient's body must be quenched. Finally, some toxic exposures cause catastrophic, permanent, and irreversible damage, either immediately or by promoting and inducing a cascade of disease processes. Therefore, the preventively minded clinician can achieve exceptional results when addressing disease processes by searching for and addressing the triggers within the body that have become the disease cascade that manifests as symptoms.

REFERENCES

[1]Calmels S, Béréziat JC, Ohshima H, Bartsch H. Bacterial formation of N-nitroso compounds from administered precursors in the rat stomach after omeprazole-induced achlorhydria. Carcinogenesis. 1991 Mar;12(3):435–439.

[2]Goldberg T, Cai W, Peppa M, Dardaine V, Baliga BS, Uribarri J, Vlassara H. Advanced glycoxidation end products in commonly consumed foods. J Am Diet Assoc. 2004 Aug;104(8):1287–1291.

[3]Koschinsky T, He CJ, Mitsuhashi T, Bucala R, Liu C, Buenting C, Heitmann K, Vlassara H. Orally absorbed reactive glycation products (glycotoxins): An environmental risk factor in diabetic nephropathy. Proc Natl Acad Sci USA. 1997 Jun 10;94(12):6474–6479.

[4]Li SY, Liu Y, Sigmon VK, McCort A, Ren J. High-fat diet enhances visceral advanced glycation end products, nuclear O-Glc-Nac modification, p38 mitogen-activated protein kinase activation and apoptosis. Diabetes Obes Metab. 2005 Jul;7(4):448–454.

[5]Gallagher JE, et al. Comparison of DNA adduct levels in human placenta from polychlorinated biphenyl exposed women and smokers in which CYP 1A1 levels are similarly elevated. Terato Carcino Mutagens. 1994;14:183–192.

[6]Lindstrom K. et al. Occupational solvent exposure and neuropsychiatric disorders. Scan J Work Environ Health. 1984;10:321–323.

[7]Campbell ME, et al. Biotransformation of caffeine, paraxanthine, theophylline and theobromine by polycyclic aromatic hydrocarboninducable cytochrome P-450 in human liver microsomes. Drug Metab Dis. 1987;15:237–249.

[8]Yee GC, et al. Effect of grapefruit juice on blood cyclospor in concentration. Lancet. 1995;345:955–956.

[9]Skvortsova RI, et al. Role of vitamin factor in preventing phenol poisoning, Vopr Pitan. 1981;2:32–35.

[10]Bobardieri G, et al. Effects of SAMe in the treatment of Gilbert's syndrome. Curr Ther Res. 1985;37:580–585.

[11]Peterson S, Bigler J, Horner NK, Potter JD, Lampe JW. Cruciferae interact with the UGT1A1*28 polymorphism to determine serum bilirubin levels in humans. J Nutr. 2005 May;135(5):1051–1055.

[12]Pemberton PW, Smith A, Warnes TW. Non-invasive monitoring of oxidant stress in alcoholic liver disease. Scand J Gastroenterol. 2005 Sep;40(9):1102–1108.

[13]Witschi A, et al. The systemic availability of oral glutathione. Eur J Clin Pharmacol. 1992;43:667–669.

[14]Barzatt R, et al. Inhibition of phenol sulfotransferase by pryidoxal phosphate. Biochem Pharmacol. 1994;47:2087–2095.

[15]Birkmayer JGD, et al. Biological and clinical relevance of trace elements. Arztl Lab. 1990;36:284–287.

[16]Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer—analysis of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000;343:78–85.

[17]Murray MT, et al., Encyclopedia of Natural Medicine, 2nd Edition. Rocklin, CA: Prima Publishing, 1998.

[18]Polasa K, et al. Effect of turmeric on urinary mutagens in smokers. Mutagenesis. 1992;7:107–109.

[19]Valensuela A, et al. Selectivity of silymarin on the increase of the glutathione content in different tissues of the rat. Planta Med. 1989;55:420–422.

[20]Yu R, Jiao JJ, Duh JL, Gudehithlu K, Tan TH, Kong AN. Activation of mitogen-activated protein kinases by green tea polyphenols: potential signaling pathways in the regulation of antioxidant-responsive element-mediated phase II enzyme gene expression. Carcinogenesis. 1997 Feb;18(2):451–456.

[21]Zhu M, Yeung RY, Lin KF, Li RC. Improvement of phase I drug metabolism with Schisandra chinensis against CCl4 hepatotoxicity in a rat model. Planta Med. 2000 Aug;66(6):521–525.

[22]Chiu PY, Mak DH, Poon MK, Ko KM. In vivo antioxidant action of a lignan-enriched extract of Schisandra fruit and an anthraquinone-containing extract of Polygonum root in comparison with schisandrin B and emodin. Planta Med. 2002 Nov;68(11):951–956.

[23]Beecher CWW. Cancer preventive properties of varieties of Brassica oleracea: A review. Am J Clin Nutr. 1994;59(suppl.):1166–1170.

[24]Zhang Y, Callaway EC. High cellular accumulation of sulphoraphane, a dietary anticarcinogen, is followed by rapid transporter-mediated export as a glutathione conjugate. Biochem J. 2002 May 15;364(Pt 1): 301–307.

[25]Barch DH, Rundhaugen LM, Stoner GD, Pillay NS, Rosche WA. Structure-function relationships of the dietary anticarcinogen ellagic acid. Carcinogenesis. 1996 Feb;17(2):265–269.

[26]Crowell PL, et al. Chemoprevention and therapy of cancer by D-Limonene. Crit Rev Oncogenesis. 1994; 5:1–22.

[27]Jain A, et al. Effect of ascorbate or N-acetylcysteine treatment in a patient with hereditary glutathione synthetase deficiency. J Pediatr. 1994;124:229–233.

[28]Zavorsky GS, Kubow S, Grey V, Riverin V, Lands LC. An open-label dose-response study of lymphocyte glutathione levels in healthy men and women receiving pressurized whey protein isolate supplements. Int J Food Sci Nutr. 2007 Sep;58(6):429–436.

10

COLON CANCER

Nutritional Strategies for Prevention

Many of us have known, or will know, someone who suffers with colon cancer. Colorectal cancer is the third leading cause of cancer death in the United States. According to the Center for Disease Control and Prevention (CDC), 73,182 men and 70,763 women were diagnosed with colorectal cancer, and 27,990 men and 27,793 women died from colorectal cancer in 2003.[1] Commonly recognized risk factors for colon cancer include obesity and low consumption of vegetables, fish, and whole-grain cereals.[2] Additional risk factors include a genetic predisposition, as in the case of familial polyposis, and other conditions, such as chronic ulcerative colitis. This article reviews a portion of the growing evidence that nutrition and supplementation may have very significant roles to play in maintaining a healthy, cancer-free colon.

WHAT IS THE ROLE OF FIBER?

Since it was first suggested that a high-fiber diet was protective against colon cancer,[3] several potentially preventative mechanisms against cancer have been proposed and studied to varying degrees, including the reduction of irritating secondary bile acids, decreasing transit time, and lowering the pH of the colon.[4–6] Some attention has recently focused, however, on two significant studies, both published in the New England Journal of Medicine,[7,8] which have failed to show the benefit of fiber consumption. The first study, a prospective nurses' study, was published in 1999 and reported no protective effect of total dietary fiber or fiber from cereals, fruits, or vegetables against colon cancer or adenomas.[6] While this study was large, and apparently extremely well-done, an interesting perspective is added by another prominent researcher, Bandaru S. Reddy of the Nutritional Carcinogenesis and Chemoprevention Program, Valhalla, New York. In a lecture presented at the 90th Annual Meeting of the American Association for Cancer Research, Dr. Reddy pointed out that, in the nurses' study, median total daily dietary intake ranged from 9.8 g in the lowest fiber consumers to 24.8 g in the highest fiber consumers, 1.0–4.8 g of which was cereal fiber. In contrast, Finnish researchers reported an average daily intake of 35 g per day and a cereal fiber intake range of 17–21 g per day.[9,10] This difference leads to the suggestion that it is vital to consider the effects of specific kinds of fiber as well as the total fiber intake. While the results of the nurses' study are certainly real, it may be that the consumption of cereal fiber, in particular, was just not high enough in the study population to produce significant results.

The second study, published in 2000, explored the effects of a low-fat, high-fiber diet on the recurrence of colorectal adenomas, which are precursors to colon cancers.[7] The study results showed no difference in recurrence rates between the 958 subjects in the intervention group, who lowered their fat intake and increased their dietary fiber and fruit and vegetable intake substantially, and the 947 subjects in the control group. As was pointed out in correspondence regarding the study,[11] it may be difficult to assess subject compliance accurately in a study like

this, and introducing new diet regimes successfully is a difficult task to accomplish. However, it just may be the case that this study represents the truth and that, in patients who have had previous colon adenoma, a low-fat, high-fiber diet does not hold as much promise as had been

In a recent study, the lipid-soluble portion of wheat bran was shown to inhibit chemically induced colon-tumor growth.

hoped. It is also important to realize that, even if this is the case, it does not mean that the results of the study can be translated to the general population who have not had previous colon adenomas. And there are several reasons to think that cereal fiber may be beneficial.

The fiber from wheat bran, for example, is deserving of special attention, as it may be able to decrease the risk of colon cancer via various mechanisms. One of the principal ways in which a high cereal fiber diet may be beneficial is by decreasing the amounts of secondary bile acids that are irritating to the colonic mucosa. In fact, at least one of these secondary bile acids, deoxycholic acid, increases the proliferation of colonic epithelial cells.[12] Research has shown that these bile acids, including deoxycholic acid, were significantly reduced when subjects consumed 10 g per day of wheat bran, but not oat bran, as an addition to their typical Western diet.[13] Also, intake of dietary carbohydrates, particularly from degradation-resistant starches and dietary fiber, are fermented in the colon and form short chain fatty acids (SCFA), primarily acetate, propionate, and butyrate. These SCFAs have been shown to decrease proliferation and migration in experimentally induced cancer cell lines. (See the section ''Prebiotics and Probiotics.'') In addition, research has shown there are several parts of wheat bran that may have complementary actions in maintaining a healthy colonic environment. For example, phytic acid, or inositol-6-phosphate as it is also known, is an antioxidant and inducer of increased natural-killer cell activity that, in animal studies, has been shown to inhibit chemically induced carcinogenesis.[14] In addition, it may be important to bear in mind that dietary fiber makes up less than half of wheat bran, with other constituents such as phenolic acids, lignans, and flavonoids also being present.[15] In fact, the core structure of the flavonoids, flavone, has recently been shown to be a more potent inducer of apoptosis in human colon cancer cells than the established antitumor agent camptothecin.[16]

Moreover, in a recent study, the lipid-soluble portion of wheat bran was shown to inhibit chemically induced colon-tumor growth.[17] In this study, the researchers started rats on diets that were fortified with different fractions of wheat bran. At seven weeks, the rats were injected

Factors That Increase the Risk of Colon Cancer

- Low levels of antioxidants (vitamins A, C, and=or E)
- Daily consumption of beef
- High intake of refined carbohydrates
- Multiple juvenile polyposis
- Gardner's syndrome
- Crohn's disease
- Ulcerative colitis
- Previous history of colon cancer or polyps
- Familial polyposis
- Family history of colon cancer or polyps

twice per week with azoxymethane, a carcinogen. For the rats who initially received wheat bran that was missing phytate and lipids, the wheat bran was subsequently fortified with bran oil and phytic acid. These rats had a decreased incidence and number of tumors. Other rats were fed wheat bran that was missing phytate and lipids, and the wheat bran was subsequently fortified with only phytic acid and not bran oil. These rats experienced no decrease in incidence or number of tumors. Thus, this study indicated a protective effect of the bran oil against cancer. In addition, rats who were given normal wheat bran were compared to those who were given wheat bran that was deficient in oil and phytic acid. The rats on the deficient wheat bran had increased total cyclo-oxygenase (COX) and COX-2 enzyme activities.

In a significant study, intake of greater than 400 lg of folic acid per day at the beginning of the study was associated with a significant decrease in colon cancer risk.

NUTRITIONAL VIEW OF INTESTINAL INFLAMMATION

The role that inflammatory processes, such as those modulated by COX-1 and -2 have in colon cancer, may well be significant; in fact, several studies have demonstrated a definite inverse relationship between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the risk of colon cancer.[18,19] In fact, this has led some authorities to recommend aspirin as a preventive. One of the proposed mechanisms of protection by NSAIDs is that, by inhibiting the action of the COX enzymes, production of potentially tumor-favoring prostaglandins is reduced. While it may be the case that the advent of specific COX-2 inhibitors will allow for benefit in this regard without the side effects (such as gastrointestinal bleeding and renal damage) of less-specific NSAIDs, there may be distinct advantages to taking a more broad anti-inflammatory approach that includes supplementation with omega-3 fatty acids, such as those found naturally in fish oil such as docosahexaenoic acid and eicosapentaenoic acid. Several reviewers have pointed out various mechanisms via which omega-3 fatty acids can fight inflammation.[20,21] For example, they can be released from cell membranes instead of arachidonic acid (AA) and compete with AA for subsequent oxidation via the COX, lipoxygenase (LOX), and P450 monooxygenase pathways. These fatty acids may also, at least partially, inhibit these pathways directly. A broader approach than exclusive COX-2 inhibition makes sense because products of COX action are not the only concern in colon cancer. For example, one of the products made in the lipoxygenase pathway, 12(S)-HETE, may increase the ability of tumors to metastasize.[22]

An additional note regarding different types of fatty acids is worth mentioning—at least in chemically induced colon cancer, the incidence and volume of tumors in rats that are fed fish oil is significantly lower than in groups who are fed beef tallow, soybean oil, or alkana oil.[23] And, while a diet high in cereal fiber and containing enough omega-3 fatty acids is certainly important, there are also other factors to consider. A recent review of European studies suggests the importance of maintaining a reasonable body weight and including regular exercise in order to decrease colon cancer risk.[24]

There is also evidence that draws attention to the importance of healthy gut microflora. For instance, ingestion of fermentable probiotics, such as oligofructose and inulin, has been shown to lead to an increase in the growth of friendly bacteria, such as bifidobacteria.[25,26] An increase in friendly bacteria has been reported to decrease colonic mucosal cell proliferation and to

Table 10–1. Preventing Colon Cancer: What to Tell Your Patients

Suggested for Prevention ...	Tell your Patients ...
Increase intake of total fiber cereals	Aim for roughly 20 g per day of cereal fiber.
Increase omega-3 fatty acids	Include cold water fish in the diet (such as salmon) weekly; also, include flaxmeal or cold-pressed flaxseed (Linum usitatissimum) oil, 2,000 mg 3 times per day.
Support healthy gut flora	Eat a variety of fresh fruits and vegetables that contain the oligosaccharides that are necessary for the growth of friendly bacteria; consider a quality probiotic supplement containing bifidobacteria and lactobacillus.
Folic acid	Take a quality multivitamin that provides at least 400 mg per day.
Vitamin E (g- or mixed- tocopherol)	Take 400–1,200 IU per day.
Curcumin	440 to 2,200 mg curcuma extract, containing curcumin 36 to 180 mg per day.
Selenium	Take 200 mg per day.
Calcium	Take 1,200 mg per day.
Vitamin D	1,000–2,000 IU per day.

decrease tumor biomarkers, such as tumor ornithine decarboxylase and ras-p21.[25] One of the products made by bifidobacteria, butyrate, may be of special interest in colon cancer. In fact, in a model that included rats with induced colitis (itself a risk factor for colon cancer) or with colitis plus induced colon cancer, rats that received butyrate enemas showed a significantly lower incidence and size of induced tumors. An added finding was that the rats with colitis showed a normalization of glutamine metabolism,[27] the most abundant amino acid in intestinal tissue.

In addition to telling your patients to consume generous amounts of cereal fiber and foods that are rich in omega-3 fatty acids, while maintaining healthy gut microflora, there are several other key nutrients that may be considered in an effort to maintain a healthy and cancer free-colon. (See Table 10–1 above.)

KEY NUTRIENTS

Folic Acid

One nutrient that is especially important for colon health is folic acid. In 1998, the results of a significant prospective study of more than 88,000 nurses suggested that intake of greater than 400 mg per day at the beginning of the study was associated with a significant decrease in colon cancer risk, even after controlling for other factors such as intake of vitamins A, C, D, and E, and calcium. In addition, women who consumed multivitamins that contained folic acid, for 15 years throughout the study, had a dramatic decrease in colon cancer risk compared to women who did not consume such vitamins.[28] In fact, the relative risk (RR) was 0.25 for women ages 55–69 who used a multivitamin that contained folic acid. This dramatic decrease in risk after a number of years may be not only be an important indication of the benefits of folic acid but also of the synergistic benefit of taking the needed vitamins and minerals supplied in multivitamins

consistently over a significant portion of the lifetime. Also, it is useful to remember that it can take years before a study is able to detect a statistically significant difference between groups that are and are not getting supplements.

Curcumin's ability to block initial DNA damage and to limit progression make curcumin a very promising preventive agent.

Another prospective trial highlights the importance of assuring adequate folate intake, especially when methionine levels are low and alcohol consumption is heavy.[29] In this study of almost 48,000 men, those who drank more than two drinks a day had a substantially increased risk (roughly double) of developing colon cancer compared to those who drank less than or equal to a quarter of a drink per day. In men who drank more than two drinks per day and had a low-folate, low-methionine diet, their risk roughly tripled for occurrence of any kind of colon cancer and was higher still for cancer of the distal colon. While there may be several mechanisms via which folic acid helps to prevent colon cancer, recent research suggests that one important role may be maintaining the genetic integrity of the DNA coding for the important tumor-suppressor gene, p53.[30] Interestingly, however, in a recent double-blind, placebo-controlled, randomized clinical trial with 1,021 men and women with a recent history of colorectal adenomas, patients were given 1 mg per day of folic acid or placebo and=or aspirin. Folic acid supplementation was associated with higher risks of having three or more adenomas and of noncolorectal cancers and the incidence of at least one advanced lesion was 11.6% for the folic acid group compared to 6.9% in the placebo group.[31]

Vitamin E

Another vitamin that has been associated with decreased colon cancer risk is vitamin E as shown in another prospective trial that included more than 35,000 women, ages 55–69.[32] While the data from this study did not show lowered risks for developing colon cancer with intake of other vitamins, the data did show a substantial decrease in risk for women in the study who consumed the most dietary and supplemental vitamin E. Women who had the highest intake of vitamin E had an RR of developing colon cancer of 0.32 compared to women who had the lowest intake of vitamin E.

Curcumin

Curcumin is also worthy of continued research. This nutrient is one the constituents of the spice turmeric. Widely used for its anti-inflammatory actions, curcumin has been shown to inhibit AA metabolism and to prevent the occurrence of chemically induced pre-neoplastic colon lesions in rats.[33] Some of curcumin's antitumor effects also extend beyond the initial stage of initiation to the late premalignant progression stage, during which curcumin is associated with an increased rate of apoptosis.[34] Additionally, curcumin has been shown to decrease inflammation by inhibiting TNF-induced NF-kappaB activation by suppression of NF-kappaB-regulated COX-2 and cyclin D1 protein expression as well as inhibition of the proliferation of tumor cells.[35] Curcumin's ability to block initial DNA damage and to limit progression make curcumin a very promising preventive agent.

Selenium

Another key nutrient is selenium. The importance of this nutrient was initially suggested by epidemiologic data that showed an inverse relation between its levels and colon cancer occurrence.[36] This relationship seems to be confirmed by the results of data from a prospective human study with brewer's yeast that had been fortified with selenium.[37] Subjects who consumed 200 mg per day of selenium over the course of the study had significantly lower levels of colon, lung, and prostate cancers, compared to subjects in a control group. In one animal study, selenium, in the form that it occurs in broccoli, provided protection against chemically induced pre-neoplastic lesions, indicating that this natural and available source might be an effective chemopreventive agent.

Calcium

A final nutrient that has been well-studied in colon cancer recurrence and prevention is calcium. In a study of 930 patients who had recently been diagnosed with colorectal adenoma, subjects received either 3 g of calcium carbonate (1,200 mg of elemental calcium) per day or placebo.[38] The subjects were then followed for four years. Of the 913 subjects who had at least one follow-up, there was a moderate, although significant, decrease in the risk for recurrence of adenoma. At least one adenoma was diagnosed in 127 of the subjects in the calcium-treated group (31%) and in 159 subjects in the placebo group (59%). However, as in the earlier-cited study of fiber in the recurrence of polyps, it is still uncertain if the results of this study in patients with histories of adenoma can be translated to patients with no past histories of adenoma. In fact, the results of a significantly sized prospective trial in cancer-free men produced nonconclusive results; initially calcium appeared to offer a statistically significant protective effect, but that effect became nonsignificant when factors in addition to age and total energy intake were taken into account.[39] The conclusion of the study was that, while a strong protective effect of calcium was not apparent, a modest one could not be excluded. Because calcium is a very inexpensive and widely available intervention, it makes sense to emphasize its inclusion in a prevention strategy.

Calcium-D-glucarate is the calcium salt of D-glucaric acid. Oral supplementation of calcium-D-glucarate has been shown to inhibit the enzyme beta-glucuronidase, which is produced by colonic microflora. Elevated beta-glucuronidase activity is associated with an increased risk for various cancers, including colon cancers.[40] Rats with experimentally induced intestinal cancers were fed calcium-D-glucarate for 32 weeks. The results demonstrated significant inhibition in the overall induction of adenocarcinomas in the intestine showing decreased incidence and tumor size.[41]

Vitamin D

Vitamin D levels have been correlated with cancer incidence. Recent research has shown that individuals who have the highest levels of vitamin D_3 have a significantly reduced risk of colon cancer.[42] Currently, the median adult intake of vitamin D in the United States is 230 IU per day. Recent analysis of data has shown that daily intake of 1,000–2,000 IU per day of vitamin D_3 could reduce the incidence of colorectal cancer by 50%.[43] Serum 25-hydroxyvitamin D concentrations have been shown to be significant, independent predictors of cancer risk in postmenopausal women, and research has shown that improving vitamin D and calcium levels substantially reduces all-cancer risk in this population.[44] Vitamin D has been shown to have

antiproliferative action on cancer cells. In fact, an inverse correlation between serum levels of the active metabolite of vitamin D, 1,25(OH)2D3, and colorectal carcinoma stage has been shown in colorectal carcinoma patients. Because 1,25(OH)2D3 has been shown to inhibit proliferation of colonic epithelial cells, it is proposed that decreased serum levels may facilitate the growth of colorectal carcinoma.[45] The anticancer effects restricting cellular growth are thought to involve various mechanisms, including cell-cycle arrest, inducing apoptosis, inhibition of angiogenesis, and up-regulation of the expression of pro-apoptotic proteins.[46]

Conjugated Linoleic Acid (CLA)

The antiproliferative effects of two isomers of CLA (c9, t11-CLA, t10, c12 -CLA) on human colon adenocarcinoma cell line were investigated. Both of these isomers effectively inhibited cell proliferation.[47] Using animal models, CLA treatment significantly decreased metastasis of colon cancer in the peritoneal cavity. Additionally, survival rate in the mice treated with CLA was significantly improved.[48]

Garlic

Analysis of several studies has shown that garlic consumption decreases the risk of colorectal cancer. A double-blind, randomized, clinical trial was done using high-dose aged garlic extract in patients with colorectal adenomas for 12 months. The results showed that the garlic extract significantly suppressed both the size and number of colon adenomas in these patients.[49] One randomized controlled trial reported a statistically significant 29% reduction in both size and number of colon adenomas in colon cancer patients taking aged garlic extract. A meta-analysis of the published literature indicates a 30% reduction in relative risk with garlic supplementation.[50]

Green Tea

There is a great deal of research underway on the benefits of green tea consumption and a reduced risk of various cancers. Several studies have identified the green tea polyphenol epigallocatechin gallate (EGCG) as a potent chemopreventive agent that can induce apoptosis and suppress the formation and growth of human cancers, such as colorectal cancers. In a recent study, mice were treated with an agent that induces colon tumors and given water or green tea for four to eight weeks. The results showed that green tea significantly inhibited the formation of new tumors, but it was not effective against large tumors already present. Green tea administration also decreased the total levels of biomarkers involved in early colon cancer development.[51] Another study examined green tea consumption in Chinese women age 40–70. In this study, the women who regularly drank green tea at the beginning of the study showed a 37% reduced risk of colorectal cancer compared to those who irregularly consumed green tea. According to the study, the risk reduction was related to the duration of lifetime green tea consumption and the dose of green tea regularly consumed. Overall, the women who consumed green tea both before the study started and during follow-up surveys experienced a 57% reduced risk of colon cancer.[52]

Prebiotics and Probiotics

Probiotics such as lactobacillus and bifidobacteria species have been shown to benefit numerous intestinal disorders. Prebiotics, such as fiber and indigestible dietary starches, promote

the growth and activity of specific species of bacteria in the gut. In animal models, ingestion of lactic acid bacteria was shown to prevent carcinogen-induced pre-neoplastic lesions and tumors.[53] Additionally, prebiotic intake in humans has been shown to increase probiotic bacteria, decrease pathogenic bacteria, decrease the activity of pro-carcinogenic enzymes, and increase the amount of beneficial short-chain fatty acids (SCFAs).[54] As mentioned previously, increased production of short-chain fatty acids leads to a decrease in the pH of colon content, which is associated with a reduced incidence of colon cancer.[55] Using colon-cancer-prone mice, researchers have shown that a diet high in the prebiotic short-chain fructo-oligosaccharides dramatically reduced the incidence of colon tumors in this model.[56]

The SCFAs have numerous functions in the intestines. SCFAs are readily absorbed by the intestinal mucosa and have been shown to stimulate intestinal mucosal growth. Particularly, butyrate is the major energy source for the cells that line the colon. Butyrate has been shown to induce enzymes promoting mucosal cell restoration. SCFAs also stimulate sodium and water absorption in the colon.[57] In addition, SCFAs enhance the motility of the intestinal tract by stimulating contractions and shortening emptying of the ileum, which may protect ileal mucosa against the potentially harmful effects of the reflux of colonic contents.[58] Also, the secretion of mucus, an important part of the intestinal mucosal barrier, has been shown to be stimulated by SCFAs, especially butyrate, in the colon.[59] Butyrate, propionate, and acetate inhibited the proliferation and migration and increased the differentiation of a human colon cancer cell line in studies.[60] Particularly, butyrate has been investigated for its inhibition of pro-inflammatory markers and the role this plays in prevention of inflammatory bowel disease (IBD) and cancer.[61] Butyrate has also been studied in the prevention of colon cancer, by promoting cell differentiation, cell-cycle arrest, and apoptosis (programmed cell death) of transformed colon cells. In fact, butyrate has been shown to decrease experimentally induced DNA damage in human colon cells and colon cancer cell lines by approximately 50%.[62]

CONCLUSIONS

In light of the evidence, it is evident that there are still many questions to be answered concerning the central role of nutrition in colon cancer prevention. Certainly, future research will help to elucidate the roles that different kinds of fiber play—or do not play—in the prevention of colon cancer. There is much to be understood, as yet, concerning the proper ecology of gut microflora and the importance of limiting gut inflammation. Moreover, there are a variety of key nutrients that will, no doubt, continue to be studied and that may play pivotal roles in preventing colon cancer, such as folic acid, vitamin D, vitamin E, curcumin, selenium, and calcium. By nourishing the body with a spectrum of these vital nutrients, the combined effects of their unique and complementary actions may best improve our patients' chances of avoiding this all-too-common form of cancer.

REFERENCES

[1]Center for Disease Control and Prevention. Colorectal Cancer: Statistics. Available at: www.cdc.gov=cancer=colorectal=statistics. Accessed November 13, 2007.

[2]Hill MJ Mechanisms of diet and colon carcinogenesis [review]. Eur J Cancer Prev. 1999;8(suppl. 1): S95–S98.

[3]Burkitt DP. Epidemiology of cancer of the colon and rectum. Cancer. 1971;28(1):3–13.

[4]Kritchevsky D. Epidemiology of fibre, resistant starch and colorectal cancer. Eur J Cancer Prev. 1995;4(5):345–352.
[5]Reddy BS, et al. Biochemical epidemiology of colon cancer: Effect of types of dietary fiber on fecal mutagens, acid, and neutral sterols in healthy subjects. Cancer Res. 1989;49(16):4629– 4635.
[6]Reddy BS, Engle A, Simi B, Goldman M. Effect of dietary fiber on colonic bacterial enzymes and bile acids in relation to colon cancer. Gastroenterology. 1992;102(5):1475–1482.
[7]Fuchs C, et al. Dietary fiber and the risk of colorectal cancer and adenoma in women. N Engl J Med. 1999;340(3):169–176.
[8]Schatzin A, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenoma: Polyp Prevention Trial Study Group. N Engl J Med. 2000;342(16):1149–1155.
[9]Reddy BS. The fourth DeWitt S. Goodman Lecture: Novel approaches to the prevention of colon cancer by nutritional manipulation and chemoprevention. Cancer Epidemiol Biol Prev. 2000;9:239–247.
[10]Reddy BS, Hedges,AR, Laakso K, Wynder EL. Metabolic epidemiology of large bowel cancer: Fecal bulk and constituents of high-risk North American and low-risk Finnish population. Cancer. 1978;42(6): 2832–2838.
[11]Gerber M, Ornish D. Letters to the editor [two letters published together]. N Engl J Med. 2000;343(10): 736–77.
[12]Ochsenkuhn T, et al. Colonic mucosal proliferation is related to serum deoxycholic acid levels. Cancer. 1999;85(8):1664–1669.
[13]Reddy BS, Engle A, Katsifis S, Simi B, Bartram HP, Perrino P, Mahan C. Biochemical epidemiology of colon cancer: Effect of types of dietary fiber on fecal mutagens, acid, and neutral sterols in healthy subjects. Cancer Res. 1989;49(16):4629– 4635.
[14]Reddy BS. Prevention of colon carcinogenesis by compounds of dietary fiber [review]. Anticancer Res. 1999;19(5A):3681–3683.
[15]Ferguson LR, Harris PJ. Protection against cancer by wheat bran: Role of dietary fibre and phytochemicals [review]. Eur J Cancer Prev. 1999;8(1):17–25.
[16]Wenzel U, Kuntz S, Brendel MD, Daniel H. Dietary flavone is a potent apoptosis inducer in human colon carcinoma cells. Cancer Res. 2000;60(14):3823–3831.
[17]Reddy BS, Hirrose Y, Cohen LA, Simi B, Coom I, Rao CV. Preventive potential of wheat bran fractions against experimental colon carcinogenesis: Implications for human colon cancer prevention. Cancer Res. 2000;60(17):4792– 4797.
[18]Kune GA, Kune S, Watson LF. Colorectal cancer risk, chronic illness, operations and medications: Case-control results from the Melbourne Colorectal Cancer Study. Cancer Res. 1988;48(15):4399– 4404.
[19]Thun MH, Namboodiri MM, Heath CW. Aspirin use and reduced risk of colorectal cancer. N Engl J Med. 1991;325(23):1593–1596.
[20]Heller A, Koch T, Schmeck J, van Ackern K. Lipid mediators in inflammatory disorders [review]. Drugs. 1998;55(4):487– 496.
[21]Sperling RI. Dietary omega-3-fatty acids: Effects on lipid mediators of inflammation and rheumatoid arthritis [review]. Rheum Dis Clin North Am. 1991;17(2):373–389.
[22]Taylor JD. Lipoxygenase regulation of membrane expression of tumor cell glycoproteins and subsequent metastasis. Adv Pros taglandin Thromboxane Leukotr iene Res. 1989;19:439– 443.
[23]Zhou S, Wang G, Chen B, Wang P. Effect of dietary fatty acids on tumorigenesis of colon cancer induced by methyl nitrosourea in rats. J Environ Pathol Toxicol Oncol. 2000;19(1–2):81–86.
[24]Giacosa A, Franceschi S, La Vecchia C, Favero A, Andreatta R. Energy intake, overweight, physical exercise and colorectal cancer risk [review]. Eur J Cancer Prev. 1999;8(suppl. 1):S53–S60.
[25]Campbell JM, Fahey GC Jr., Wolf BW. Selected indigestible oligosaccharides affect large bowel mass, cecal and fecal short-chain fatty acids, pH and microflora in rats. J Nutr. 1997;127(1):130–136.
[26]Reddy BS. Possible mechanism by which pro- and prebiotics influence colon carcinogenesis and tumor growth [review]. J Nutr. 1999;129(7[suppl.]):1478S–1482S.
[27]D'Agenio G, Cosenza V, Delle Cave M, Lovino P, Delle Valle N, Lombardi G, Mazzacca G. Butyrate enemas in experimental colitis and protection against large bowel cancer in a rat model. Gastroenterology. 1996;110(6):1727–1734.
[28]Giovannucci E, et al. Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. Ann Intern Med. 1998;129(7):517–524.
[29]Giovannucci E, Rimm EB, Ascherio A, Stampfer MJ, Colditz GA, Willett WC. Alcohol, low-methionine-low-folate diets, and risk of colon cancer in men. J Natl Cancer Inst. 1995;87(4):265–273.
[30]Kim YI, Shirwadkar S, Choi SW, Puchyr M, Wang Y, Mason JB. Effects of dietary folate on DNA strand breaks within mutation-prone exons of the p53 gene in rat colon. Gastroenterology. 2000;119(1):151–161.
[31]Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, McKeown-Eyssen G, Summers RW, Rothstein RI, Burke CA, Snover DC, Church TR, Allen JI, Robertson DJ, Beck GJ, Bond JH, Byers T,

Mandel JS, Mott LA, Pearson LH, Barry EL, Rees JR, Marcon N, Saibil F, Ueland PM, Greenberg ER; Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA. 2007 Jun 6;297(21):2351–2359.

[32]Potter JD, et al. Reduced risk of colon cancer with high intake of vitamin E: The Iowa Women's Health Study. Cancer Res. 1993;53(18):4230–4270.

[33]Rao CV, Simi B, Reddy BS. Inhibition by dietary curcumin of azoxymethane-induced ornithine decarboxylase, tyrosine protein kinase, archidonic acid metabolism and aberrant crypt foci in the rat colon. Carcinogenesis. 1993;14(11):2219–2225.

[34]Kawamori T, et al. Chemopreventive effect of curcumin, a naturally occurring anti-inflammatory agent, during the promotion=progression stages of colon cancer. Cancer Res. 1999;59(3):597–601.

[35]Takada Y, Bhardwaj A, Potdar P, Aggarwal BB. Nonsteroidal anti-inflammatory agents differ in their ability to suppress NF-kappaB activation, inhibition of expression of cyclooxygenase-2 and cyclin D1, and abrogation of tumor cell proliferation. Oncogene. 2004 Dec 9;23(57):9247–9258.

[36]Clark LC. The epidemiology of selenium and cancer. Fed Proc. 1985;44(9):2584–2589.

[37]Combs GF Jr, Clark LC, Turnball BW. Reduction of cancer mortality and incidence by selenium supplementation. Med Klin. 1997;92(suppl. 3):42–55.

[38]Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, Rothstein R, Summers RW, Snover DC, Beck GJ, Bond JH, Greenberg ER. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. N Engl J Med. 1999 Jan 14;340(2):101–107.

[39]Kearney J, et al. Calcium, vitamin D, and dairy foods and the occurrence of colon cancer in men. Am J Epidemiol. 1996;143(9):907–917.

[40]Anon. Calcium-D-glucarate. Altern Med Rev. 2002 Aug;7(4):336–339.

[41]Dwivedi C, Oredipe OA, Barth RF, Downie AA, Webb TE. Effects of the experimental chemopreventative agent, glucarate, on intestinal carcinogenesis in rats. Carcinogenesis. 1989 Aug;10(8):1539–1541.

[42]Garland, CF, et al. What is the dose-response relationship between vitamin D and cancer risk? Nutrition Reviews. 2007;65;8 (suppl.):91–95.

[43]Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, Newmark HL, Giovannucci E, Wei M, Holick MF. Vitamin D and prevention of colorectal cancer. J Steroid Biochem Mol Biol. 2005 Oct;97(1-2):179–194. Epub 2005 Oct 19.

[44]Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: Results of a randomized trial. Am J Clin Nutr. 2007 Jun;85(6):1586–1591.

[45]Niv Y, Sperber AD, Figer A, Igael D, Shany S, Fraser G, Schwartz B. In colorectal carcinoma patients, serum vitamin D levels vary according to stage of the carcinoma. Cancer. 1999 Aug 1;86(3):391–397.

[46]Harris DM, Go VL. Vitamin D and colon carcinogenesis. J Nutr. 2004 Dec;134(12 suppl.):3463S–3471S.

[47]Cho HJ, Kim EJ, Lim SS, Kim MK, Sung MK, Kim JS, Park JH. Trans-10,cis-12, not cis-9,trans-11, conjugated linoleic acid inhibits G1-S progression in HT-29 human colon cancer cells. J Nutr. 2006 Apr;136(4):893–898.

[48]Kuniyasu H, Yoshida K, Sasaki T, Sasahira T, Fujii K, Ohmori H. Conjugated linoleic acid inhibits peritoneal metastasis in human gastrointestinal cancer cells. Int J Cancer. 2006 Feb 1;118(3):571–576.

[49]Tanaka S, Haruma K, Yoshihara M, Kajiyama G, Kira K, Amagase H, Chayama K. Aged garlic extract has potential suppressive effect on colorectal adenomas in humans. J Nutr. 2006 Mar;136(3 suppl.):821S–826S.

[50]Ngo SN, Williams DB, Cobiac L, Head RJ. Does garlic reduce risk of colorectal cancer? A systematic review. J Nutr. 2007 Oct;137(10):2264–2269.

[51]Issa AY, Volate SR, Muga SJ, Nitcheva D, Smith T, Wargovich MJ. Green tea selectively targets initial stages of intestinal carcinogenesis in the AOM-ApcMin mouse model. Carcinogenesis. 2007 Sep;28(9): 1978–1984. Epub 2007 Jul 17.

[52]Yang G, Shu XO, Li H, Chow WH, Ji BT, Zhang X, Gao YT, Zheng W. Prospective Cohort Study of Green Tea Consumption and Colorectal Cancer Risk in Women. Cancer Epidemiology Biomarkers & Prevention. 2007 Jun.16:1219–1223.

[53]Challa A, Rao DR, Chawan CB, Shackelford L. Bifidobacterium longum and lactulose suppress azoxymethane-induced colonic aberrant crypt foci in rats. Carcinogenesis. 1997;18:517–521.

[54]Ballongue J, Schumann C, Quignon P. Effects of lactulose and lactitol on colonic microflora and enzymatic activity. Scand J Gastroenterol Suppl. 1997;222:41–44.

[55]Segal I, Hassan H, Walker ARP, Becker P, Braganza J. Fecal short chain fatty acids in South African urban Africans and whites. Dis Colon Rectum. 1995;38:732–734

[56]Pierre F, Perrin P, Champ M, Bornet F, Meflah K, Menanteau J. Short-chain fructo-oligosaccharides reduce the occurrence of colon tumors and develop gut-associated lymphoid tissue in Min mice. Cancer Res. 1997 Jan 15;57(2):225–228.

[57]D'Argenio G, Mazzacca G. Short-chain fatty acid in the human colon. Relation to inflammatory bowel diseases and colon cancer. Adv Exp Med Biol. 1999;472:149–158.

[58]Cherbut C, Aubé AC, Blottière HM, Galmiche JP. Effects of short-chain fatty acids on gastrointestinal motility. Scand J Gastroenterol. 1997;222(suppl.):58–61.

[59]Shimotoyodome A, Meguro S, Hase T, Tokimitsu I, Sakata T. Short chain fatty acids but not lactate or succinate stimulate mucus release in the rat colon. Comp Biochem Physiol A Mol Integr Physiol. 2000 Apr;125(4):525–531.

[60]Fu H, Shi YQ, Mo SJ. Effect of short-chain fatty acids on the proliferation and differentiation of the human colonic adenocarcinoma cell line Caco-2. Chin J Dig Dis. 2004;5(3):115–117.

[61]Andoh A, Tsujikawa T, Fujiyama Y. Role of dietary fiber and short-chain fatty acids in the colon. Curr Pharm Des. 2003;9(4):347–358.

[62]Rosignoli P, Fabiani R, De Bartolomeo A, Spinozzi F, Agea E, Pelli MA, Morozzi G. Protective activity of butyrate on hydrogen peroxide-induced DNA damage in isolated human colonocytes and HT29 tumour cells. Carcinogenesis. 2001 Oct;22(10):1675–1680.

11

NATURAL APPROACHES TO THE PREVENTION AND MANAGEMENT OF DIABETES MELLITUS

According to facts and figures provided by the American Diabetes Association, there are an estimated 20.8 million people in the United States, approximately 7% of the population, with diabetes. Approximately 6.2 million of these people have not yet been diagnosed. Additionally, there are 54 million Americans that are pre-diabetic with higher than normal blood glucose levels yet not elevated enough for the ''diabetes'' diagnosis.[1] The hyperglycemia resulting from types I and II diabetes mellitus can lead to multiple challenges for the person with diabetes. Patients who are struggling to compensate for a lack of insulin secretion and=or a lack of insulin efficiency face possible complications, such as retinopathy, nephropathy, neuropathy, and atherosclerosis. At the core of preventing and dealing with diabetes mellitus is an understanding of how the body regulates the metabolism of its principal energy source, glucose, and how specific nutrients, diet modifications, and supportive botanical medicines can be utilized to optimize glucose metabolism.

PHYSIOLOGY: AGES, CROSS-LINKING, AND ELEVATED BLOOD SUGAR

Elevated blood sugar has been shown to cause several physiological reactions in the body leading to disease states. One of these reactions involves adding sugars to molecules, a process known as glycosylation. ''Advanced glycosylation end products'' (AGEs) are formed by the attachment of reducing sugars onto biological proteins. This reaction is irreversible causing these proteins with sugars attached to accumulate over time. One well-known example of AGEs is hemoglobin A1C, which is frequently measured to evaluate long-term blood sugar control in diabetics. It is proposed that AGE formation is a normal physiological process that functions as a signal for recognition of old molecules to be broken down and excreted by the kidneys. With increasing age, the excretion of these molecules decreases. AGE formation and accumulation is greatly accelerated with high levels of circulating sugars and oxidative stress seen in conditions such as diabetes.[2] A study was performed with individuals diagnosed with type 1 diabetes comparing various inflammatory markers and AGE levels with blood sugar control after eating. The investigation demonstrated a significant increase in AGE levels and pro-inflammatory markers with increased blood sugar levels after eating.[3] AGEs are also ingested in the diet generally in the form of foods undergoing prolonged heating, particularly fats, meat and meat-substitutes, and broiled foods.[4] In individuals with normal kidney function, only about one-third of ingested AGEs are excreted in the urine within 48 hours, and less AGE excretion is found with kidney disease. Also, this study found that serum AGE cross-linking is significantly increased after ingestion of an AGE-containing meal.[5] Animal studies also indicate that high-fat diets are correlated with obesity, tissue damage, and increased levels of AGEs.[6] AGEs can be inhaled through tobacco smoke as well.[7] Physiological reactions involving AGEs have been implicated in the pathology of numerous diseases.

Table 11–1. Common Complications of Diabetes

Complications of Diabetes	Statistics of Secondary Diseases[a]
Heart disease	Adults with diabetes have heart disease death rates about 2 to 4 times higher than adults without diabetes.
Stroke	The risk for stroke is 2 to 4 times higher and the risk of death from stroke is 2.8 times higher among people with diabetes.
Hypertension	About 73% of adults with diabetes have high blood pressure.
Retinopathy	Diabetes is the leading cause of new cases of blindness in adults 20 to 74 years of age.
Nervous system	About 60% to 70% of people with diabetes have mild to severe forms of nervous system damage.
Amputations	The rate of amputation for people with diabetes is 10 times higher than for people without diabetes.
Dental disease	Almost one-third of people with diabetes have severe periodontal disease with loss of attachment of the gums to the teeth measuring 5 mm or more.
Renal disease	Diabetes is the leading cause of kidney failure, accounting for 44% of new cases in 2002.
Metabolic syndrome	About 47 million U.S. residents have metabolic syndrome[b].

[a]According to the American Diabetes Association.[68]
[b]See Chapter 24 on metabolic syndrome.

AGEs react with molecules creating cross-linkages. Proteins and other large molecules, such as lipids, can undergo cross-linking reactions that cause them to become less elastic and less digestible by enzymes for degradation. Conditions such as diabetes show an increase in glycosylation of proteins, which may be the causative link with the increase in chronic diseases seen with these diseases.[8] AGEs have been implicated in the vascular changes found with diseases of the nerves, kidneys, and eyes in diabetic individuals.[9]

AGEs and Cardiovascular Disease

AGE accumulation is associated with cardiovascular dysfunction and diseases such as atherosclerotic plaque formation, decrease in vascular and cardiac elasticity, endothelial dysfunction, and hypertension.[10] More specifically, AGEs have been shown to quench nitric oxide (NO) which is an endothelium-derived relaxing factor in smooth muscle. Quenching NO impairs this relaxation and is associated with the pathology seen with hypertension, atherosclerosis, and diabetes.[11] AGEs also interact with specific cell receptors, such as RAGE, leading to chronic activation of these receptors. Studies indicate that RAGE activation may lead to an increase in inflammatory markers and cellular injury.[12]

AGEs and Metabolic Syndrome

Metabolic syndrome is a medical condition characterized by central obesity, elevated triglycerides, small low-density lipoprotein (LDL) particles, low beneficial high-density

lipoprotein (HDL) cholesterol, elevated blood pressure, increased inflammation, and insulin resistance. AGE accumulation and RAGE expression is correlated with the symptoms of this condition. A variant of RAGE known as endogenous secretory RAGE (esRAGE) is believed to be a decoy receptor for AGEs and increased levels of esRAGE have been shown to be protective in atherosclerosis and metabolic syndrome. Additionally, esRAGE levels are inversely correlated with body mass index, blood pressure, insulin resistance, and triglycerides.[13] (See Chapter 24 on metabolic syndrome.)

AGEs are not the only cause of pathology related to diabetes. Glucotoxicity and lipotoxicity are important factors in the development and progression of diabetes. For example, hyperglycemia induces oxidative stress, which causes significant damage to proteins and lipids.[14] Also, intracellular lipid accumulation disrupts kinases and other intracellular signaling pathways, leading to chronic inflammation. Furthermore, hyperglycemia has several pathological consequences, such as atherogenic dyslipidemia and endothelial dysfunction.[15]

SPECIFIC NUTRIENTS AND BOTANICALS FOR GLUCOSE METABOLISM

Chromium

Trivalent chromium is one of the most studied nutrients in glucose metabolism. In one study that highlights the need for chromium supplementation in patients with type 2 diabetes,

Table 11–2. Key Nutrients for Controlling Glucose Metabolism

Supplement	Dosage	Notes
Chromium (as polynicotinate or picolinate)	200–1000 mg per day of actual chromium	Response time varies from <10 days to >3 months.
Vanadium (as sulfate)	150 mg–50 mg per day of combined vanadium–sulfate salt	Watch closely for signs of GI intolerance. Smaller doses in mg noted here because these doses are often helpful. If using larger doses (in mg as cited in the text), monitor intake very closely; may also require concurrent supplementation with coenzyme Q10.
Niacinamide (vitamin B_3)	25 mg=kg	Monitor liver enzymes and glucose levels.
Vitamin B complex	100 mg complex	Taken with food to lessen GI (including B_1, B_6, and B_{12}) upset.
Maganese	10–30 mg per day	Gradual dosing is recommended.
Magnesium	350–500 mg per day	Divided doses may be necessary if (aspartate=citrate) loose stool occurs.
Biotin	16 mg per day	Conduct a trial of 1 week while monitoring blood glucose levels closely.

GI gastrointestinal

researchers compared fasting blood and second-morning urine samples between 93 patients with type 2 diabetes and 33 healthy controls. The researchers found that mean serum chromium levels were approximately 33% lower and urine levels were almost 100% higher in the patients with diabetes versus the controls.[16] In addition, while subjects who did not have diabetes showed a negative correlation between fasting levels of plasma chromium and insulin, no such correlation existed in the subjects with diabetes. Moreover, the authors noted, based on their work over several years, that, in the early stages of diabetes, an inverse relationship between plasma chromium and glucose levels has been observed, which disappears after two years. The authors suggested that chromium loss over years may worsen an already existing chromium deficiency in patients with type 2 diabetes and contribute to their insulin resistance.

In a recent review,[17] more than a dozen clinical trials in patients with type 2 diabetes have shown positive results from supplementation with chromium. The multiple benefits reported include improved fasting glucose, improved glucose tolerance, decreased insulin levels 60 minutes after eating, decreased glycosylated hemoglobin levels, and an increase in high-density lipoprotein (HDL). These metabolic improvements seem to be caused by several mechanisms, including an increase in the number of insulin receptors in insulin-dependent cells, such as adipocytes and hepatocytes, and an increase in phosphorylation of the insulin receptor, which results in increased sensitivity of receptors to insulin. With regard to this second mechanism of action, an increased phosphorylation of insulin receptors, there is now some elucidation of how

> Some patients with newly diagnosed type 1 diabetes have experienced complete reversal of their diabetes with niacinamide.

chromium might act at a very basic molecular level. According to one recently proposed model,[18] four chromium ions are needed to bind to a low–molecular-weight oligopeptide so that the resulting complex of the oligopeptide and chromium can assume the correct geometrical shape needed to bind to the phosphorylating portion of the insulin receptor. A potentially important suggestion made in this model is that, in order for the bioactive form of chromium to release its chromium ion to enter a cell, the chromium must first undergo a reduction reaction, which may generate hydroxyl radicals. These hydroxyl radicals from chromium reduction have been shown to cause DNA damage.[19] Although current evidence is lacking, it may be beneficial to include antioxidant support with high-dose chromium supplementation.

While there are occasional studies that do not report benefits of chromium supplementation in glucose metabolism,[20] these studies typically use a dose of chromium that is less than 200 mg per day or use a form of chromium, such as chromium chloride, which seems not to be as bioavailable as chromium polynicotinate or picolinate. A reasonable dosage range for chromium supplementation, suggested in the literature, would be 200–1000 mg per day, with greater benefit expected from the larger dose. It is also important to educate patients about research demonstrating that simple sugar consumption increases the amount of chromium excreted in the urine.[21]

Vanadium

Vanadium, which is positioned next to chromium as a transition metal on the periodic table, has also been studied for its effects on glucose metabolism. In one study of subjects who received

150 mg per day or 300 mg per day of vanadyl sulfate for six weeks, there was improvement in three of the five subjects who received 150 mg and in four of the eight subjects who received 300 mg.[22] Reductions in fasting glucose and glycosylated hemoglobin were enough to be significant, although not dramatically so. In addition, this work demonstrated that, in skeletal muscle, vanadium also appears to modulate the number of insulin receptors and their phosphorylation. Two other small studies also demonstrated improvement in glycemic control using only 100 mg per day (see Table 11–2 on page 133) of vanadyl sulfate for three or four weeks, and, in both studies, the improvement in blood glucose control continued for periods of two or four weeks after supplementation had ended.[23,24] It is important to note that that even the lower doses of vanadyl sulfate (100 mg per day) caused some gastrointestinal intolerance (see Table 11–2 on page 133). A different, organic form of vanadium, bis(maltolato)-oxovanadium (BMOV), has also been shown to be effective in lowering glucose levels, at least in rat models. The dosage of BMOV needed, however, to lower glucose levels effectively, was only half of the dose of vanadyl sulfate required to obtain the same effect. Large doses of vanadyl sulfate have been shown to increase markers of oxidative stress in diabetic animal models. Taking antioxidants in combination with vanadium supplementation may be beneficial.[25]

There is research showing that magnesium levels tend to be low in subjects with diabetes and that three months of supplementation is adequate for reversing the problem.

B Vitamins

The water-soluble B vitamins are required cofactors for many of the enzymes required for metabolizing glucose via glycolysis and the Kreb's cycle, and a growing body of literature suggests their importance in diabetes. For example, in the case of vitamin B_6, a study of the serum levels of 518 patients with diabetes revealed that pyridoxal levels were significantly lower compared to levels in 371 controls, with 25% of the patients with diabetes having levels below the lower limit of the normal range.[26] In another study comparing 50 patients with diabetic neuropathy to patients with diabetes but without neuropathy, serum pyridoxal levels were significantly lower in the patients with diabetic neuropathy.[27]

There are also several studies demonstrating the clinical effects of B vitamins supplementation on diabetes. One study of 24 patients with diabetic neuropathy utilized a treatment with a complex of vitamins B_6, B_{12}, and a form of B_1 modified to be more lipid soluble. After 12 weeks, there was significant improvement in the nerve conduction velocity of the peroneal nerve and a trend toward improvement in the threshold level of vibration perception.[28]

One informative study of a B vitamin in diabetes research was done some years ago by researchers who took a small group of patients with type 1 diabetes off insulin treatment and gave them either 16 mg per day of biotin or a placebo.[29] Compared to the control group, the mean blood glucose level of the biotin-treated group was significantly lower after one week of treatment (126 mg per dL in the biotin group versus 266 mg per dL in the control group). In examining the levels of tissue biotin compared to plasma biotin among patients with type 1 diabetes and controls without diabetes, it was found that an increasing ratio of tissue biotin to

plasma biotin was associated with increasing fasting blood sugar levels in the subjects with diabetes, but not in subjects without the disorder. Perhaps future work will help to confirm that biotin can control blood glucose levels and elucidate the differences in how biotin is utilized in people with or without diabetes.

Niacinamide is also worth specific mention because it has been shown to help prevent type 1 diabetes in laboratory animals. These observations have been noted in at least ten clinical trials of which six were double-blinded. These studies involved patients with type 1 diabetes who had been diagnosed with the disorder five years or less prior to the study. Of the positive studies, some patients with newly diagnosed type 1 diabetes have experienced complete reversal of their diabetes with niacinamide. Other positive findings included prolonged remissions, lower insulin requirements, increased beta-cell function, and enhanced metabolic control.[30,31]

Pterocarpus

Rich in the flavonoid (-)-epicatechin, pterocarpus (Pterocarpus marsupium), an Ayurvedic herb, may be helpful for patients with both type 1 and type 2 diabetes. In an animal study, rats whose beta-islet cells were first destroyed with the toxin alloxan and then given large intravenous doses of (-)-epicatechin experienced a return of normal blood glucose levels.[32] Histologic examination of pancreas samples showed regeneration of the beta-islet cells. In a human trial in India, among subjects who had been recently diagnosed with type 2 diabetes, 67 of 97 patients studied were able to control blood glucose levels (measured both for fasting and postprandial levels) after 12 weeks of treatment. Doses needed for control ranged between 2–4 g of extract, and there were no side effects reported.[33]

Fenugreek

In a study of patients with type 1 diabetes given 50 g of defatted fenugreek (Trigonella foenumgracum) seed powder with both lunch and dinner for 10 days, there was a 54% decrease in 24-hour urine glucose excretion. Other benefits from this high source of fiber in this study included

Table 11–3. Select Botanical Considerations for Treating Diabetes

Herb	Amount	Notes
Bitter melon (Momordica charantia)	15–50 g per day	Start low and work up to higher doses.
Fenugreek (Trigonella foenumgracum)	15–50 g per day	Administer in divided doses.
Gymnema (Gymnema sylvestre)	400 mg of extract	Monitor glucose levels closely.
Corosolic acid (Lagerstroemia speciosa)	32–48 mg	Adjustment of medicines often needs close attention.
Pterocarpus (Pterocarpus marsupium)	Varied	Dose varies depending widely upon the extraction process.
Puncture vine or tribulus (Tribulus terrestris)		Variable; 250–1,500 mg per day; standardized to 30%–45% steroidal saponins (also known as furostanol).

decreases in total serum cholesterol, low-density lipoprotein, and very low-density cholesterol and triglycerides, while levels of HDL remained unchanged.[34] Another study was performed with patients with type 2 diabetes. After two months, fenugreek seed extract supplementation of 1 gm per day was shown to improve glycemic control, decreases insulin resistance, decrease serum triglycerides, and increase HDL cholesterol.[35] Animal models have elucidated some of the mechanisms that Fenugreek provides these positive effects. A study with both type 1 and type 2 diabetic rats has shown that supplementation with Fenugreek soluble dietary fiber fraction decreases sugar digestion and absorption. It also increases insulin action peripherally and enhanced total antioxidant status.[36]

Bitter Melon

Bitter melon (Momordica charantia) has historically been used for blood sugar control. In a small study of nine patients with type 2 diabetes, a simple water extract of the fruit of bitter melon was enough to lower blood glucose levels significantly during a 50 g oral glucose tolerance test. This improvement was not associated with an increase in serum insulin.[37] Another study with 100 patients with moderate non-insulin-dependent diabetes examined the efficacy of drinking the aqueous homogenized suspension of bitter melon vegetable pulp. The results showed significant reduction of both fasting and postprandial serum glucose levels in 86% of cases while 5% showed lowering of fasting serum glucose only.[38] Animal models have shown that in addition to hypoglycemic activity, whole-plant extracts of Momordica charantia also exert hypotensive action as well.[39] Animal models have elucidated some of the mechanisms of bitter melon's anti-diabetic activity. Momordica charantia extract was shown to reduce glycogenesis in liver tissue, enhance insulin secretion by the islets of Langerhans, restore the altered histological architecture of the islets of Langerhans, enhance peripheral glucose utilization, and increase serum protein levels.[40]

Gymnema

A simple water extract from the leaf of gymnema (Gymnema sylvestre) may hold promise for patients who have either type 1 or type 2 diabetes. Twenty-seven subjects with type 1 diabetes who received 400 mg of gymnema extract per day showed a reduction in the need for insulin as well as decreases in fasting blood glucose, glycosylated hemoglobin, and glycosylated plasma protein levels.[41] In a similar study, a water extract at a dose of 400 mg of gymnema extract per day was given to 22 patients with type 2 diabetes for 18 to 20 months. There were, again, significant decreases in the same biomarkers used in the study with patients who have type 1 diabetes.[42] One promising aspect of the study with subjects who have type 2 diabetes is that the extract was given safely in conjunction with other conventional medications that the subjects were already using. Five of the 22 subjects were able to discontinue their use of conventional medications and manage their conditions solely with the gymnema extract.

Cinnamon

Cinnamon (Cinnamomum cassia) has also been shown to be an effective therapy for diabetes. In a randomized double-blind placebo-controlled study with type 2 diabetic patients, supplementation of cinnamon powder as an aqueous extract equivalent to 3 g per day was given in addition to oral medication. The results showed significantly better reduction in fasting plasma glucose levels in the cinnamon supplemented group (10.3%) than placebo, and the data showed

that people with higher initial plasma glucose levels may benefit more from cinnamon intake.[43] Another study with type 2 diabetic patients examined the effect of 1, 3, or 6 g of cinnamon supplementation per day on blood glucose and lipids. After 40 days, all three levels of cinnamon reduced the mean fasting serum glucose levels by 18%–29%, triglycerides by 23%–30%, LDL cholesterol by 7%–27%, and total cholesterol by 12%–26%.[44] A study was done with healthy individuals supplemented with 6 g of cinnamon added to rice pudding to evaluate changes in the rate of gastric emptying and postprandial glucose levels in this population. The addition of cinnamon to the rice pudding significantly delayed gastric emptying, which may explain, at least partially, the mechanism of the lowered postprandial glucose response.[45]

Goats Rue

Goats rue or French lilac (Galega officinalis) is a plant traditionally used for the treatment of diabetes, although it is not used much today due to potential toxicity. This herb has also demonstrated anti-platelet-aggregation and antibacterial activity.[46,47] The active ingredient found to lower blood glucose is galegine or isoamylene guanidine. The widely prescribed biguanide Metformin is a derivative of guanidine and shows significant efficacy in blood sugar control.[48]

Carnosine

Carnosine is a dipeptide consisting of beta-alanine and L-histidine. It is found only in animal tissues and particularly in high concentrations in skeletal muscle, cardiac muscle, and the brain.[49] Research shows that carnosine can prevent the formation of AGEs, cross-linking, glycation, and protein carbonyl group formation.[50] Studies indicate that muscle carnosine levels decrease significantly with age demonstrating a 63% decrease from age 10 to age 70.[51] Carnosine acts as an antioxidant decreasing lipid oxidation, protecting membranes from free radical damage, regulating white blood cell function, and chelating reactive metals. In fact, carnosine has been shown to scavenge metabolites from lipid peroxidation preventing DNA-protein and protein-protein cross-linking reactions. These researchers also suggest that carnivorous diets may be protective for complications associated with high blood sugar and aging due to the high carnosine levels found in animal tissue.[52] Preliminary studies also indicate that AGEs increase cell proliferation and death. Specifically, AGEs were added to skin cell cultures and incubated. Increased cell death was seen beginning at the seventh day and continued for up to 10 days. Antibodies to AGE cell receptors were used with similar results. Treatment of these cell cultures with free radical scavengers such as L-carnosine decreased AGE-induced cell death. This finding suggests that free radical damage may be involved with AGE-induced cellular death.[53]

Lipoic Acid

Alpha lipoic acid (ALA) is a potent antioxidant and free-radical scavenger. It is both water and fat soluble and can regenerate endogenous antioxidants. ALA has been shown to both decrease blood sugar in diabetics as well as attenuate secondary conditions associated with diabetes. Research has shown that oral ALA supplementation improves insulin sensitivity in patients with type 2 diabetes.[54] Studies with obese diabetes-prone rats have shown that ALA can prevent the onset of diabetes in these animals. This model showed that ALA reduced body weight, protected pancreatic beta-cells from destruction, and reduced triglyceride

accumulation in skeletal muscle and pancreatic islets.[55] ALA has also been shown to exhibit antiglycating effects. A study examined ALA administration in high fructose-fed rats. The results showed a significant decrease in glucose, glycated protein, glycated hemoglobin, and fructosamine with ALA in high fructose-fed rats. ALA also prevented glycation and the accumulation of advanced glycation end products in vitro.[56] Another animal study examined the effect of ALA apolipoprotein E-deficient diabetic mice fed a high fat diet to evaluate the effects of ALA on atherosclerosis and cardiovascular complications with diabetes. ALA completely prevented the increase in plasma total cholesterol and atherosclerotic lesions. There was also a reduction of plasma glucose and an accelerated recovery of insulin-producing cells in the pancreas.[57]

A study was performed in individuals with symptomatic diabetic polyneuropathy and oral ALA supplementation. The results indicated that oral ALA in doses of 600 mg, 1,200 mg, and 1,800 mg per day was effective in reducing neuropathic symptoms of diabetic distal symmetric polyneuropathy at five weeks evaluation.[58] In addition, studies using diabetic rats have shown that oral supplementation with dihydrolipoic acid, the reduced form of ALA, delayed the development and progression of cataract in these rats.[59]

CAVEAT

Whenever supplementation with nutrients that are key to glucose metabolism is undertaken with the objective of reducing hyperglycemia significantly, it is important to monitor blood glucose levels adequately in order to avoid severe hypoglycemia during treatment. See Table 11–2 on page 133 for more detailed caveats.

Curcumin's ability to block initial DNA damage and to limit progression make curcumin a very promising preventive agent.

DIETARY INTERVENTIONS IN DIABETES MELLITUS

Dietary modifications can be a powerful tool for preventing and treating diabetes. If, for example, a clinician is treating a patient who is at a high risk of developing type 2 diabetes before symptoms of hyperinsulinemia and=or hyperglycemia become acute, this is an excellent opportunity to emphasize the potential benefit of cereal fiber. In a large prospective study of 65,173 females over six years, researchers looked for associations between the glycemic index of subjects' diets and their risk of developing type 2 diabetes.[60] A glycemic index is an indication of a food's potential to raise blood glucose and the demand the food creates for insulin. Foods with a high glycemic index generally include items such as white bread, mashed potatoes, white rice, and cola beverages. More intermediate-range glycemic foods are items such as apples and orange juice. Low-glycemic foods are generally those that maintain their natural unprocessed fibers, such as broccoli and peanut butter. In this prospective study, women in the quintile with the highest average glycemic index had a significantly higher risk of developing type 2 diabetes compared to women with the lowest average glycemic index. One of the strongest associations for an individual food type was seen in the analysis of cereal fiber

intakes and the risk for developing diabetes. Women in the study quintile with the highest median cereal fiber intake (7.5 g per day) had an RR of 0.72 of developing type 2 diabetes compared to the women in the quintile with the lowest median intake of cereal fiber (2.0 g per day). In contrast, women with a diet characterized by a high glycemic load and a low cereal fiber intake had an RR of 2.50 for developing type 2 diabetes compared to women eating a diet with a low glycemic load and high cereal fiber. Results from the same research team following a sample of more than 42,000 men prospectively were similar.[61]

An additional association in this work that was significant was the risk of diabetes and magnesium intake. In the women's study, subjects with a median intake of 338 mg per day had an RR of 0.62 compared to women with a median intake of 222 mg per day. This is especially important to keep in mind because a lack of sufficient magnesium is so easily remedied by magnesium supplementation. In fact, although supplementation did not seem to improve glycemic control in subjects who were already diagnosed with type 2 diabetes, there is research showing that magnesium levels tend to be low in subjects with diabetes and that three months of supplementation is adequate for reversing the problem.[62]

One form of fiber that may be particularly useful for treating patients once they are diagnosed with either type 1or type 2 diabetes is the fiber from legumes. In one study of 9 patients with type 1 diabetes and 18 with type 2 diabetes, subjects were placed for six weeks on a high carbohydrate diet that was rich in legumes and then also a low-carbohydrate diet for six weeks.[63] In subjects with diabetes of either type, the mean preprandial and two-hour postprandial blood glucose levels were significantly lower when the subjects were on the diet that was rich in legumes. The amount of glucose passed in the subjects' urine was also significantly less when they were on the high legume diet.

An additional consideration in the diet of patients with diabetes is the amount of protein they consume in relation to the health of their kidneys. One commonly referred to hypothesis suggests that too much protein intake causes hyperfiltration and glomerular hypertension, which leads to reduced kidney function and eventual nephropathy in some patients with diabetes.[64] Clinical data that seem to support this hypothesis come from trials that have utilized limited protein intake and have shown subsequent, significant drops in glomerular filtration rate (GFR) and=or the amount of albumin excretion in subjects with diabetes.[65,66] The complete relationship between protein consumption and kidney health in patients who have diabetes is a complex one and is beyond the scope of this book. One interesting hypothesis, however, is that, while some forms of protein, especially beef, increase postprandial renal plasma flow and GFR, soy does not seem to alter postprandial renal function, suggesting that substituting soy for animal protein might protect patients who have diabetes from nephropathy.[67] Unfortunately, a small pilot study designed to test this hypothesis, in which eight men with type 2 diabetes replaced half of their protein intake with soy protein, failed to show reduction in proteinuria. However, the study is important because it helps us to consider the concept that effects of protein intake on kidney health in patients with diabetes may be dependent on the type of protein being consumed. While we are still a long way from understanding the perfect diet for patients with diabetes, understanding which types of proteins will spare kidney function most effectively, and thus delay the onset of nephropathy, could certainly be a fruitful field for future research.

CONCLUSIONS

There is still much to learn about maximizing the benefits of nutrient supplementation, diet modification, and botanical medicines in preventing and treating diabetes. What information is

available, however, provides many potential complementary approaches that are worth trying to enable patients with this disorder to live longer and healthier lives.

REFERENCES

[1]American Diabetes Association. Diabetes Statistics. Available at: www.diabetes.org=diabetes-statistics .jsp. Accessed November 11, 2007.

[2]Forbes JM, Soldatos G, Thomas MC. Below the radar: Advanced glycation end products that detour ''around the side.'' Is HbA1c not an accurate enough predictor of long term progression and glycaemic control in diabetes? Clin Biochem Rev. 2005 Nov;26(4):123–134.

[3]Ahmed N, Babaei-Jadidi R, Howell SK, Thornalley PJ, Beisswenger PJ. Glycated and oxidized protein degradation products are indicators of fasting and postprandial hyperglycemia in diabetes. Diabetes Care. 2005 Oct;28(10):2465–2471.

[4]Goldberg T, Cai W, Peppa M, Dardaine V, Baliga BS, Uribarri J, Vlassara H. Advanced glycoxidation end products in commonly consumed foods. J Am Diet Assoc. 2004 Aug;104(8):1287–1291.

[5]Koschinsky T, He CJ, Mitsuhashi T, Bucala R, Liu C, Buenting C, Heitmann K, Vlassara H. Orally absorbed reactive glycation products (glycotoxins): An environmental risk factor in diabetic nephropathy. Proc Natl Acad Sci USA. 1997 Jun 10;94(12):6474–6479.

[6]Li SY, Liu Y, Sigmon VK, McCort A, Ren J. High-fat diet enhances visceral advanced glycation end products, nuclear O-Glc-Nac modification, p38 mitogen-activated protein kinase activation and apoptosis. Diabetes Obes Metab. 2005 Jul;7(4):448–454.

[7]Cerami C, Founds H, Nicholl I, Mitsuhashi T, Giordano D, Vanpatten S, Lee A, Al-Abed Y, Vlassara H, Bucala R, Cerami A. Tobacco smoke is a source of toxic reactive glycation products. Proc Natl Acad Sci USA. 1997 Dec 9;94(25):13915–13920.

[8]Wautier JL, Guillausseau PJ. Advanced glycation end products, their receptors and diabetic angiopathy. Diabetes Metab. 2001 Nov;27(5 Pt 1):535–542.

[9]Huebschmann AG, Regensteiner JG, Vlassara H, Reusch JE. Diabetes and advanced glycoxidation end products. Diabetes Care. 2006 Jun;29(6):1420–1432.

[10]Zieman SJ, Kass DA. Advanced glycation endproduct crosslinking in the cardiovascular system: Potential therapeutic target for cardiovascular disease. Drugs. 2004;64(5):459–470.

[11]Bucala R, Tracey KJ, Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes. J Clin Invest. 1991 Feb;87(2): 432–438.

[12]Wendt TM, Tanji N, Guo J, Kislinger TR, Qu W, Lu Y, Bucciarelli LG, Rong LL, Moser B, Markowitz GS, Stein G, Bierhaus A, Liliensiek B, Arnold B, Nawroth PP, Stern DM, D'Agati VD, Schmidt AM. RAGE drives the development of glomerulosclerosis and implicates podocyte activation in the pathogenesis of diabetic nephropathy. Am J Pathol. 2003 Apr;162(4):1123–1137.

[13]Koyama H, Shoji T, Yokoyama H, Motoyama K, Mori K, Fukumoto S, Emoto M, Shoji T, Tamei H, Matsuki H, Sakurai S, Yamamoto Y, Yonekura H, Watanabe T, Yamamoto H, Nishizawa Y. Plasma level of endogenous secretory RAGE is associated with components of the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol. 2005 Dec;25(12):2587–2593. Epub 2005 Oct 13.

[14]Ramakrishna V, Jailkhani R. Oxidative stress in non-insulin-dependent diabetes mellitus (NIDDM) patients. Acta Diabetol. 2007 Oct 9;[Epub ahead of print].

[15]Rebolledo OR, Actis Dato SM. Postprandial hyperglycemia and hyperlipidemia-generated glycoxidative stress: its contribution to the pathogenesis of diabetes complications. Eur Rev Med Pharmacol Sci. 2005 Jul–Aug;9(4):191–208.

[16]Morris BW, MacNeil S, Hardisty CA, Heller S, Burgin C, Gray TA. Chromium homeostasis in patients with type II (NIDDM) diabetes. J Trace Elem Med Biol. 1999;13(1–2):57–61.

[17]Anderson RA. Chromium, glucose tolerance and diabetes. J Am Coll Nutr. 1998;17:548–555.

[18]Sun Y, Ramirez J, Woski SA, Vincent JB. The binding of trivalent chromium to low–molecular-weight chromium-binding substance (LMWCr) and the transfer of chromium from transferrin and chromium picolinate to LMWCr. J Biol Inorg Chem. 2000;5(1):129–136.

[19]Speetjens JK, Collins RA, Vincent JB, Woski SA. The nutritional supplement chromium(III) tris(picolinate) cleaves DNA. Chem Res Toxicol. 1999 Jun;12(6):483–487.

[20]Trow LG, et al. Lack of effect of dietary chromium supplementation on glucose tolerance, plasma insulin and lipoprotein levels in patients with type 2 diabetes. Int J Vitam Nutr Res. 2000;70(1):14–18.

[21]Kozlovsky AS, Moser PB, Reiser S, Anderson RA. Effects of diets high in simple sugars on urinary chromium losses. Metabolism. 1986;35:515–518.

[22]Goldfine AB, et al. Metabolic effects of vanadyl sulfate in humans with non–insulin-dependent diabetes mellitus: In vivo and in vitro studies. Metabolism. 2000;49(3):400–410.
[23]Boden G, Chen X, Ruiz J, van Rossum GD, Turco S. Effects of vanadyl sulfate on carbohydrate and lipid metabolism in patients with non–insulin-dependent diabetes mellitus. Metabolism. 1996;45(9):1130–1135.
[24]Cohen N, Halberstam M, Shlimovich P, Chang CJ, Shamoon H, Rossetti L. Oral vanadyl sulfate improves hepatic and peripheral insulin sensitivity in patients with non–insulin-dependent diabetes mellitus. J Clin Invest. 1995;95(6):2501–2509.
[25]Tas S, Sarandol E, Ayvalik SZ, Serdar Z, Dirican M. Vanadyl sulfate, taurine, and combined vanadyl sulfate and taurine treatments in diabetic rats: Effects on the oxidative and antioxidative systems. Arch Med Res. 2007 Apr;38(3):276–283. Epub 2007 Jan 22.
[26]Davis RE, Calder JS, Curnow DH. Serum pyridoxal and folate concentrations in diabetics. Pathology. 1976;8(2):151–156.
[27]McCann VJ, Davis RE. Serum pyridoxal concentrations in patients with diabetic neuropathy. Aust NZ J Med. 1978;8(3):259–261.
[28]Stracke H, Lindemann A, Federlin K. A benfotiamine–vitamin B combination in treatment of diabetic polyneuropathy. Exp Clin Endocrinol Diabetes. 1999;104(4):311–316.
[29]Coggeshall JC, Heggers JP, Robson MC, Baker H. Biotin status and plasma glucose in diabetics. Ann NY Acad Sci. 1985;447:389–392.
[30]Cleary JP, Vitamin B_3 in the treatment of diabetes mellitus: Case reports and review of literature. J Nutr Med. 1990;1:217–225.
[31]Mandrup T, et al. Nicotinamide in the prevention of insulin dependent diabetes mellitus. Diabetes Metabol Rev. 1993;9:295–309.
[32]Chakravarthy BK, Gupta S, Gode KD. Functional beta cell regeneration in the islets of pancreas in alloxan induced diabetic rats by (-)-epicatechin. Life Sci. 1982;31(24):2693–2697.
[33]Indian Council of Medical Research (ICMR), Collaborating Centres, New Delhi [no authors listed]. Flexible dose open trial of Vijayasar in cases of newly diagnosed non–insulin-dependent diabetes mellitus. Indian J Med Res. 1998;108:24–29.
[34]Sharma RD, Roghurem TC, Rao NS. Effect of fenugreek seeds on blood glucose and serum lipids in type 1 diabetes. Eur J Clin Nutr. 1990;44(4):301–306.
[35]Gupta A, Gupta R, Lal B. Effect of Trigonella foenum-graecum (fenugreek) seeds on glycaemic control and insulin resistance in type 2 diabetes mellitus: A double blind placebo controlled study. J Assoc Physicians India. 2001 Nov;49:1057–1061.
[36]Hannan JM, Ali L, Rokeya B, Khaleque J, Akhter M, Flatt PR, Abdel-Wahab YH. Soluble dietary fibre fraction of Trigonella foenum-graecum (fenugreek) seed improves glucose homeostasis in animal models of type 1 and type 2 diabetes by delaying carbohydrate digestion and absorption, and enhancing insulin action. Br J Nutr. 2007 Mar;97(3):514–521.
[37]Leatherdale BA, et al. Improvement in glucose tolerance due to Momordica charantia (karela). Br Med J (Clin Res Ed). 1981;282(6279):1823–1824.
[38]Ahmad N, Hassan MR, Halder H, Bennoor KS. Effect of Momordica charantia (Karolla) extracts on fasting and postprandial serum glucose levels in NIDDM patients. Bangladesh Med Res Counc Bull. 1999 Apr;25(1):11–13.
[39]Ojewole JA, Adewole SO, Olayiwola G. Hypoglycaemic and hypotensive effects of Momordica charantia Linn (Cucurbitaceae) whole-plant aqueous extract in rats. Cardiovasc J S Afr. 2006 Sep–Oct;17(5):227–232.
[40]Fernandes NP, Lagishetty CV, Panda VS, Naik SR. An experimental evaluation of the anti-diabetic and antilipidemic properties of a standardized Momordica charantia fruit extract. BMC Complement Altern Med. 2007 Sep 24;7:29.
[41]Shanmugasundaram ER, et al. Use of Gymnema sylvestre leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. J Ethnopharmacol. 1990;30(3):281–294.
[42]Shanmugasundaram ER, et al. Antidiabetic effect of a leaf extract from Gymnema sylvestre in non–insulin-dependent diabetes mellitus patients. J Ethnopharmacol. 1990;30(3):295–300.
[43]Mang B, Wolters M, Schmitt B, Kelb K, Lichtinghagen R, Stichtenoth DO, Hahn A. Effects of a cinnamon extract on plasma glucose, HbA, and serum lipids in diabetes mellitus type 2. Eur J Clin Invest. 2006 May;36(5):340–344.
[44]Khan A, Safdar M, Ali Khan MM, Khattak KN, Anderson RA. Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care. 2003 Dec;26(12):3215–3218.
[45]Hlebowicz J, Darwiche G, Björgell O, Almér LO. Effect of cinnamon on postprandial blood glucose, gastric emptying, and satiety in healthy subjects. Am J Clin Nutr. 2007 Jun;85(6):1552–1556.
[46]Atanasov AT, Tchorbanov B. Anti-platelet fraction from Galega officinalis L. inhibits platelet aggregation. J Med Food. 2002 Winter;5(4):229–234.

[47]Pundarikakshudu K, Patel JK, Bodar MS, Deans SG. Anti-bacterial activity of Galega officinalis L. (Goat's Rue). J Ethnopharmacol. 2001 Sep;77(1):111–112.
[48]Witters LA. The blooming of the French lilac. J Clin Invest. 2001 Oct;108(8):1105–1107.
[49]Jackson MC, Lenney JF. The distribution of carnosine and related dipeptides in rat and human tissues. Inflamm Res. 1996 Mar;45(3):132–135.
[50]Hipkiss AR. Would carnosine or a carnivorous diet help suppress aging and associated pathologies? Ann NY Acad Sci. 2006 May;1067:369–374.
[51]Stuerenburg HJ. The roles of carnosine in aging of skeletal muscle and in neuromuscular diseases. Biochemistry (Mosc). 2000 Jul;65(7):862–865.
[52]Guiotto A, Calderan A, Ruzza P, Borin G. Carnosine and carnosine-related antioxidants: A review. Curr Med Chem. 2005;12(20):2293–2315.
[53]Peterszegi G, Molinari J, Ravelojaona V, Robert L. Effect of advanced glycation end-products on cell proliferation and cell death. Pathol Biol (Paris). 2006 Sep;54(7):396–404. Epub 2006 Aug 21.
[54]Kamenova P. Improvement of insulin sensitivity in patients with type 2 diabetes mellitus after oral administration of alpha-lipoic acid. Hormones (Athens). 2006 Oct–Dec;5(4):251–258.
[55]Song KH, Lee WJ, Koh JM, Kim HS, Youn JY, Park HS, Koh EH, Kim MS, Youn JH, Lee KU, Park JY. alpha-Lipoic acid prevents diabetes mellitus in diabetes-prone obese rats. Biochem Biophys Res Commun. 2005 Jan 7;326(1):197–202.
[56]Thirunavukkarasu V, Anitha Nandhini AT, Anuradha CV. Lipoic acid improves glucose utilization and prevents protein glycation and AGE formation. Pharmazie. 2005 Oct;60(10):772–775.
[57]Yi X, Maeda N. alpha-Lipoic acid prevents the increase in atherosclerosis induced by diabetes in apolipoprotein E-deficient mice fed high-fat=low-cholesterol diet. Diabetes. 2006 Aug;55(8):2238–2244.
[58]Tang J, Wingerchuk DM, Crum BA, Rubin DI, Demaerschalk BM. Alpha-lipoic acid may improve symptomatic diabetic polyneuropathy. Neurologist. 2007 May;13(3):164–167.
[59]Kojima M, Sun L, Hata I, Sakamoto Y, Sasaki H, Sasaki K. Efficacy of alpha-lipoic acid against diabetic cataract in rat. Jpn J Ophthalmol. 2007 Jan–Feb;51(1):10–13. Epub 2007 Feb 9.
[60]Salmeron J, et al. Dietary fiber, glycemic load, and risk of non–insulin dependent diabetes mellitus in women. JAMA. 1997;277(6):472–477.
[61]Saleron J, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care. 1997;20(4): 545–550.
[62]Eibl NL, Schmack CJ, Kopp HP, et al. Hypomagnesemia in type II diabetes: Effect of a 3-month replacement therapy. Diabetes Care. 1996;18(2):188–192.
[63]Simpson HC, et al. A high carbohydrate leguminous fibre diet improves all aspects of diabetic control. Lancet. 1981;(8210):1–5.
[64]Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: The role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med. 1982;307:652–659.
[65]Cohen D, Dodds R, Viberti G. Effect of protein restriction in insulin dependent diabetics at risk of nephropathy. Br Med J (Clin Res Ed). 1987;294(6575):795–798.
[66]Pedersen MM, et al. Renal effects from limitation of high dietary protein in normoalbuminuric diabetic patients. Kidney Int. 1989;27(suppl.):S115–S121.
[67]Anderson JW, Blake JE, Turner J, Smith B. Effects of soy protein on renal function and proteinuria in patients with type 2 diabetes. Am J Clin Nutr. 1998;68(6 suppl.):1347S–1353S.
[68]American Diabetes Association. Complications of Diabetes in the United States. Available at: www .diabetes.org=diabetes-statistics=complications.jsp. Accessed November 11, 2007.

12

NATURAL APPROACHES TO RELIEVING ENDOMETRIOSIS

Endometriosis is a common gynecologic condition in which endometrial tissue grows in ectopic locations. It is estimated that 5 million women of reproductive age, or 10% of women in the United States, are affected by this disease.[1] Approximately 20% of women with chronic pelvic pain and 30%–45% of women with infertility have endometriosis.[2] Endometrial tissue outside the uterus responds to normal hormonal signaling from estrogen and progesterone. Just as in the uterus, these hormones cause cyclic growth and bleeding of the tissues, often into the peritoneal cavity. Adhesions and inflammation also develop from the accumulation of tissue. The etiology of endometriosis is still unknown and no current theory explains all the aspects of the disease. However, increasing evidence suggests that environmental estrogenic toxins, stress, and the immune dysfunction they cause may be implicated in the etiology and progression of the disease.

ETIOLOGY

Researchers have found a genetic correlation in endometriosis development. Women who have first-degree relatives with the disease have 10 times the risk of developing endometriosis.[3] In addition, women with family histories of endometriosis are statistically more likely to experience an earlier onset and increased severity of the disease.[4] Recent studies suggest oxidative stress, environmental toxin exposure, and immune dysfunction as possible factors in the onset and progression of endometriosis. Chlorinated hydrocarbons such as dioxin and polychlorinated biphenyls (PCBs), which have adverse clinical effects on the immune and endocrine systems, have been associated with endometriosis. For example, several studies on monkeys have demonstrated a direct correlation between dioxin exposure and endometriosis. In these studies, the amount of dioxin exposure was correlated with severity of disease. The monkeys showed immune system dysfunction similar to the immune abnormalities seen in women with endometriosis.[5,6] Studies have also shown that dioxin modulates steroid receptor expression (thus changing hormonal responses) decreases natural-killer (NK) cell activity, inhibits T-lymphocytes, and stimulates macrophages in the peritoneal fluid, thus affecting angiogenesis and concentration of cytokines and growth factors.[7–9] Dioxins and PCBs suppress the immune system; impair reproductive capabilities; increase the risk of multiple cancers, diabetes, and cardiovascular disease; and reduce memory function. Exposure to dioxin and dioxin-like PCBs occurs primarily via food such as animal fat and fish, and pesticides and other environmental sources.[10–14] Other risk factors have been implicated in endometriosis, such as menstrual cycles that are less than 28 days, heavy flows lasting 5 or more days, menses that last more than 7 days, and increased estrogen levels. Endometriosis development is also associated with increased body fat, a high-fat diet, lack of exercise, and use of intrauterine devices.[15] In a small study, researchers found a significant association between natural red hair color and frequency of the disease.[16]

SYMPTOMS

Classically, patients with endometriosis present with chronic or cyclic pelvic pain and infertility. Pain often begins 1 to 2 days prior to onset of menstruation and may last several days or throughout the menstrual period. Additional symptoms may include dyspareunia, abnormal uterine bleeding, cyclic pain with defecation or urination, blood in urine or stool, constipation, diarrhea, nausea, vomiting, and fainting. However, one-third of women diagnosed with endometriosis are asymptomatic. The severity of pelvic pain does not correlate with the extent of the disease though it may correlate with the proximity of adhesions to nerve endings (see the box below entitled "Symptoms of Endometriosis").[17]

PATHOLOGY

Endometriomas are commonly found on the ovaries; fallopian tubes; peritoneal lining; cervix; colon; appendix; vagina; and uterosacral, broad, and round ligaments. In severe cases, adhesions are also found on the bladder, kidney, vulva, arms, legs, lungs, nasal mucosa, spinal column, and sites of previous surgical incisions.[2] Two-thirds of women with endometriosis have their ovaries affected; in 30% of women, local lymph nodes are involved; and in 10%–15% of women, the sigmoid colon is affected.[2]

The immune system is implicated in the development, progression, and symptoms of endometriosis. Both humoral and cell-mediated acquired immune responses are abnormal in women who have this disease. Humoral immune responses are mediated by immunoglobulins or antibodies such as immunoglobulin E (IgE), IgG, IgD, IgA, and IgM. T-lymphocytes mediate the cellular immune responses and have receptors on their membranes, which respond to antigens. Antigens binding to these receptors activate the cells to release a number of cytokines, which cause inflammation and tissue damage. Studies have shown that many of these pro-inflammatory chemical mediators are elevated in the peritonea of women with endometriosis.[18] Women with endometriosis have abnormalities in immune functioning cells, such as NK cells, cytotoxic T-cells, B-lymphocytes, macrophages, and monocytes.[19] NK cells are responsible for destroying ectopic endometrial cells and are decreased in function and concentration in women with endometriosis.[18,20] Studies have also shown that, in affected women, cytotoxic T-cells are decreased and T-suppressor cells are increased. T-suppressor cells reduce the immune response to foreign or host agents; the increase in these cells may reduce the ability of the immune system to identify and remove the ectopic endometrial tissue.[21] The macrophage count has been shown to be elevated in the peritoneal fluid in women with endometriosis. Macrophages secrete cellular mediators, such as prostaglandins, fibronectins, integrins,

Symptoms of Endometriosis

- Chronic pelvic pain
- Infertility
- Dyspareunia
- Abnormal uterine bleeding
- Cyclic pain with defecation or urination
- Blood in urine or stool
- Constipation, diarrhea
- Nausea, vomiting
- Fainting

Procedures for Diagnosing Endometriosis

- Physical examination
- Ultrasound or magnetic resonance imaging
- Laparoscopy or laparotomy
- Serum CA-125 testing

and other cytokines that promote the development and progression of endometriosis. In women with endometriosis, the macrophages do not appear to phagocytize. Failure of the macrophages to phagocytize may also explain the persistence of ectopic endometrial tissue in the peritoneal cavity.[22] Other studies have shown that macrophages secrete high levels of the cytokine transforming growth factor-beta (TGF-b) that inhibits NK cells while increasing scarring and fibrosis. TGF-beta also stimulates angiogenesis, which allows the ectopic endometrial tissue to generate its own blood supply.[23] Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-a), interleukin-1 (IL-1), and IL-6, are also elevated in the peritoneal fluid of women with endometriosis.[18] Researchers have shown that B-lymphocyte antibody production is abnormal in women with endometriosis, who have increased levels of IgG and IgM antibodies. In addition, autoantibodies against the ectopic endometrium are found in the cervical and vaginal secretions and sera in these women.[24,25]

Stress may also play a role in the initiation and=or progression of this disease. Studies have shown that the hormones increased in the stress response are also elevated in women with endometriosis. In fact, levels of cortisol, the main glucocorticoid in the stress response, are increased in direct proportion to the severity of the disease. Prolactin is also elevated with increasing severity and may be a factor in the infertility seen with this condition. Also, elevated cortisol is known to adversely affect the immune response such as inhibition of NK cells and T lymphocytes, which is notably abnormal in affected women.[26]

Researchers have linked endometriosis to such diseases as systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and Sjögren's syndrome, which suggests that endometriosis may have an autoimmune component. Other conditions, such as fibromyalgia, chronic fatigue syndrome, hypothyroidism, allergies, asthma, and eczema, are significantly more common in women with endometriosis than in the general female population of the United States.[27] Endometriosis is also correlated with an increased risk of ovarian cancer and non-Hodgkin's lymphoma.[28,29]

DIAGNOSIS

Diagnosis of endometriosis is often difficult because the disease has various presentations. Physical examination of a patient may reveal a fixed retroverted uterus, enlarged ovaries, and nodules on the uterosacral ligaments. Transvaginal sonography is often utilized to access large ovarian, intestinal, or bladder endometriomas. It is less accurate for rectovaginal, vaginal, or uterosacral lesions. CA-125 is a blood test that can indicate the presence of endometriosis, although the test is not utilized often for diagnostic purposes because of its low sensitivity. Laparoscopy with biopsy provides a definitive diagnosis (see the box above entitled "Procedures for Diagnosing Endometriosis").

Figure 12–1. Walnuts.

CONVENTIONAL TREATMENT

Conventional medical treatment focuses on reducing estrogen stimulation, managing pain, and preserving fertility. At the time of laparoscopic diagnosis, treatment often begins as visible lesions are removed or destroyed. Hormone therapy is commonly utilized because endometrial tissue responds to hormone stimulation. Estrogen has been shown to increase aberrant endometrial lesions, while progesterone and androgens may decrease implant size. Hormone modulation does not cure endometriosis and the disease often returns upon discontinuation of pharmaceutical therapy.[2]

PHARMACOLOGY

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed to manage pelvic pain. Prostaglandins are responsible for much of the pain associated with endometriosis; because NSAIDs inhibit prostaglandin synthesis, they often reduce pain. Hormones typically used in treatment are danazol, a weak androgen that decreases follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secreted from the pituitary gland, thereby inhibiting ovulation and menstruation; oral contraceptives; progestins; and gonadotropin-releasing hormone agonists (GnRH agonists) that suppress FSH and LH and inhibit ovulation. Studies have demonstrated reduction of symptoms in 67% or more individuals on oral contraceptive treatment (see the box on page 149 entitled "Pharmacologic Interventions for Treating Endometriosis").[30]

Figure 12–2. Sunflower.

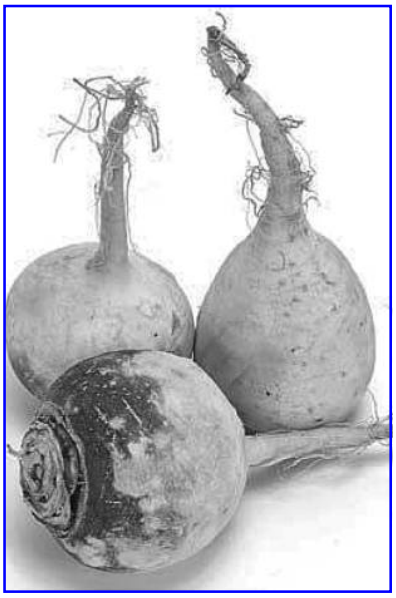

Figure 12–3. Turnip.

NUTRIENT AND HERBAL INTERVENTIONS

Fatty-Acid Supplements

Supplementation with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), and gamma-linolenic acid (GLA) can reduce inflammation. The omega-3 fatty acids EPA and DHA compete with arachidonic acid (AA) in the lipo- and cyclo-oxygenase pathways and, therefore, decrease levels of inflammatory eicosanoids.[31–33] Studies have demonstrated that fish oils high in DHA and EPA reduce the production of pro-inflammatory cytokines, such as IL-1, IL-2, and TNF. These fish oils also can suppress B- and T-lymphocyte synthesis and decrease antibody production.[34–37]

GLA, an omega-6 fatty acid found in borage (Borago officinalis) seed oil, evening primrose (Oenothera biennis) oil, and black currant (Ribes nigrum) oil, is metabolized in the body to the anti-inflammatory series 1 prostaglandins and inhibits AA from forming pro-inflammatory leukotrienes.[38] Linoleic acid (LA) is an omega-6 fatty acid that is the precursor to GLA and can be used to stimulate the anti-inflammatory pathway. LA is commonly found in the oils of corn, safflowers, sesame, soybeans, sunflowers, walnuts, grape seeds, and wheat germ. ALA is an omega-3 fatty acid found in flax (Linum usitatissimum), rapeseed (Brassica napus), and soy (Glycine soja) beans as well as in walnuts, pumpkin seeds, and perilla seeds and is a precursor to EPA. The enzyme delta-6-desaturase converts LA and ALA to GLA and EPA and requires magnesium, vitamin B_6, and zinc as cofactors. Often, clinical failure of essential fatty acid (EFA) intervention results from the inadequate presence of these cofactors. Due to decreased conversion in some individuals, taking EPA=DHA and GLA is usually recommended.

Figure 12–4. Corn.

Vitamin E

Lipoxygenase catalyzes the conversion of AA to leukotrienes, which are potent inflammatory mediators. Vitamin E alters the leukotriene and cyclo-oxygenase pathway by inhibiting pro-inflammatory prostaglandin E2 and leukotriene B4 formation. Gamma-Tocopherol, the most

Pharmacologic Interventions for Treating Endometriosis

- Non-steroidal anti-inflammatory drugs
- Danazol
- Oral contraceptives
- Progestins
- Gonadotropin-releasing hormone agonists

common form of vitamin E in American diets, decreases TNF-alpha, which is elevated in women with endometriosis.[39] Studies also indicate that vitamin E succinate and vitamin A protect tissues against damage from dioxin exposure.[40,41] It is important to keep in mind, however, that high-dose vitamin E therapy may have antiplatelet aggregating effect, which thins the blood and increases the likelihood of hemorrhage, independently or in conjunction with anticoagulant and antithrombotic pharmaceutical drugs.[41]

Vitamin C

Vitamin C increases T-lymphocyte activity, phagocyte function, leukocyte mobility, and interferon production. Studies have shown abnormal phagocytes, antibodies, and cytokines in women with endometriosis, so vitamin C may be therapeutically useful. Because it is an antioxidant, vitamin C can protect cells from reactive oxygen species known to cause tissue damage and disease. This protective effect may also prevent tissue damage from dioxin and PCBs. Women with high estrogen levels, oral contraceptive users, and nicotine users will have increased vitamin C excretion and measurably lower plasma levels, and these women might require higher levels of supplementation.[42,43]

Beta-Carotene

Beta-carotene has been shown to prevent lipid peroxidation and reduce free-radical DNA damage.[44,45] Beta-carotene can also increase the function of NK cells.[46] Carotenoids provide approximately 50% of the vitamin A in the American diet, and studies have shown that vitamin A has protective effects against dioxin-induced tissue damage.[43,47] Supplementation with mixed carotenoids is generally recommended.

Milk Thistle

Silymarin, the main active constituent in milk thistle (Silybum marianum), has been shown to reduce TNF cytotoxic and pro-inflammatory functions.[48] Constituents of milk thistle inhibit lipid peroxidation and are antioxidants and free-radical scavengers.[49] Silymarin also prevents toxin penetration into liver cells and may be able to decrease toxic metabolite formation in the liver. In addition, estrogen clearance may be increased as a result of silymarin inhibition of beta-glucuronidase.[50]

Crampbark and Black Haw

Crampbark (Viburnum opulus) and black haw (Viburnum prunifolium) are antispasmodics. Scopoletin and viopudial are two constituents that, because of their antispasmodic action on

smooth muscle, can decrease menstrual cramps and other muscle spasms. In addition, the scopoletin in black haw has been shown to relax the uterus.[51] Animal studies have shown that viopudial in crampbark has cholinergic activity that can decrease blood pressure, heart rate, and myocardial contractility.[52]

Black Cohosh

Constituents of black cohosh (Cimicifuga racemosa) are anti-inflammatory and have estrogen-like activity.[53,54] Animal studies suggest that black cohosh suppresses pituitary secretion of LH. Studies indicate that the herb may be a selective estrogen receptor–modulator that has estrogenic effects on some tissues and antiestrogenic effects on other tissues.[55] New data suggest that black cohosh does not bind estrogen receptors, stimulate the growth of estrogen-dependent tumors, or up-regulate estrogen-dependent genes.[56]

Natural Progesterone

Progesterone is commonly prescribed to treat menopausal symptoms, abnormal uterine bleeding, premenstrual syndrome, endometrial hyperplasia, and infertility. Progesterone causes uterine smooth-muscle relaxation.[57] Low levels of progesterone can cause a relative estrogen excess; excessive estrogen is implicated in endometriosis. Thus, a clinical trial of progesterone therapy in conjunction with immunologic and inflammatory modulation of the internal biochemical milieu appears to be a rational approach to treating endometriosis.

Chaste tree

Chaste tree (Vitex agnus castus) may provide some benefit in women with endometriosis, although direct evidence is lacking. Studies show that it alleviates many symptoms associated

Table 12–1. Natural Interventions for Endometriosis

Interventions	Doses
Eicosapentaenoic acid	1–3 g per day
Docosahexaenoic acid	1–3 g per day
a-linolenic acid	1.2–2 g per day
g-linolenic acid	900–1,500 mg per day
Vitamin E (mixed tocopherols)	400–800 IU per day
Vitamin C	1–3 g per day
b-carotene	25,000–50,000 IU per day
Milk thistle (Silybum marianum)	420 mg per day, standardized to 70%–80% silymarin
Crampbark (Viburnum opulus); black haw (Viburnum prunifolium)	5–10 mL, 3 times per day
Black cohosh (Cimicifuga racemosa)	40–80 mg, 2 times per day, providing 4–8 mg triterpene glycosides
Natural progesterone	1=8 to 1=4 tsp topically, 2 times per day, on days 15–28 of the menstrual cycle

IU international units.

with premenstrual syndrome, such as irritability, mood alteration, anger, headache, and breast fullness.[58]

Adaptogenic Herbs

Numerous botanicals are used to moderate the stress response and may provide benefit in these women. Adaptogenic herbs are those that are believed to normalize cortisol and adrenal function. These include Rhodiola rosea, Withania somnifera (Ashwagandha), Eleutherococcus senticosus (Siberian Ginseng), Panax ginseng, and Glycyrrhiza glabra (Licorice). (See Chapter 1 on adrenal fatigue.)

DIETARY INTERVENTIONS

A well-nurtured body is a more resilient one. A healthy diet and stress reduction can help alleviate not only the symptoms but also the imbalances that underlie endometriosis. Diets high in fruits and vegetables provide the vitamins and flavonoids required to decrease inflammation and oxidation. Nutritional status affects the immune response, inflammation, and hormone regulation. Studies have demonstrated that dietary vitamins and minerals protect patients against immune suppression caused by dioxin exposure and that dietary fiber promotes fecal excretion of dioxin.[59] The phytochemical indole-3-carbinol found in cruciferous vegetables, such as kale, turnips, broccoli, cauliflower, cabbage, collard greens, and mustard greens, may prove to be clinically useful for treating endometriosis because this phytochemical modulates estrogen levels. Liver function can be improved by increasing intake of artichokes, burdock root, beets, dandelion greens, lemons, carrots, onions, and garlic. Diets high in EFAs and low in dairy products and red meat decrease AA and thus act as inflammatory mediators. GLA is found in black currant seed, borage oil, and evening primrose oils. EPA and DHA are found in fatty fish including herring, salmon, cod, mackerel, sardines, trout, and kipper. Studies suggest a correlation between endometriosis and caffeine consumption; caffeine should therefore be strictly avoided.[60] In addition, alcohol should be limited because of its potential estrogenic effects and depletion of B vitamins.

CONCLUSIONS

Endometriosis can be treated with a variety of herbs, supplements, and dietary interventions, thus reducing or eliminating the need for conventional pharmaceutical treatments. As with any intervention, the approach to each patient needs to be individualized, taking into account each patient's body chemistry and needs.

REFERENCES

[1]Frankiewics J. Endometriosis: An overview of the disease and its treatment. J Am Pharm Assoc. 2000; 40:645–657.

[2]Herbst A, Droegemueller W, et al. Comprehensive Gynecology, 3rd Edition. St. Louis: Mosby-Year Book, 1997.

[3]American College of Obstetricians and Gynecologists (ACOG). Endometriosis. ACOG Technical Bulletin 194. Washington, DC: ACOG, 1993.

[4]Dmowski WP, Lesniewicz R, et al. Changing trends in the diagnosis of endometriosis: A comparative study of women with pelvic endometriosis presenting with chronic pelvic pain or infertility. Fertil Steril. 1997;67:238–243.

[5]Rier SE, Martin DC, et al. Endometriosis in rhesus monkeys (Macaca mulatta) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Fundam Appl Toxicol. 1993;21:433–441.

[6]Rier SE, Turner WE, et al. Serum levels of TCDD and dioxin-like chemicals in rhesus monkeys chronically exposed to dioxin: Correlation of increased serum PCB levels with endometriosis. Toxicol Sci. 2001;59:147–159.

[7]Safe S, Astroff B, et al. 2,3,7,8-Tetrachlorodibenzo-p-dioxin and related compounds as antiestrogens: Characterization and mechanism of action. Pharmacol Toxicol. 199;69:400–409.

[8]Clark GC, Taylor J, et al. Tumor necrosis factor involvement in 2,3,7,8-tetrachlorodibenzo-p-dioxin–mediated endotoxin hypersensitivity in C57BL=6J mice congenic at the Ah locus. Toxicol Appl Pharmacol. 1991;111:422–431.

[9]Neubert R, Jacob-Muller U, et al. Polyhalogenated dibenzo-p-dioxins and dibenzofurans and the immune system: 2. In vitro effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on lymphocytes of venous blood from man and a non-human primate (Callithrix jacchus). Arch Toxicol. 1991;65:213–219.

[10]Barrett DH, Morris RD, et al. Serum dioxin and cognitive functioning among veterans of Operation Ranch Hand. Neurotoxicology. 2001;22:491–502.

[11]Lind PM, Orberg J, et al. The dioxin-like pollutant PCB 126 (3,3'4,4',5-pentachlorobiphenyl) affects risk factors for cardiovascular disease in female rats. Toxicol Lett. 2004;150:293–299.

[12]Crump KS, Canady R, et al. Meta-analysis of dioxin cancer dose response for three occupational cohorts. Environ Health Perspect. 2003;111:681–687.

[13]Michalek JE, Akhtar FZ, et al. Serum dioxin, insulin, fasting glucose, and sex hormone-binding globulin in veterans of Operation Ranch Hand. J Clin Endocrinol Metab. 1999;84:1540–1543.

[14]Roman BL, Peterson RE. In utero and lactational exposure of the male rat to 2,3, 7,8-tetrachlorodibenzo-p-dioxin impairs prostate development:1. Effects on gene expression. Toxicol Appl Pharmacol. 1998;150: 240–253.

[15]Cramer DW, Wilson E, et al. The relation of endometriosis to menstrual characteristics, smoking, and exercise. JAMA. 1986;255:1904–1908.

[16]Woodworth SH, Singh M, et al. A prospective study on the association between red hair color and endometriosis in infertile patients. Fertil Steril. 1995;64:651–652.

[17]Lauersen N, deSwaan C. The Endometriosis Answer Book: New Hope, New Help. New York: Ballantine Books, 1998:27.

[18]Ho HN, Wu MY, et al. Peritoneal cellular immunity and endometriosis. Am J Reprod Immunol. 1997; 38:400–412.

[19]Dmowski WP, Gebel HM, et al. The role of cell-mediated immunity in pathogenesis of endometriosis. Acta Obstet Gynecol Scand Suppl. 1994;159(suppl.):7–14.

[20]Garzetti GG, Ciavattini A, et al. Natural killer activity in stage III and IV endometriosis: Impaired cytotoxicity and retained lymphokine responsiveness of natural killer cells. Gynecol Endocrinol. 1995; 9: 125–130.

[21]Iwasaki K, Makino T, et al. Leukocyte subpopulations and natural killer activity in endometriosis. Int J Fertil Menopausal Stud. 1993;38:229–234.

[22]Gazvani R, Templeton A. Peritoneal environment, cytokines, and angiogenesis in the pathology of endometriosis. Reproduction. 2002;123:217–226.

[23]Oosterlynck DJ, Meuleman C, et al. Transforming growth factor-beta activity is increased in peritoneal fluid from women with endometriosis. Obstet Gynecol. 1994;83:287–292.

[24]Iborra A, Palacio JR, et al. Autoimmune response in women with endometriosis. Am J Reprod Immunol. 2000;44:236–241.

[25]Gleicher N, el-Roeiy A, et al. Is endometriosis an autoimmune disease? Obstet Gynecol. 1987;70: 115–122.

[26]Lima AP, Moura MD, Rosa e Silva AA. Prolactin and cortisol levels in women with endometriosis. Braz J Med Biol Res. 2006 Aug;39(8):1121–1127.

[27]Sinaii N, Cleary SD, et al. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: A survey analysis. Hum Reprod. 2002;17:2715–2724.

[28]Olson JE, Cerhan JR, et al. Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study. Cancer. 2002;94:1612–1618.

[29]Ness RB, Grisso JA, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology. 2000;11:111–117.

[30]Vercellini P, De Giorgi O, et al. Cyproterone acetate versus a continuous monophasic oral contraceptive in the treatment of recurrent pelvic pain after conservative surgery for symptomatic endometriosis. Fertil Steril. 2002;77:52–61.
[31]Leaf A. On the reanalysis of the GISSI-Prevenzione. Circulation. 2002;105:1874–1875.
[32]Connor WE. n-3 Fatty acids from fish and fish oil: Panacea or nostrum? Am J Clin Nutr. 2001;74;415–416.
[33]Calder PC. N-3 polyunsaturated fatty acids, inflammation and immunity: Pouring oil on troubled waters or another fishy tale? Nutr Res. 2001;21:309–341.
[34]Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration. Letter regarding dietary supplement health claim for omega-3 fatty acids and coronary heart disease. Online document at: http:=vm.cfsan.fda.gov=~dms=ds-ltr11.html. Accessed May 10, 2005.
[35]Kelley DS, Rudolph IL. Effect of individual fatty acids of omega-6 and omega-3 type on human immune status and role of eicosanoids. Nutrition. 2000;16:143–145.
[36]Meydani SN, Dinarello CA. Influence of dietary fatty acids on cytokine production and its clinical implications. Nutr Clin Pract. 1993;8:65–72.
[37]Burns CP, Halabi S, et al. Phase II study of high-dose fish oil capsules for patients with cancer-related cachexia. Cancer. 2004;101:370–378.
[38]Leventhal LJ, Boyce EG, et al. Treatment of rheumatoid arthritis with gamma linolenic acid. Ann Intern Med. 1993;119:867–873.
[39]Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington, DC: National Academy Press, 2000. Online document at: www.nap.edu=books=0309069351=html. Accessed May 10, 2005.
[40]Jiang Q, Ames BN. Gamma-tocopherol, but not alpha-tocopherol, decreases proinflammatory eicosanoids and inflammation damage in rats. FASEB J. 2003;17:816–822.
[41]Alsharif NZ, Hassoun EA. Protective effects of vitamin A and vitamin E succinate against 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)–induced body wasting, hepatomegaly, thymic atrophy, production of reactive oxygen species and DNA damage in C57BL=6J mice. Basic Clin Pharmacol Toxicol. 2004; 95:131–138.
[42]Lykkesfeldt J, Christen S, et al. Ascorbate is depleted by smoking and replaced by moderate supplementation: A study in male smokers and nonsmokers with matched dietary antioxidant intakes. Am J Clin Nutr. 2000;71:530–536.
[43]Thorp VJ. Effect of oral contraceptive agents on vitamin and mineral requirements. J Am Diet Assoc. 1980;76:581–584.
[44]Manda K, Bhatia AL. Pre-administration of beta-carotene protects tissue glutathione and lipid peroxidation status following exposure to gamma radiation. J Environ Biol. 2003;24:369–372.
[45]Omenn GS. Chemoprevention of lung cancer: The rise and demise of beta-carotene. Ann Rev Public Health. 1998;19:73–99.
[46]Carlos TF, Riondel J, et al. Beta-carotene enhances natural killer cell activity in athymic mice. In Vivo. 1997;11:87–91.
[47]Hickenbottom SJ, Follett JR, et al. Variability in conversion of beta-carotene to vitamin A in men as measured by using a double-tracer study design. Am J Clin Nutr. 2002;75:900–907.
[48]Manna SK, Mukhopadhyay A, et al. Silymarin suppresses TNFinduced activation of NF-kappa B, c-Jun N-terminal kinase, and apoptosis. J Immunol. 1999;163:6800–6809.
[49]Flora K, Hahn M, et al. Milk thistle (Silybum marianum) for the therapy of liver disease. Am J Gastroenterol. 1998;93:139–143.
[50]Agency for Healthcare Research and Quality. Milk thistle: Effects on liver disease and cirrhosis and clinical adverse effects. Summary, Evidence Report=Technology Assessment: Number 21. Rockville, MD: Agency for Healthcare Research and Quality, September 2000. Online document at: www.ahrq.gov=clinic=epcsums=milktsum.htm. Accessed May 10, 2005.
[51]Leung AY, Foster S. Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics, 2nd Edition. New York: John Wiley and Sons, 1996.
[52]Nicholson JA, Darby TD, et al. Viopudial, a hypotensive and smooth muscle antispasmodic from Viburnum opulus. Proc Soc Exp Biol Med. 1972;140:457–461.
[53]Loser B, Kruse SO, et al. Inhibition of neutrophil elastase activity by cinnamic acid derivatives from Cimicifuga racemosa. Planta Med. 2000;66:751–753.
[54]Kruse SO, Lohning A, et al. Fukiic and piscidic acid esters from the rhizome of Cimicifuga racemosa and the in vitro estrogenic activity of fukinolic acid. Planta Med. 1999;65:763–764.
[55]Seidlova-Wuttke D, Hesse O, et al. Evidence for selective estrogen receptor modulator activity in a black cohosh (Cimicifuga racemosa) extract: Comparison with estradiol-17 beta. Eur J Endocrinol. 2003;149: 351–362.
[56]Mahady GB. Is black cohosh estrogenic? Nutr Rev. 2003;61:183–186.

[57]Freeman EW, Rickels K, et al. A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. JAMA. 1995;274:51–57.

[58]Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. BMJ. 2001 Jan 20;322(7279):134–137.

[59]Aozasa O, Ohta S, et al. Enhancement in fecal excretion of dioxin isomer in mice by several dietary fibers. Chemosphere. 2001;45:195–200.

[60]Ferrini RL, Barrett-Connor E. Caffeine intake and endogenous sex steroid levels in postmenopausal women. The Rancho Bernardo Study. Am J Epidemiol. 1996:144:642–644.

13

ALTERNATIVE AND COMPLEMENTARY APPROACHES TO TREATING COMMON OCULAR DISORDERS

Cataracts, Glaucoma, Retinopathy, and Macular Degeneration

It has been said that the eye is the ''window'' to a person's soul. For the physician, the eye is a window to a person's body. The eye provides a direct view of blood vessels and nerves and can reflect the state of a person's overall health. The eye can also be affected by conditions within the body. This chapter examines four common eye disorders—cataracts, glaucoma, diabetic retinopathy, and macular degeneration—and discusses alternative and complementary medicine (ACM) approaches to treating these disorders. The etiologies and clinical presentation for each disorder are described and then popular ACM interventions are outlined.

CATARACTS: DESCRIPTION AND ETIOLOGY

Cataracts, the clouding and opacification of the crystalline lenses of the eyes,[1] are the leading cause of decreased vision and blindness in the United States. It is estimated that 20.5 million (17.2%) Americans older than 40 years have cataracts in either eye. Women are almost 40% more likely to develop cataracts than men. The total number of persons who have cataracts is estimated to rise to 30.1 million by 2020.[2] Cataract surgery is the most prevalent procedure performed on patients over 65, with an estimated 1.3 million operations a year at an annual cost of approximately $3 billion.[1] With such a heavy burden on U.S. health care dollars, there is a great deal of interest in defining and describing the causes for lens dysfunction. The etiologies of cataracts are predominately developmental (congenital and disease-related), degenerative (senile, traumatic, drug-related [iatrogenic] and exposure to causative substances), and inflammatory.[1] Because cataracts can be acquired, ophthalmologists and research scientists believe that many people, if they live long enough, will develop clinical symptoms of cataracts.[3] The disorder occurs more frequently in patients who smoke, have uncontrolled diabetes that can lead to glycosylation and lens damage, or are exposed to excessive unfiltered sunlight. All of these factors create oxidative-related damage. Early research has shown that oxidative injury to the eye lens appears to be a major causative factor in the development of degenerative cataracts in human and animal study models.[4,5] Signs and symptoms of cataracts include blurring vision; a gradual, painless loss of vision; subjective myopia; ''halo vision'' during night driving; altered color perception; cloudiness of the lens; and an absent or abnormal red reflex and a ''dark defect''; which are determined via opthalmoscopic examination.[6] (See Table 13–1 on page 156.)

Table 13–1. Quick Reference to Common Signs and Symptoms of Cataracts or Glaucoma

	BV	VL	HV	EP	M	S	RR
Cataracts	X	X	X				X
Glaucoma	X	X	X	X	X		

BV blurred vision, VL vision loss, HV halo vision, EP eye pain, M mydriasis; S scotoma, RR absent red reflex.

PREVENTION OF CATARACTS: THE BEST INTERVENTION

When addressing cataracts, the role of primary care physicians must be focused on prevention. This can be clinically accomplished with minor dietary and lifestyle modifications. Reducing the oxidative burden on the ocular structures can have lasting effects on the function of the lens and its ability to interact with the neurologic aspects of vision. Prevention includes the use of proper eye protection to filter the harmful effects of ultraviolet-B light.[7] Consumption of a diet replete with antioxidant-rich fruits and vegetables is also important. In fact, The Nurses' Health Study revealed that regular consumption of spinach and kale was moderately protective against cataracts in women, and the Health Professionals Follow-Up Study revealed that spinach and broccoli decreased the risk of cataract development in men.[8,9] Annual eye examinations are also vital for patients who are in high-risk categories for developing ocular disease.

> Some studies reveal that eating more foods rich in vitamin A and beta-carotene, or the judicious use of vitamin A, lowers the risk of cataract development.

Patients with low blood levels of antioxidants and who eat few antioxidant-rich fruits and vegetables are excellent candidates for nutraceutical supplementation (e.g., lutein; beta-carotene; vitamins A, C, and E; selenium; the reduced form of glutathione; lipoic acid; etc.) to boost these patients' free-radical scavenging capabilities.[10–12]

The major antioxidants in the lens of the eye are vitamin C[10] and glutathione, a tripeptide molecule composed of the amino acids cysteine, glutamic acid, and glycine. In its reduced form, glutathione is the body's most potent antioxidant.[11] Vitamin C is needed as a cofactor to activate vitamin E,[9] which, in turn, amplifies the effects of glutathione. Vitamin E has been shown to decrease the development of age-related cataracts in human and animal study models.[13,14] The Vitamin E and Cataract Prevention Study (VECAT), a four-year, prospective, randomized, controlled trial of vitamin E versus placebo for the prevention of cataract development in healthy volunteers, tested subjects ages 55–80.[15] The researchers found a statistically significant relationship between prior use of vitamin E and a lowered incidence of cataract in 1,111 participants (unpublished data). A statistically significant inverse relationship was found between past vitamin E supplementation and the development of cortical cataracts.[16] During aging, the levels of vitamin C in the eye lens decrease[12]; however, taking vitamin C prevents this decrease[17] and is linked to a lower risk of developing cataracts.[18,19] In the Nurses' Health Study, vitamin C supplementation for a period of 10 years or longer resulted in a 77% lower incidence of early lens opacities and an 83% lower incidence of moderate lens

opacities. However, the same study demonstrated no significant protection from vitamin C supplementation of less than 10 years' duration.[14]

Some studies reveal that eating more foods rich in vitamin A and beta-carotene, or the judicious use of vitamin A, lowers the risk of cataract development.[8,20] It is still not clear what the exact role of carotenoids is in protecting the lens from opacification and oxidative damage. Studies have shown that people who eat a lot of spinach, which is high in lutein, a nutrient similar to beta-carotene, appear to be at a low risk for developing cataracts.[20]

Additional protection has been achieved with vitamin B_2 (riboflavin) and vitamin B_3 (niacin), which are needed to protect against glutathione degradation. Vitamin B_2 deficiency has

Therapeutics for Eye Conditions

1. Vitamin C—At least 500–1,000 mg per day often recommended; however, much greater dosages are not uncommon.
2. Vitamin E—400–800 international units (IU) per day for adults.
3. Vitamin A—10,000 IU, in divided doses, per day; for males and postmenopausal women, up to 25,000 IU (7,500 mcg) of vitamin A per day considered safe; for women who could become pregnant, the safest intake level is being reevaluated; less than 10,000 IU (3,000 mcg) per day is widely accepted as safe.
4. Beta-carotene—Most common beta-carotene supplement intake is probably 25,000 IU (15 mg) per day, although some people take as much as 100,000 IU (60 mg) per day.
5. Lutein—6 mg (with food to decrease gastric upset) per day for adults.
6. Quercetin—400 mg, 3–4 times per day.
7. Coenzyme Q10—20–150 mg per day, in divided doses.
8. Selenium—100–200 mcg per day for adults.
9. Rutin—400–1,000 mg per day.
10. Alpha-lipoic acid—150 mg per day for glaucoma; 20–50 mg per day recommended for general antioxidant protection.
11. Magnesium—250–350 mg per day for adults.
12. Bioflavonoids—1,000 mg of citrus bioflavonoids or 400 mg of quercetin, each 3 times per day.
13. Gingko—120–160 mg of Gingko biloba extract, standardized to contain 6% terpene lactones and 24% flavone glycosides, 2–3 times per day.
14. Bilberry—in capsules or tablets standardized to provide 25 percent anthocyanosides, 240–480 mg per day.
15. Coleus—2% forskoliin solutions applied topically.
16. Melatonin—200 mcg; however, doses from 1–3 mg, 2–3 hours before bedtime have shown efficacy.

Table 13–2. Quick Reference to Therapeutics for Cataracts or Glaucoma

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Cataracts		X	X	X	X	X		X	X					X		
Glaucoma	X	X	X							X	X	X	X	X	X	X

been linked to cataracts in a number of studies.[21,22] Older patients who take riboflavin and niacin daily may be partially protected against cataract development.[22] Quercitin, a molecule belonging to the water-soluble bioflavonoids, has been shown to potentiate the vitamin C activity[23] as well as block enzymatic activity (aldose reductase) in the sorbitol pathway.[23] This influence on the polyol pathway could prove to be very significant in managing cataract-related dysfunction in patients with diabetes who have altered sorbitol metabolism.

Numerous animal models have demonstrated efficacy of alpha-lipoic acid supplementation against cataracts. Alpha-lipoic acid, a potent antioxidant, also regenerates endogenous antioxidants, such as vitamin E, vitamin C, and glutathione. Studies show that oral lipoic acid supplementation delayed development and progression of cataracts in rats with experimentally induced diabetes.[24] Another study treated newborn rats with buthionine sulfoximine to induce cataract formation. Treatment with R- and racemic alpha-lipoate decreased cataract formation from 100% buthionine sulfoximine to 55% with buthionine sulfoximine and R-alpha-lipoic acid and to 40% with buthionine sulfoximine and rac-alpha-lipoic acid. Buthionine sulfoximine treatment decreased the lens antioxidants showing a decrease in glutathione by 45%, ascorbate by 62%, and vitamin E by 23%, but were maintained at 84%–97% of control levels when R-alpha-lipoic acid or rac-alpha-lipoic acid were administered with buthionine sulfoximine.[25]

> Although the benefits of rutin or other bioflavonoids for people with glaucoma have been recognized, they have not been investigated thoroughly.

BOTANICAL TREATMENTS FOR CATARACTS

Botanical agents that may be helpful for treating and managing cataracts include Vaccinium myrtillus (bilberry), a close relative of blueberry, which is high in bioflavonoid complex anthocyanosides.[26] Anthocyanosides have been shown to protect both the lens and the retina from oxidative damage. Bilberry also helps patients to adapt to bright light, but research on effects on night vision have produced mixed results. Pulsatilla pratensis (pulsatilla) has historically been used internally for the treatment of senile cataracts; however, careful attention must be used when prescribing this toxic herb. Cineraria maritime (silver ragwort) has been used in the form of eye drops for treating patients who are in the early stages of senile cataracts; but, note that use of this herb is contraindicated for patients with glaucoma.[27]

GLAUCOMA: DESCRIPTION AND ETIOLOGY

Glaucoma is the second leading cause of blindness in the United States. The term glaucoma describes a group of eye conditions involving increased pressure within the intraocular mechanism. Glaucoma is characterized by a neuropathy of the optic nerve, usually the result of the increased pressure within the eyeball. Closed-angle glaucoma occurs when the chamber angle is narrowed or completely closed because of forward displacement of the final roll and root of the iris. The closure obstructs the flow of aqueous humor and results in increased pressure. Open-angle glaucoma results from increased resistance to the outward flow of aqueous humor.

The changes in normal pressure accommodation can ultimately lead to blindness and account for more than 150,000 cases per year. In many circumstances, the cause is unknown. In some cases, however, glaucoma is caused by an underlying pathologic condition that must be arrested. Therefore, it is important for people with glaucoma to be diagnosed by, and to remain under the care of, an ophthalmologist. Regular eye examinations are especially important for patients with high-risk profiles. These include patients with familial histories of the disorder, African-American patients (who have a four to six times higher incidence of glaucoma), patients with long-term metabolic disorders (e.g., diabetes mellitus, thyroid-hormone dysregulation), patients who take high-dose oral corticosteroids for prolonged periods of time, patients with food sensitivities or allergies,[28] or patients who are more than 40 years old.[1]

With regard to clinical signs and symptoms, it is important to note that acute-angle closure glaucoma is painful while chronic open-angle glaucoma (COAG) is not. Thus, the presence or absence of pain is not always a clear indicator of whether a patient has glaucoma or not.[6] Other indicators include a frequent need to change prescriptions for glasses or contact lenses, impaired adaptation to dark environments, seeing halos around lights, mild headaches, or undefined visual disturbances. In addition, COAG may be totally asymptomatic and may require a work-up with intraocular pressure measurement, slit-lamp examination, visual fields assessment, and gonioscopy. Fundoscopic examination may reveal an enlarged cup size within the optic disc. If glaucoma is suspected, or if a patient is at a high risk for developing glaucoma, referral to an ophthalmologist for further evaluation is essential to gain a greater understanding of the degree of ocular dysfunction.[29]

NUTRITIONAL TREATMENTS FOR GLAUCOMA

The conventional approach to managing glaucoma includes a proper referral to an ophthalmologic surgeon for a thorough evaluation. When surgical intervention—an iridotomy—is performed, the majority of patients will be totally cured and have no visual loss.[30] However, when surgery is performed, there are potential risks that must be weighed. Specific adjuvant ACM modality management may include the use of nutrients and herbs to strengthen the vasculature of the eye and provide antioxidant protection. Homeopathy may be effective for acute pain relief. Regular aerobic exercise may also be helpful for treating the condition.[31,32] Dietary changes that may be influential in preventing the progression and occurrence of glaucoma, as well as hastening recovery from iridotomy include reducing or eliminating exposure to allergens that produce altered vascular permeability and increased intraocular pressure. All known food allergens should be eliminated. In addition, it is important to reduce foods that may dramatically alter blood glucose, such as simple sugars, high glycemic index fruits, and refined foodstuffs. The diet should also provide foods rich in bioflavonoids and carotenes, such as dark seasonal berries, dark leafy greens, and yellow=orange vegetables. These foods will provide valuable micronutrients for ocular functioning.[33–35]

Vitamin C is perhaps the most extensively researched ACM agent for treating glaucoma. The vitamin has reduced elevated intraocular pressure significantly in numerous studies.[36] These studies used at least several grams per day of vitamin C, but the intake varied widely. ACM physicians who prescribe the vitamin for managing COAG vary widely in the amounts they prescribe.[37] Usually, physicians will advise patients to take oral doses of vitamin C equal to ''bowel tolerance.'' Prescriptions ranging from approximately 5 to 20 or more g per day have been shown to be effective for treating increased intraocular pressure. Of course, vitamin C does not cure glaucoma and must be used continually to reduce ocular pressure.[38]

Several botanical agents have been shown to be helpful for managing glaucoma.

Rutin, a bioflavonoid with collagen-stabilizing effects, was historically used to reduce intraocular pressure in glaucoma.[39] The amount used—20 mg, three times per day—was quite moderate. In one study, 17 of 26 people showed clear improvement.[39] Although the benefits of rutin or other bioflavonoids for people with glaucoma have been recognized, they have not been investigated thoroughly.

Intraocular pressure follows a very temporal variation, with the lowest pressure commonly occurring in the early morning hours. Research has shown that intraocular pressure also parallels fluctuations in cortisol levels, with high cortisol conferring higher intraocular pressures. Diurnal variations in intraocular pressure are more pronounced in people with glaucoma, leading scientists to believe that a connection exists between intraocular pressure levels and other diurnal variants in the body. Because melatonin levels peak around 2 am, a time when intraocular pressure is on a downward trend, researchers studied melatonin's effect on intraocular pressure.[29,40,41] Less than 1 mg of melatonin has lowered pressure within the eyes of healthy people,[41] but there is only a limited amount of research on the effects of melatonin on people who have glaucoma.

Coenzyme Q10 has been shown to reduce significantly the deleterious influence of the beta-blocker medication timolol, which is used to lower intraocular pressure.[42] Additional antioxidant activity may be generated by 150 mg of alpha-lipoic acid daily. Studies have revealed improved visual function in people with either stage 1 or stage 2 glaucoma taking alpha-lipoic acid daily for one to two months.[43]

Epidemiologic and animal studies point to a possible protective effect of omega-3 fatty acids against glaucoma. Both topical administration of prostaglandin E3 and D3 and intramuscular injections of cod liver oil (which is high in omega-3 fatty acids) led to decreased intraocular pressure in animal studies.[42,44] Epidemiologic evidence has revealed a low prevalence of chronic open-angle glaucoma among Inuits on a native diet high in omega-3 fatty acids.[45] The preliminary data from these investigative reports have led researchers to assume that essential fatty acids may be potent tools for managing glaucoma and other ocular diseases. At this point, more research is a reasonable next step.[29]

Glaucoma is not solely caused by increased intraocular pressure, being that approximately 20% of patients have normal intraocular pressure levels.[30] It is in this subcategory of patients that magnesium has been studied. One study examined whether magnesium might improve vision in people with glaucoma by enhancing blood flow to the eyes (patients with normal intraocular pressure in which optic-nerve damage is caused by vasospasm leading to a decreased blood supply to the optic nerve). In this trial, participants were given 245 mg of magnesium per day. Improvement in vision was noted after four weeks, but the change did not quite reach statistical significance.[46]

BOTANICAL AGENTS FOR TREATING GLAUCOMA

Several botanical agents have been shown to be helpful for managing glaucoma. These include Vaccinium myrtillus (limited research);[47] Crataegus monogyna (hawthorn berries), especially

with concurrent hypertension; and Ginkgo biloba (ginkgo),[48,49] especially for compromised circulation (mixed review data). Combine equal parts of ginkgo, hawthorn, bilberry, and elderberry (Sambucus nigra) in a tincture to strengthen vascular tissues and improve circulation.

Additional interest has been directed toward Coleus forskoliin. The triterpene forskoliin from the plant stimulates the enzyme adenylate cyclase.[50] Adenylate cyclase then stimulates the ciliary epithelium to produce cyclic adenosine monophosphate (cAMP). This cascade then leads toward reducing aqueous humor inflow and decreasing intraocular pressure. A clinical study on the topical use of forskoliin has been promising in healthy human subjects, but use for patients with glaucoma has historically been lacking. What is more, while oral standardized extracts of Coleus forskoliin are known to raise cAMP, it is not clear if oral dosages have any effect on cAMP levels in the eye. As such, more research is needed.

Regardless of the medical armamentarium enlisted to treat glaucoma, prevention of this is critical. It is also important to consider altering the biochemical terrain toward regaining homeostasis. There are promising preliminary data that support the use of vitamin C, melatonin, alpha-lipoic acid, G. biloba, V. myrtillus, and topical forskoliin. However, many of these studies have been performed on normal, healthy eyes and have yet to withstand the scrutiny of research with patients who have glaucoma—the next vital step in developing therapeutics for treating ocular disease.

DIABETIC RETINOPATHY: DESCRIPTION AND ETIOLOGY

Several conditions can cause damage to the retina of the eye, with long-term uncontrolled diabetes mellitus and poorly managed hypertension being the two most frequent problems. This book covers, specifically, diabetic retinopathy (DR). DR is an ocular abnormality that is associated with poorly controlled diabetes and is defined by the presence of microaneurysms, punctate hemorrhages, white and yellow exudates, flame hemorrhages, and neovascular vessel growth.[51] DR is the leading cause of blindness in patients with type 1 diabetes. The degree of retinal damage is closely associated with the length (generally not less than 10 years) of the disease process and the degree of glucose regulation and monitoring. There are numerous mechanisms that have been proposed to explain the development of retinal changes in diabetes. One of the causes of diabetic retinopathy is the development of glycosylated proteins (the attachment of sugars to proteins in the presence of high blood glucose).[52] Glycosylated proteins lead to the development of oxidative free radicals, resulting in tissue damage and glutathione depletion. Studies on laboratory-induced diabetes in dogs and rats have shown a deficiency of glutathione in the retinas.[53] Human patients with diabetes who have retinopathy have higher levels of an oxidative stress by-product called malondialdehyde compared to patients with

Table 13–3. Quick Reference to Common Signs and Symptoms of Diabetic Retinopathy and Age-Related Macular Degeneration

	BV	VL	HV	EP	M	S	RR
Diabetic retinopathy	X	X					
Age-related macular degeneration	X	X				X	

BV blurred vision, VL vision loss, HV halo vision, EP eye pain, M mydriasis, S scotoma, RR absent red reflex.

diabetes who do not have retinopathy and who have healthy sugar control.[54] Glycosylated proteins can be combined with lipids and become influenced and altered by free radicals; this leads to the formation of advanced glycated end products (AGEs), which can be deposited in blood vessels of the retina and contribute to neovascularization. Alternative and complimentary medicine (ACM) research has been oriented toward the use of antioxidants to alter the free-radical pathway and to reduce retinal damage.[55] It is no wonder that the sentinel treatment for DR is closely controlling blood-sugar levels. The Diabetes Control and Complications Trial studied 1,439 patients with diabetes who used insulin and who had retinopathy. The effect of standard insulin dosing (two daily injections) was compared to tighter control with frequent glucose testing and injections throughout the day. During the first few months of the study, tighter blood-sugar control appeared to worsen retinopathy more than the conventional approach; however, better glucose monitoring resulted in a significant decrease in long-term risk.

Study data indicated that patients who took a vitamin B_6 supplement seemed to have an absence of retinal involvement.

PREVENTION AND TREATMENT OF DIABETIC RETINOPATHY

Preliminary evidence points to the influence of free-radical formation and the development and progression of many forms of retinopathy.[56] Antioxidant formulas have long been the frontline defense in preventing and managing retinopathy. With properties that include free-radical scavenging, preventing protein glycosylation, and decreasing capillary permeability and fragility, it is no wonder that vitamin C is chief among these therapies.[57–60] Vitamin E, also a potent intracellular antioxidant, is considered to be effective, at a level of 1,200 international units (IU) per day or more, for preventing and treating similar conditions.[61] Vitamins C and E have been shown, in limited investigations, to be present in lower levels in patients with diabetes compared to healthy controls.[62,63] In addition, vitamin E has been shown to protect people with very high cholesterol levels from developing retinopathy.[64] A combination of 500 mcg of selenium, 800 IU of vitamin E, 10,000 IU of vitamin A, and 1,000 mg of vitamin C, taken each day for several years, has reduced diabetic retinopathy in a single research study.[65] Additional research has yielded similar benefits from the administration of alpha-lipoic acid, a powerful inhibitor of oxidative glycosylated proteins.[66]

Researchers have found an increase in activity of the enzymatic diacylglycerol protein kinase C (DAG-PKC) pathway in the retinas of animals with diabetes.[67] This increased enzyme activity appears to interfere with normal circulation to the retina. Vitamin E has been found to normalize the activity of the DAG-PKC pathway, which leads to improved retinal blood flow. Research has shown an additional possible mechanism for improved retinal blood flow via supplementation with vitamin E because of its influence on decreasing platelet aggregation.[68] Low blood levels of magnesium, a nutrient that is vital to vascular health and integrity, have been linked to DR.[69,70] In a study of 71 people with insulin-dependent diabetes, subjects were divided into two groups, depending on the severity of their DR. All subjects had some degree of magnesium deficiency. The subjects with the most severe DR had the most significant

deficiency of the mineral.[70] However, using magnesium supplementation to treat DR has not been fully studied. In a preliminary analysis, a group of researchers proposed that vitamin B_6 supplementation could be used to prevent diabetic retinopathy.[71] The researchers studied data gathered over a period ranging from 8 months to 28 years. The data indicated that patients who took a vitamin B_6 supplement seemed to have an absence of retinal involvement. Bioflavonoids, such as quercetin, hesperidin, and naringin, are known to be involved in sorbitol metabolism and the additional development of oxygen free radicals. Thus, when treating patients with diabetes, these bioflavonoids should be considered as a means of inhibiting the enzyme aldose reductase.[72] Although human studies have not been done using quercetin to treat retinopathy, many natural-medicine doctors prescribe 400 mg of quercetin three times per day for patients with diabetes.

Botanical medications that have been helpful for treating DR include:

Vaccinium myrtillus (bilberry), standardized to contain 25% anthocyanosides (a flavonoid that stabilizes connective tissues[73] and decreases capillary fragility[74]), produces powerful antioxidant effects and appears to have a particular affinity for the retina. Such an extract, when taken in doses between 80 and 160 mg, three times per day, has benefited patients with DR.[75]

A standardized extract of Ginkgo biloba (ginkgo) has been shown to improve impaired color vision in people with DR.[76] The extract was standardized to 24% glycosides. In animal experimentation, ginkgo had significantly greater efficacy for reducing DR after two months compared to animals that were given a placebo. The effect was attributed to this herb's antioxidant effects.[77] Most often, 60 mg of an extract is taken two to four times per day.

Improving blood flow, normalizing blood-sugar levels, and correcting for underlying metabolic disturbances appears to be the main therapy for retinal pathology. Considerable evidence points to the benefits of potent antioxidant supplements. Vitamin E is the major choice at this time. However, like many other popular ACM modalities, extensive prospective clinical studies have not been conducted. The future seems bright indeed for patients with DR as more research emphasis is pushed toward ACM studies on treating this condition.

MACULAR DEGENERATION: DESCRIPTION AND ETIOLOGY

Macular degeneration (MD), a group of diseases associated with loss of the central vision portion of ocular activity, is marked by damage to the pigment and neural and vascular layers of the macula. The leading cause of blindness among Caucasian Americans is age-related MD,

Table 13–4. Quick Reference to Therapeutics for Diabetic Retinopathy and Age-Related Macular Degeneration

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Diabetic retinopathy	X	X	X	X		X	X				X	X				
Age-related macular degeneration	X	X	X	X	X	X		X					X	X		

See p. 157 for more information on numbers in this table.

accounting for 54% of all blindness in the United States, and more than 1 in 10 Caucasian Americans over age 80 has vision loss from age-related MD.[78] Macular degeneration, also called age-related macular degeneration (ARMD), is a painless, degenerative eye disease. Because the macula is the primary site affected by this condition, central visual acuity is affected while peripheral vision may be completely spared. There are two forms of ARMD: (1) Nonexudative or dry ARMD involves the accumulation of drusen (debris deposits) between the pigment epithelium and the underlying basement membrane (Bruch's membrane); (2) the exudative or wet form involves neovascularization in response to the degenerative changes.[79] ARMD is the leading cause of legal blindness in the United States in persons over 55. This condition affects more than 10 million Americans, and this number will increase as the baby boomers age. Although the etiology of macular degeneration is not fully understood, evidence from animal studies indicates free-radical damage from light exposure as a potential contributing factor.[29] The photoreceptors of the eye are high in polyunsaturated fatty acids, particularly docosahexaenoic acid (DHA). DHA is readily oxidized in the oxygen-rich environment of the retina.[80,81] Several of the known risk factors for ARMD, including cigarette smoking and sunlight exposure, appear to be at least partially related to oxidative stress.

Bilberry has also been shown to strengthen capillaries and reduce hemorrhaging in the retina.

PREVENTION AND TREATMENT OF AGE-RELATED MACULAR DEGENERATION

Sunlight triggers oxidative damage in the eye that, in turn, can cause ARMD.[82] Animals that were given antioxidants, which protect tissues against oxidative damage, have had a lower risk of developing this vision problem.[83] People with high blood levels of antioxidants also have a lower risk.[84] Those with the highest levels of the antioxidants selenium, vitamin C, and vitamin E may have a 70% lower risk of developing ARMD.[85] People who eat diets that are rich in beta-carotene, another antioxidant, also appear to be at a lower risk for developing ARMD.[86] As such, many people who want to lower their risk for macular degeneration take antioxidants. Reasonable adult levels include 200 mcg of selenium, 1,000 mg of vitamin C, 400 IU of vitamin E, and 25,000 IU of natural beta-carotene per day. The carotenoids lutein and zeaxanthin are antioxidants much like beta-carotene. These carotenoids, which are found in high concentrations in spinach and kale, concentrate in the part of the retina where ARMD strikes. The macula acquires its yellow appearance from the accumulation of carotenoid pigments. Lutein is found in higher concentrations outside of the fovea while zeaxanthin concentrates closer to the fovea.[86] Research has shown that carotenoids act to protect the retina from damage caused by sunlight.[87] People who eat spinach and kale have a lower risk of developing ARMD, although blood levels of lutein have not been correlated with a risk of macular degeneration.[88]

Two important enzymes needed for vision in the retina require zinc (an outstanding ally in free-radical defense). Double-blinded research, using 80 mg of zinc versus placebo for two years, found that zinc prevented 42% of vision loss in subjects with ARMD.[89] Additional research did not, however, confirm the data generated from this earlier study.[90] Active bioflavonoid compounds (anthocyanosides) in bilberry act as antioxidants in the retina. This

makes the herb a potential preventive measure against macular degeneration.[91] Bilberry has also been shown to strengthen capillaries and reduce hemorrhaging in the retina.[92] Many people take 240–480 mg per day of bilberry extract in capsules or tablets standardized to 25% anthocyanosides. Additional research has shown promise for the antioxidant effects of gingko for preventing or treating macular disorders.[93] Promising preliminary research points toward the profound effect that vitamin and nutrient antioxidants have on macular function. Once again, the future of therapies relies strongly on preventive medical measures. Counseling patients regarding reducing exposure to oxidative damaging environments and activities, increasing antioxidant-rich food sources, and increasing activities that influence blood flow to the eye, will be the most potent therapeutics. However, in circumstances when treatment is needed, sound scientific support is becoming available to justify treatment with nutrients and botanicals including carotenoids, vitamins C and E, zinc, selenium, and ginkgo.

REFERENCES

[1]Danakas GT, Fagan MJ, Ferri FF, et al. Ferri's Clinical Advisor: Instant Diagnosis and Treatments. St. Louis: Mosby, 2001.

[2]National Eye Institute. Statistics and Data Prevalence of Cataract and Pseudophakia=Aphakia Among Adults in the United States. Available at: www.nei.nih.gov=eyedata=pbd6.asp. Accessed November 23, 2007.

[3]Kahn HA, Leibowitz HM, Ganley JP, et al. The Framingham Eye Study: I. Outline and major prevalence findings. Am J Epidemiol. 1977;106:17–32.

[4]Schocket SS, Esterson J, Bradford B, et al. Induction of cataracts in mice by exposure to oxygen. Isr J Med Sci. 1972;8:1596–1601.

[5]Palmquist B, Phillipson B, Barr P. Nuclear cataract and myopia during hyperbaric oxygen therapy. Br J Ophthalmol. 1984;68:113–117.

[6]Altschuler SL, Baer CL, Barnes LP, et al. Handbook of Signs and Symptoms. Springhouse, PA: Springhouse Corp., 1998.

[7]Taylor HR. Epidemiology of age-related cataract. Eye. 1999;13:445–448.

[8]Chasen-Taber L, Willet WC, Seddon JM., et al. A prospective study of carotenoid and vitamin A intakes and risk of cataract extraction in U.S. women. Am J Clin Nutr. 1999;70:509–516.

[9]Leske MC, Chylack LT, Jr, He Q, et al. Antioxidant vitamins and nuclear opacities: The longitudinal study of cataract. Ophthalmology. 1998;105:831–836.

[10]Knekt P, Heliovaara M, Rissanen A, et al. Serum antioxidant vitamins and risk of cataract. Br Med J. 1992;305:1392–1394.

[11]Taylor A, Jacques PF, Nadler D, et al. Relationship in humans between ascorbic acid consumption and levels of total and reduced ascorbic acid in lens, aqueous humor, and plasma. Curr Eye Res. 1991;10: 751–759.

[12]Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. Proc Nat l Acad Sci USA. 1993;90:7915–7922.

[13]Trevithick JR, Creighton MO, et al. Modelling cortical cataractogenesis: In vitro effects on the lens of agents preventing glucose- and sorbitol-induced cataracts. Can J Ophthalmol. 1981;16:32–38.

[14]Robertson JM, Donner AP, Trevithick JR. A possible role for vitamins C and E in cataract prevention. Am J Clin Nutr. 1991;53(suppl.):346S–351S.

[15]Robertson JM, Donner AP, Trevithick JR. Vitamin E intake and risk of cataracts in humans. Ann NY Acad Sci. 1989;570:372–382.

[16]Garrett SK, McNeil JJ, Silagy C, et al. Methodology of the VECAT study: Vitamin E intervention in cataract and age-related maculopathy. Ophthalmic Epidemiol. 1999;6:195–208.

[17]Reddy VN. Glutathione and its function in the lens—an overview. Exp Eye Res. 1990;150: 771–778.

[18]Packer JE, Slater TF, Willson RL. Direct observation of a free radical interaction between vitamin E and vitamin C. Nature. 1979;278:737–738.

[19]Taylor A. Cataract: Relationship between nutrition and oxidation [review]. J Am Coll Nutr. 1993;12: 138–146.

[20]Hankinson SE, Stampfer JM, Colditz GA, et al. Nutrient intake and cataract extraction in women: A prospective study. Br Med J. 1992;305:335–339.

[21]Bhat KS. Nutritional status of thiamine, riboflavin and pyridoxine in cataract patients. Nutr Rep Intl. 1987;36:685–692.
[22]Prchal JT, Conrad ME, Skalka HW. Association of presenile cataracts with heterozygosity for galactosaemic states and with riboflavin deficiency. Lancet. 1978;i:12–3.
[23]Varma SD, et al. Diabetic cataracts and flavonoids. Science. 1977;195:205.
[24]Kojima M, Sun L, Hata I, Sakamoto Y, Sasaki H, Sasaki K. Efficacy of alpha-lipoic acid against diabetic cataract in rat. Jpn J Ophthalmol. 2007 Jan–Feb;51(1):10–13. Epub 2007 Feb 9.
[25]Maitra I, Serbinova E, Tritschler HJ, Packer L. Stereospecific effects of R-lipoic acid on buthionine sulfoximine-induced cataract formation in newborn rats. Biochem Biophys Res Commun. 1996 Apr 16; 221(2):422–429.
[26]Salvayre R, Braquet P, et al. Comparison of the scavenger effect of bilberry anthocyanosides with various flavonoids. [roceedings of the International Bioflavonoids Symposium, Munich, 1981, pp. 437–442.
[27]Weiss RF. Herbal Medicine, 4th Edition. Beaconsfield, England: Beaconsfield Publisher, 1996.
[28]Berens C, et al. Allergy in glaucoma: Manifestations of allergy in three glaucoma patients as determined by the pulse-diet method of Coca. Ann Allerg. 1947;5:526.
[29]Head K. Natural therapies for ocular disorders: Part two. Cataracts and glaucoma. Alt Med Rev. 2001;6:231.
[30]Alward WL. Medical management of glaucoma. N Engl J Med. 1998;339:1298.
[31]Murray MT, Pizzorno JE, Jr. Encyclopedia of Natural Medicine, 2nd Edition. Rocklin, CA: Prima Publishing, 1998, pp. 455–458.
[32]Murray MT, Pizzorno JE, Jr. Macular degeneration. In: Murray, MT, Pizzorno JE, Jr, eds. Textbook of Natural Medicine. Volume 2, 2nd Edition. New York: Churchill Livingstone, 1999, p. 1375.
[33]Bunin AI, Filina AA, Erichev VP. A glutathione deficiency in open-angle glaucoma and the approaches to its correction. Vestn Oftalmol. 1992;108:13–15.
[34]Filina AA, Davydova NG, Kolomoitseva EM. The effect of lipoic acid on the components of the glutathione system in the lacrimal fluid of patients with open-angle glaucoma. Vestn Oftalmol. 1993;109:5–7.
[35]Kurysheva NI, Vinetskaia MI, Erichev VP, et al. Contribution of free-radical reactions of chamber humor to the development of primary open-angle glaucoma. Vestn Oftalmol. 1996;112:3–5.
[36]Ringsdorf WM Jr, Cheraskin E. Ascorbic acid and glaucoma: A review. J Holistic Med. 1981;3:167–172.
[37]Boyd HH. Eye pressure lowering effect of vitamin C. J Orthomol Med. 1995;10:165–168.
[38]Aleksidze AT, Beradze IN, Golovachev OG. Effect of the ascorbic acid of the aqueous humor on the lipid peroxidation process in the eye in primary open-angle glaucoma. Oftalmol Zh. 1989;2:114–116.
[39]Stocker FW. New ways of influencing the intraocular pressure. NY State J Med. 1949;49:58–63.
[40]Samples JR, Krause G, Lewy AJ. Effect of melatonin on intraocular pressure. Curr Eye Res. 1988;7: 649–653.
[41]Topper J, Brubaker R. Effects of timolol, epinephrine and acetazolamide on aqueous flow during sleep. Invest Ophthalmol Vis Sci. 1985;26:1315–1319.
[42]Takahashi N, Iwasaki T, Sugiura T, et al. Effect of coenzyme Q10 on hemodynamic response to ocular timolol. J Cardiovasc Pharmacol. 1989;14:462–468.
[43]Filina AA, Davydova NG, Endrikhovskii SN, et al. Lipoic acid as a means of metabolic therapy of open-angle glaucoma. Vestn Oftalmol. 1995;111:6–8.
[44]Kulkarni PS, Srinivasan BD. Prostaglandins E3 and D3 lower intraocular pressure. Invest Ophthalmol Vis Sci. 1985;26:1178–1182.
[45]Mancino M, Ohia E, Kulkarni P. A comparative study between cod liver oil and liquid lard intake on intraocular pressure on rabbits. Prostagl and ins Leuk ot Essent Fatty Acids. 1992;45:239–243.
[46]Gaspar AZ, et al. The influence of magnesium on visual field and peripheral vasospasm in glaucoma. Ophthalmol ogica. 1995;209:11–13.
[47]Caselli L. Clinical and electroretinographic study on activity of anthocyanosides. Arch Med Intl. 1985; 37:29–35.
[48]Merte HJ, Merkle W. Long-term treatment with Ginkgo biloba extract of circulatory disturbances of the retina and optic nerve. Klin Monatsbl Augenheilkd. 1980;177:577–583.
[49]Chung HS, Harris A, Kristinsson JK, et al. Ginkgo biloba extract increases ocular blood flow velocity. J Ocul Pharmacol Ther. 1999;15:233–240.
[50]Caprioli J, Sears M, Bausher L, et al. Forskoliin lowers intraocular pressure by reducing aqueous inflow. Invest Ophthalmol Vis Sci. 1984;25:268–277.
[51]Danakas GT, Fagan MJ, Ferri FF, et al. Ferri's Clinical Advisor: Instant Diagnosis and Treatments. St. Louis: Mosby, Inc., 2002.
[52]Freitas JP, Filipe P, Guerra Rodrigo F, et al. Glycosylation and lipid peroxidation in the skin and in plasma of diabetic patients [in French]. C R Seances Soc Biol Fil. 1997;191:837–843.

[53]Kowlura R, Kern TS, Engerman RL. Abnormalities of retinal metabolism in diabetes or galactosemia: II. Comparison of gamma-glutamyl transpeptidase in retina and cerebral cortex, and effects of antioxidant therapy. Curr Eye Res. 1994;13:891–896.
[54]Losada M, Alio JL. Malondialdehyde serum concentration in type 1 diabetics with and without retinopathy. Doc Ophthalmol. 1996;93:223–229.
[55]Lu M, Kuroki M, Amano S, et al. Advance glycation end-products increase retinal vascular endothelial growth factor expression. J Clin Invest. 1998;101:1219–1224.
[56]Alieva ZA, Gadzhiev RV, Sultanov M. Possible role of the antioxidant system of the vitreous body in delaying the development of diabetic retinopathy. Oftalmol Zh. 1995;(3):142–145.
[57]Ceriello A, Quatraro A, Gugliano D. New insights on non-enzymatic glycosylation may lead to therapeutic approaches for the prevention of diabetic complications. Diabet Med. 1992;9:297–299.
[58]Davie SJ, Gould BJ, Yudkin JS. Effect of vitamin C on glycosylation of protein. Diabetes. 1992;41: 167–173.
[59]Cox BD, Butterfield WJ. Vitamin C supplements and diabetic cutaneous capillary fragility. Br Med J. 1975;3:205.
[60]Ali SM, Chakraborty SK. Role of plasma as corbate in diabetic microangiopathy. Bangladesh Med Res Counc Bull. 1989;15:47–59.
[61]Johnson L, Quinn GE, Abbasi S, et al. Effect of sustained pharmacological vitamin E levels on incidence and severity of retinopathy of prematurity: A controlled clinical trial. J Pediatr. 1989;114:827–838.
[62]Sinclair AJ, Girling AJ, Gray L, et al. An investigation of the relationship between free radical activity and vitamin C metabolism in elderly diabetic subjects with retinopathy. Gerontology. 1992;38:268–274.
[63]Rema M, Mohan V, Bhaskar A, Shanmugasundaram KR. Does oxidant stress play a role in diabetic retinopathy? Indian J Ophthalmol. 1995;43:17–21.
[64]Runge P, Muller DP, McAllister J, et al. Oral vitamin E supplements can prevent the retinopathy of abetalipoproteinaemia. Br J Ophth. 1986;70:166–173.
[65]Crary EJ, McCarty MF. Potential clinical applications for high-dose nutritional antioxidants. Med Hypoth. 1984;13:77–98.
[66]Schleicher ED, Wagner E, Nerlich AG. Increased accumulation of the glycoxidation product, N-e-(carboxymethy)lysine in human tissues in diabetes and aging. J Clin Invest. 1997;99:457–468.
[67]Murray MT, Pizzorno JE Jr. Macular degeneration. In: Murray MT, Pizzorno JE Jr., eds. Textbook of Natural Medicine. Volume 2, 2nd Edition. New York, NY: Churchill Livingstone, 1999, p. 1375.
[68]Creter D, Pavlotzky F, Savir H. Effect of vitamin E on platelet aggregation in diabetic retinopathy. Acta Haematol. 1979;62:74–77.
[69]Jialal I, Joubert SM. The biochemical profile in Indian patients with non–insulin-dependent diabetes in the young with retinopathy. Diabetes Metabol. 1985;11:262–265.
[70]McNair P, Christiansen C, Madsbad S, et al. Hypomagnesemia, a risk factor in diabetic retinopathy. Diabetes. 1978;27:1075–1078.
[71]Ellis JM, Folkers K, Minadeo M, et al. A deficiency of vitamin B_6 is a plausible molecular basis of the retinopathy of patients with diabetes mellitus. Biochem Biophys Res Commun. 1991;179:615–619.
[72]Varma D. Inhibition of aldose reductase by flavonoids: Possible attenuation of diabetic complications. Prog Clin Biol Res. 1986;213:343–358.
[73]Boniface R, Robert AM. Effect of anthocyanins on human connective tissue metabolism in humans. Klinische Monatsblatter für Augenheilkunde. 1996;209:368–372.
[74]Detre Z, Jellinek H, Miskulin M, Robert AM. Studies on vascular permeability in hypertension: Action of anthocyanosides. Clin Physiol Biochem. 1986;4:143–149.
[75]Scharrer A, Ober M. Anthocyanosides in the treatment of retinopathies. Klin Monatsblatt Augenheilk. 1981;178:386–389.
[76]Lanthony P, Cosson JP. The course of color vision in early diabetic retinopathy treated with Ginkgo biloba extract: A preliminary double-blind versus placebo study. J Fr Ophtalmol. 1988;11:671–674.
[77]Doly M, Droy-Lefaix MT, Bonhomme B, Braquet P. Effect of Ginkgo biloba extract on the electrophysiology of the isolated retina from a diabetic rat [in French]. Presse Med. 1986;15:1480–1483.
[78]National Institutes of Health. National Eye Institute. Online document available at: www.nei.nih .gov=news=pressreleases=041204.asp. Accessed December 17, 2007.
[79]Fine SL, et al. Age-related macular degeneration. N Engl J Med. 2000;342:483.
[80]Young RW. Solar radiation and age-related macular degeneration. Surv Ophthalmol. 1988;32:252–269.
[81]Meltzer GE, Kravets BZ. Diet, nutrition, and diseases of the eye. J Appl Nutr. 1998;50:17–47.
[82]Katz ML, Parker KR, Handelman GJ, et al. Effects of antioxidant nutrient deficiency on the retina and retinal pigment epithelium of albino rats: A light and electron microscopic study. Exp Eye Res. 1982;34: 339–369.

[83]West S, Vitale S, Hallfrisch J, et al. Are anti-oxidants or supplements protective of age related macular degeneration? Arch Ophth. 1994;112:222–227.
[84]Eye Disease Case-Control Study Group. Antioxidant status and neovascular age-related macular degeneration. Arch Ophthalmol. 1993;111:104–109.
[85]Goldberg J, Flowerdew G, Smith E, et al. Factors associated with age-related macular degeneration. Am J Epidemiol. 1988;128:700–710.
[86]Bone RA, Landrum JT. Distribution of macular pigment components, zeaxanthin and lutein, in human retina. Methods Enzymo. 1992;l 213:360–366.
[87]Blumenkranz MS, Russell SR, Robey MG, et al. Risk factors in age-related maculopathy complicated by choroidal neovascularization. Ophthalmol. 1986;96:552–528.
[88]Mares-Perlman JA, Brady WE, Kleain R, et al. Serum antioxidants and age-related macular degeneration in a population-based case control study. Arch Ophthalmol. 1995;113:1518–1523.
[89]Newsome DA, Swartz M, Leone NC, et al. Oral zinc in macular degeneration. Arch Ophthalmol. 1988; 106:192–198.
[90]Stur M, Tihl M, Reitner A, Meisinger V. Oral zinc and the second eye in age-related macular degeneration. Invest Ophtholmol. 1966;37:1225–1235.
[91]Scharrer A, Ober M. Anthocyanosides in the treatment of retinopathies. Klin Monatsbl Augenheikld Beih. 1981;178:386–389.
[92]Mian E, Curri SB, et al. Anthocyanosides and the walls of microvessels: Further aspects of the mechanism of action of their protective in syndromes due to abnormal capillary fragility. Minerva Med. 1977;68:3565–3581.
[93]Lebuisson DA, Leroy L, Rigal G. Treatment of senile macular degeneration with Ginkgo biloba extract: A preliminary double-blind drug vs. placebo study [in French]. Presse Med. 1986;15:1556–1558.

14

ENHANCED FEMALE FERTILITY

Establishing Fertile Ground for Conception and a Baby's Health

Once a subject that was paid relatively little regard, the study of fertility has become increasingly popular, as the wear and tear of modern living has altered fertility levels. Infertility rates are increasing in the United States. According to the Centers for Disease Control and Prevention 2002 data, approximately 12% of women between 15 and 44 (roughly 7.3 million women) have impaired fertility; either a physical difficulty with getting pregnant or difficulty carrying a baby to term. This is an approximate 2% increase from the levels seen in 1988 and 1995.[1] According to the American Society of Reproductive Medicine, one in seven couples have difficulty conceiving.[2]

As a human race we must ask the question, if our fertility is on the decline, is this a reflection of the ecological and environmental consequence of our life and health in general? Environmentalists and zoologists have long held that the inability of a species to reproduce is a direct reflection of that species' strength to endure external changes that stress, to the point of threatening, the propagation of that species. Also, with the rise of autism, ADD, and numerous other early childhood conditions, it is of paramount importance to view enhanced fertility as not only increasing conception, but also the creation of a potentially stronger health future for the expectant child.

Infertility is generally defined as the inability to achieve pregnancy after one year of unprotected intercourse. Women in their 20s are usually advised to seek medical consultation after one year of attempting to conceive. Women in their 30s are recommended to seek advice after six months without conception. Female age is considered more of a factor than age of the male; thus if a woman is near or older than 35, she is advised to seek assistance sooner. Yet, because male factors actually account for an estimated 40% of conception difficulties, the first step in evaluating a couple who is having problems with conceiving is to determine which partner is infertile.[2]

CAUSES OF FEMALE INFERTILITY

There are many reasons for female infertility, ranging from anatomical to hormonal to nutritional. Complementary and alternative medicines can be helpful for addressing nearly all conditions and causes; a select few of these are covered in this article. There are also many confounding factors. Some of the better known causes of infertility include:

Ovulation problems—Ovulatory dysfunction may result from the aging process, anovulatory cycles, amenorrhea, luteal-phase defects, premature ovarian failure, polycystic ovarian syndrome, and hyperprolactinemia. (See Chapter 29 on polycystic ovary syndrome.)
Tubal defects—Anatomical problems in the structure or function of the fallopian tubes from past abdominal or pelvic surgery causing adhesions or past infections (pelvic inflammatory disease) may prevent eggs from traveling through the tubes.

Uterine growths—Growths, such as fibromas, myomas, and leiomyomas, may exist inside the uterus and negatively affect implantation of the fertilized egg.

Endometriosis—Fragments of endometrial tissue may be carried upward through the fallopian tubes and become implanted there and elsewhere in the pelvic area. Endometrial cysts may block passage of eggs through the tubes or become implanted on the ovaries, preventing release of eggs. Endometriosis can affect fertility in a number of other ways. (See Chapter 12 on endometriosis.)

Medication use—Several different types of medications have been reported to affect female fertility; among these are hormones, antibiotics, antidepressants, pain-relieving agents, and aspirin and ibuprofen when taken at midcycle.[3]

Other medical problems, such as inflammatory bowel disease, celiac sprue, epilepsy, thyroid conditions, and diabetes may all adversely affect a woman's state of fertility.[4] In sum, fertility problems are attributable to either mechanical factors, such as endometriosis and adhesions, or ovulatory dysfunction or failure.

Although there are many documented causes for infertility, unexplained infertility affects many women. Many women, after having adequate medical examination for themselves and their partners, are still unable to conceive although both members of the couple appear to be in normal health. Women, in particular, are susceptible to more influences that affect fertility than men; women typically produce one egg per month, and the entire menstrual cycle is governed by strict hormonal events. In addition, female reproductive organs are more complex than those of males; thus women are more vulnerable to anatomic and physiologic factors that could reduce fertility. Therefore, when attempting to discern the cause of female infertility, multiple factors should be taken into account.

TREATMENTS

The treatments discussed in Table 14–1 are supports that assist a woman's body to attain a state of highest fertility. When provided with adequate nutritional and environmental support, the body can achieve a state of excellent health, thus, enhancing fertility. Until then, patients who

Table 14–1. Nutritional Supplements for Enhancing Female Fertility

Supplements	Comments
B vitamins	1 B-complex capsule=day containing at least 800–1,000 mcg of folic acid and 25–50 mg of vitamin B_6; may increase to 2 capsules if patient is taking pharmaceutical medications; use to address high-stress lifestyle or inadequate diet; particularly women who have taken oral contraceptives
Iron	18 mg=day, preconceptually; 27 mg=day while pregnant
Vitamin C	500–1,000 mg=per day
Multivitamin=mineral supplement[a]	Choose a high-quality supplement; doses range from 2–6 capsules=day

[a] The majority of prenatal multivitamin=mineral supplements contain sufficient iron; extra supplementation with iron is contraindicated.

have difficulty in conceiving are advised to take as many steps toward health as necessary to prepare their bodies for reproduction.

NUTRITIONAL AND LIFESTYLE FACTORS

A number of strategies can be used to address certain female health conditions. Incorporation of all factors is important for achieving overall reproductive health, regardless of the diagnostic "label" a patient has been given. In particular, females will need to work on a variety of factors to optimize their fertility. It is also important that women who wish to use nutraceutical and botanical regimens be strongly advised to work closely with a physician as some supplements taken to improve fertility may alter the fetal environment.

Dietary Deficiencies

Regardless of research studies on the benefits of specific supplements for enhancing fertility, there is no substitute for a healthy diet. The foundation of good health has always been the proper care and feeding of the human body. Diet, in both women and men, has a profound effect on fertility; what is (and what is not) put into the body can affect the multiple things that must go right for conception to occur (or not occur). Interestingly, the human body almost seems to have a built-in mechanism to prevent conception to the degree a person is undernourished or overstressed. Certainly, pregnancy occurs often in undernourished individuals, yet, this tendency is thought-provoking at the very least. Indeed, food is the best medicine and avoiding contaminated food is equally as important as proper diet and nutrition. Consumption of therapeutic foods and correctly prescribed supplements can help offset less-controllable environmental factors.

Environmental Contaminants

Increasing evidence relates the effects of environmental exposure to chemicals, radiation, and infections on germ cells, fertilized eggs, and on hormonal balance to implantation and development.[5] Passive environmental exposures to pollutants are common, from workplace chemicals, to products in the air from manufacturing facilities, to urban water supplies with supposedly "acceptable" levels of contaminants. Environmental chemicals that affect fertility are also in most

Fertility-Promoting Lifestyle Factors

What to Tell Your Patients

Help your patients improve their fertility by advising them to:

- Maintain an optimal diet, including varied sources of nutrition.
- Avoid environmental chemicals at work, home, and in food sources.
- Do not microwave in or with any plastic.
- Avoid parabens and methylparabens in makeup and hygiene items.
- Eliminate or avoid caffeine prior to conception.
- Avoid drastic weight loss and dieting at least six months prior to conception, because fat loss causes mobilization of stored toxins within fat cells.

commercially prepared food, if not foods from organic farms or derived from similar production means. Secondhand cigarette smoke presents a problem due to cadmium, a toxic metal in smoke, which is absorbed in the body and is known to have negative effects on fertility, as well as other components of cigarette smoke.[6] It is easy to become overwhelmed by the numerous ways in which the world has become increasingly nonconducive to optimal fertility levels; patients must be trained to be diligent in protecting themselves without becoming overwhelmed.

Alcohol

Research has proven that alcohol affects the fertility of women and men adversely and that fertility can be improved when alcohol is eliminated from the diet.[7] The strong link between alcohol consumption by a pregnant mother and the incidence of fetal-alcohol syndrome provides strong evidence for alcohol avoidance during pregnancy; furthermore, research now points to the importance of avoiding alcohol prenatally as well to boost fertility.[8]

Caffeine

Caffeine, while not the most detrimental of dietary incursions, does apparently have a rather negative effect on fertility. In fact, there is strong evidence that avoidance of caffeine is important for women who are trying to conceive. One study indicated that consumption of more than two cups of coffee per day may lead to adverse effects on fertility, especially among women with fallopian-tube disease and endometriosis.[9] Other studies have shown evidence associating caffeine consumption with delayed conception. Women who consumed greater than 300 mg of caffeine per day had a 27% lower chance of achieving conception while woman who consumed less than 300 mg per day of caffeine had a 10% lower chance of conception compared to women who consumed no caffeine.[10] Studies have also shown a decreased incidence of miscarriage in women who avoid caffeine during pregnancy. Sources of caffeine other than coffee include green and black tea, soft drinks, cocoa, chocolate, and some over-the-counter medicines. Elimination of caffeine, while the research is not conclusive, may help a couple improve their chances for successful conception.

Dieting for Weight Loss

Dieting, adhering to a calorically stringent diet, may be detrimental to fertility in two ways:

1. Dramatic weight loss, especially when accompanied by excessive physical activity, can predispose women to amenorrhea. Although body weight and composition (fat versus muscle) are considered important for maintaining regular menstrual cycles, no single determinant of regularity is known at this time. Severe malnutrition, which can occur at times of intense caloric restriction, is known to result in amenorrhea and anovulation, among other ill effects.
2. Weight loss through less-drastic means that achieves a loss of 30% or more of body fat can also lead to menstrual irregularities and then amenorrhea.[11] Patients who have participated in weight-loss programs aggressively may find it easier to become pregnant once some weight is gained back; individuals vary widely in this respect.

Rapid weight loss is known to lower progesterone levels, slow follicular growth, and inhibit the luteinzing hormone surge, thus inhibiting ovulation.[12] In addition, less-intense weight loss may

also depress hormone levels to an extent that an insufficiently sized corpus luteum fails to sustain an early pregnancy. Another reason for avoiding dramatic weight loss and dieting is possibility of increased exposure to chemicals that have been previously stored in fatty tissue. As bioaccumulators, humans and other animals at the top of the food chain store certain chemicals in various tissue compartments in the body. Fat tissue is one of the main repositories of many different chemicals. By sequestering these chemicals in fatty tissue rather than storing them in more metabolically active tissue, the body is relatively protected from these chemicals.

Several studies in the literature document the biological plausibility of chemicals stored in adipose tissue creating various potential health risks.[13,14] Rapid weight loss creates the potential for increased exposure as the chemicals that are released from adipose cells are allowed to circulate throughout the body; this may affect other organ systems. Approximately six months is a safe period of time for patients to avoid rapid weight loss prior to conception, or attempts to conceive. Although this recommendation is not solidly backed by research, it is a minimal step that women who are trying to conceive may take to enhance their chances of success.

SUPPLEMENTS

Vitamin C, B-complex vitamins, and iron all can help assist women to conceive as shown by a number of studies.

B Vitamins

The grouping of B vitamins, as a whole, has multiple uses for health and medicine throughout the human body. Adequate supplementation with these vitamins may ensure fertility and healthy pregnancy in a number of ways. Folic acid is well-known as a necessary nutrient for preventing neural-tube defects in fetuses. The vitamin can also be used to maintain proper cervix health by preventing cellular oxidative damage. Folic acid acts as a chemopreventive agent that interferes with the activity of human papilloma virus infection (a leading cause of abnormalities that are revealed by Papanicolaou [PAP] smears) and of cervical cancer.[15] B-vitamin deficits may be relatively common today as a result of certain medications such as oral contraceptives, or lifestyle factors including inadequate intake of vegetables and fruits. In fact, studies indicate that oral contraceptives deplete vitamin B_2, vitamin B_6, vitamin B_{12}, and folic acid.[16–18] Inadequate B-vitamin levels may predispose a person to depression, carpal tunnel syndrome, and most importantly, altered hormone levels.[19] (See Chapter 38 on nutrient depletion caused by pharmaceuticals.) Furthermore, it is interesting to note the therapeutic ability of vitamin B_6 and folic acid to prevent and treat morning sickness; it appears that women who ingest inadequate amounts of these vitamins tend to experience more illness during the course of pregnancy.

Vitamin C

Known for its multiple health effects, vitamin C has been shown to assist certain populations of women to achieve pregnancy. An older study showed that women taking a fertility agent (clomiphene) with no results were then able to have a menstrual period and ovulate following 400 mg of vitamin C supplementation.[20] Another study, using laboratory animals as models,

showed that animals who were given vitamins C and E experienced a decrease in age-related reduction in their ovulation rates; that is, the animals were able to ovulate more frequently when given the supplements compared to other animals of similar age who were not given the supplements.[21] Although direct implications for human fertility cannot be assumed on the basis of this study, it does suggest implications for age-associated infertility in humans.

> Natural medicine approaches further increase the opportunity to treat each woman as an individual to address her specific cause of infertility.

Iron

Iron, which is important for erythropoiesis, may prove to be an important preconception nutrient for women who are trying to conceive. One report noted that women with lower levels of iron could improve their fertility by taking iron supplements.[22] Women with insufficient amounts of iron will not be able to respond to the high demand for this nutrient once conception has been achieved. It is important to note that, prior to taking iron, women should be tested to determine the actual (ferritin) and apparent (complete blood count) levels of iron in their bodies. It is also important to be aware if a woman is taking a multivitamin=mineral supplement because many of these contain required amounts of iron and additional supplementation may be contraindicated.

Multivitamins=Minerals

Prenatal vitamins, as their name suggests, should be taken during pregnancy and prior to it. Multivitamin=mineral supplements promote general health and supply the body with the nutrients it needs as well as those needed for a new, developing life. A study that evaluated multivitamin supplementation during a 28-day preconception period demonstrated a significantly increased rate of conceptions among women who took a test supplement preconceptually compared to women who took a placebo during the same time period; this difference was a 5% decreased time to achieve conception for the women who took the test supplement.[23] In addition, the same research team noted a significantly higher occurrence of multiple births among the women in the supplement-treated group compared to women in the placebo group as well as the entire population from which the study groups were taken.[24] Multivitamin supplementation seems to increase chances for successful conception when taken during preconception. Supplementation should begin 3 to 6 months prior to conception, if possible.

Progesterone

Abnormalities in progesterone levels are found in many women with infertility. In fact, studies show that progesterone may be two times lower in women with repeated loss of pregnancy compared to fertile women. Additionally, progesterone was 200 times higher in the endometrium of fertile women compared to the women with difficulty maintaining a pregnancy.[25] Natural progesterone supplementation, either intramuscularly or vaginally, is often used to support luteal phase defects and infertility in women.[26]

Table 14–2. Selected Botanicals and Applications for Enhancing Female Fertility[a]

Herbs or Preparations	Use for Addressing
Puncture vine (Tribulus terrestris)	Anovulatory cycles
Chasteberry (Vitex agnus-castus)	Luteal-phase defects
Shakuyaku-Kanzo-To	Elevated androgen levels
Zhibai Dihuang	Presence of anti–zona pellucida antibodies

[a]Once a woman becomes pregnant, she should be warned to discontinue these botanical medications

BOTANICAL MEDICINES AND FERTILITY

When utilizing herbal medicine to treat medical conditions, including infertility, it is important to note that herbal medicine, when used in traditional practice, embodies the concept of natural medicines. Herbal medicines are not necessarily meant to treat specific health problems directly but rather to support the body or organ systems to regain physiologic, functional control over a body system that needs fine-tuning. Many herbal medicines can be used to help women to become pregnant, based upon patients' individual symptoms and designed to nourish each patient's body allowing it to be at its healthiest. (See Table 14–2 above.)

Puncture Vine

Puncture vine (Tribulus terrestris) is useful for helping the body produce productive ovulatory cycles. A concentrated form of tribulus, standardized to 45% steroidal saponin content used in a clinical study, assisted women in achieving ovulatory cycles when the test preparation was administered at 250–500 mg, 3 times per day for over three months.[27]

Chasteberry

Chasteberry (Vitex agnus-castus) appears to have prolactin-inhibiting effects, among others, and has been used for women who are sterile as a result of secondary amenorrhea and luteal insufficiency.[28] The herb seems to normalize luteal-phase defects and may increase the chances of becoming pregnant for women with relative progesterone deficiency. For women with hyperprolactinemia, vitex was shown to suppress prolactin release, lengthen luteal phases, and improve progesterone synthesis after three months of treatment.[29] In another study, 120 women with polymenorrhea, oligomenorrhea, and corpus luteum insufficiency were treated with a standardized extract of vitex for six months. Sixty percent of these women had sought conception assistance previously. During the study, the women's progesterone levels were increased from an average of 6.4 ng=mL to 9.3 ng=mL while 64% of the women's cycles became normalized and 29% of the women became pregnant.[30] A combination herbal supplement consisting of chasteberry, green tea, L-arginine, vitamins, and minerals was studied in women with difficulty conceiving. The results showed significantly increased luteal-phase progesterone and basal temperature, as well as increased pregnancy rates in the supplement group compared to the controls.[31]

Two Chinese Herbal Preparations

Shakuyaku-Kanzo-To, a Chinese botanical combination of extracts from Paeonae radix and Glycyrrhizae radix, has been used to lower elevated testosterone levels in a number of settings.[32] When this preparation was given to subjects at a dose of 5–10 mg per day for two to eight weeks, women with elevated circulating levels of androgens had significant lowering of testosterone. Six of the seven subjects in this study began ovulating regularly, and two of them were able to conceive.[33] Zhibai Dihuang, another Chinese formula (comprised of the herbs Anemarrhena, Phellondendron, and Rhemannia and given in pill form), has shown promise for helping couples with antisperm and=or anti–zona pellucida antibodies. Infertile couples were treated with this formula; following treatment antibody conversion to negative was at 81.3% of the infertile couple subjects in the study.[34] Moreover, in the one to nine months following the study, all eight previously immunologically infertile couples were able to conceive, and the women's antibody status remained negative throughout their pregnancies.

CONCLUSIONS

Nutrients and botanical medicines offer an opportunity to treat each woman as an individual to address her specific cause of infertility. This approach serves patients best, especially when dealing with multiple confounders, such as those that occur in infertility. Lifestyle factors are ''fertile ground'' for addressing numerous causes of infertility. One can examine each woman's diet, place of work, home environment, and other lifestyle choices to give her options for achieving adequate nutrition. A balanced and varied diet is essential and optimal amounts of the key supplements are also important for helping women achieve conception. This is vital in addition to examining other avenues for addressing infertility fully to help woman prepare their bodies for the miracle of conception. Also, it is important to note that conception is not the end, it is the beginning of the nine-month journey of nourishing a new life. Thus, improving overall health is crucial for optimizing proper development of the fetus and for the health of the infant.

REFERENCES

[1]National Center for Health Statistics. Fertility, Family Planning, and Reproductive Health of U.S. Women: Data from the 2002 National Survey of Family Growth. Available at: www.cdc.gov=nchs=products=pubs=pubd=series=sr23=pre-1=sr23_25.htm. Accessed October 14, 2007.

[2]American Society of Reproductive Medicine. Infertility: An Overview. Available at: www.asrm.org=Patients=patientbooklets=infertility_overview.pdf. Accessed October 14, 2007.

[3]Online document at: www.ucdmc.ucdavis.edu=ucdhs=health=az=22InfertilityWomen=doc22causes.html.

[4]Bauer J, Isojarvi JI, Herzog AG, Reuber M, Polson D, Tauboll E, Genton P, van der Ven H, Roesing B, Luef GJ, Galimberti CA, van Parys J, Flugel D, Bergmann A, Elger CE. Reproductive dysfunction in women with epilepsy: Recommendations for evaluation and management. J Neurol Neurosurg Psychiatry. 2002;73:121–125.

[5]Premalatha GD, Ravindran J. Reproductive problems of the work force. Med J Malaysia. 2000;55:146–151.

[6]Younglai EV, Foster WG, Hughes EG, Trim K, Jarrell JF. Levels of environmental contaminants in human follicular fluid, serum, and seminal plasma of couples undergoing in vitro fertilization. Arch Environ Contam Toxicol. 2002;43:121–126.

[7]Eggert J, Theobald H, Engfeldt P. Effects of alcohol consumption on female fertility during an 18-year period. Fertil Steril. 2004;81:379–383.

[8]Grodstein F, Goldman MB, et al. Infertility in women and moderate alcohol use. Am J Public Health. 1994;84:1429–1432.
[9]Grodstein F, Goldman MB, Ryan L, Cramer DW. Relation of female infertility to consumption of caffeinated beverages. Am J Epidemiol. 1993;137:1353–1560.
[10]Hatch EE, Bracken MB. Association of delayed conception with caffeine consumption. Am J Epidemiol. 1993;138:1082–1092.
[11]Van Der Spuy ZM, Jacobs HS. Weight reduction, fertility and contraception. IPPF Med Bull. 1983;17: 2–4.
[12]Wynn M, Wynn A. Slimming and fertility. Mod Midwife. 1994;4:17–20.
[13]Petreas M, She J, Brown FR, Winkler J, Windham G, Rogers E, Zhao G, Bhatia R, Charles MJ. High body burdens of 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47) in California women. Environ Health Perspect. 2003;111:1175–1179.
[14]Damstra T. Potential effects of certain persistent organic pollutants and endocrine disrupting chemicals on the health of children. J Toxicol Clin Toxicol. 2002;40(4):457–465.
[15]Kelloff GJ, Boone CW, Crowell JA, Nayfield SG, Hawk E, Steele VE, Lubet RA, Sigman CC. Strategies for phase II cancer chemoprevention trials: Cervix, endometrium, and ovary. J Cell Biochem Suppl. 1995; 23:1–9.
[16]Smolders RG, de Meer K, Kenemans P, Jakobs C, Kulik W, van der Mooren MJ. Oral estradiol decreases plasma homocysteine, vitamin B_6, and albumin in postmenopausal women but does not change the whole-body homocysteine remethylation and transmethylation flux. J Clin Endocrinol Metab. 2005 Apr;90(4): 2218–2224. Epub 2005 Jan 25.
[17]Haspels AA, Bennink HJ, Schreurs WH. Disturbance of tryptophan metabolism and its correction during oestrogen treatment in postmenopausal women. Maturitas. 1978 Jun;1(1):15–20.
[18]Webb JL. Nutritional effects of oral contraceptive use: A review. J Reprod Med. 1980 Oct;25(4): 150–156.
[19]Werbach MR. Female infertility [review]. Townsend Letter for Doctors & Patients. 1995 Aug;34.
[20]Igarashi M. Augmentative effect of ascorbic acid upon induction of human ovulation in clomiphene-ineffective anovulatory women. Int J Fertil. 1977;22:168–173.
[21]Tarin J, Ten J, Vendrell FJ, de Oliveira MN, Cano A. Effects of maternal ageing and dietary antioxidant supplementation on ovulation, fertilization and embryo development in vitro in the mouse. Reprod Nutr Dev. 1998;38:499–508.
[22]Rushton DH, Ramsay ID, Gilkes JJH. Ferritin and fertility. Lancet. 1991;337:1554.
[23]Czeizel AE, Metneki J, Dudas I. The effect of preconceptional multivitamin supplementation on fertility. Int J Vitam Nutr Res. 1996;66:55–58.
[24]Czeizel AE, Metneki J, Dudas I. The higher rate of multiple births after periconceptional multivitamin supplementation: An analysis of causes. Acta Genet Med Gemellol (Roma). 1994;43(3–4):175–184.
[25]Salazar EL, Calzada L. The role of progesterone in endometrial estradiol- and progesterone-receptor synthesis in women with menstrual disorders and habitual abortion. Gynecol Endocrinol. 2007 Apr;23(4): 222–225.
[26]Tavaniotou A, Smitz J, Bourgain C, Devroey P. Comparison between different routes of progesterone administration as luteal phase support in infertility treatments. Hum Reprod Update. 2000 Mar–Apr;6(2): 139–148.
[27]Tabakova P, et al. Clinical study of Tribestan in females with endocrine sterility. Cited in: Werbach, MR, Murray MT. Botanical Influences on Illness, 2nd Edition. Tarzana, CA, Third Line Press Inc., 2000, 399.
[28]Gerhard II, Patek A, Monga B, Blank A, Gorkow C. Mastodynon in feminine sterility. Forsch Komplementarmed. 1998;5:272–278.
[29]Milewicz A, Gejdel E, Sworen H, et al. Vitex agnus castus extract in the treatment of luteal phase defects due to latent hyperprolactinemia: Results of a randomized placebo-controlled double-blind study. Arzneimittelforschung. 1993;43:752–756.
[30]Bubenzer RH. Therapy with Agnus castus extract (Strotan). Therapiewoche. 1993;43:32–33,1705–1706.
[31]Westphal LM, Polan ML, Trant AS. Double-blind, placebo-controlled study of Fertilityblend: A nutritional supplement for improving fertility in women. Clin Exp Obstet Gynecol. 2006;33(4):205–208.
[32]Online document at: www.honsousa.com=Research=Abstract_Shakuyaku-kanzo-to_SYGCT.pdf.
[33]Yaginuma T, Izumi R, Yasui H et al., Effect of traditional herbal medicine on serum testosterone levels and its induction of regular ovulation in hyperandrogenic and oligomenorrheic women. Nippon Sanka Fujinka Gakki Zasshi. 1982;34:939–944.
[34]Li DJ, Li CJ, Zhu Y. Treatments of immunological infertility with Chinese medicinal herbs of ziyin jianghuo. Chung Kuo Chung His I Chieh Ho Tsa Chih. 1995;15:3–5.

15

NATURAL WAYS TO ENHANCE MALE FERTILITY

Fertility, in one sense, is the barometer of a person's overall health, all things being equal. In order to conceive, a person must have a certain level of fertility that requires a sufficiently healthy body to maintain, whether a person is male or female. Fertility can be fleeting as well; it has been estimated that nearly 6 million Americans are infertile at any given time. The standard definition of infertility is the inability of a couple of childbearing age to conceive a child after one year of regular intercourse without the use of contraceptives. Because the large majority of couples can conceive within this time frame, it is recommended that those who do not should be assessed for fertility problems. This chapter focuses on infertility in men and natural ways to address it.

PREVALENCE

It is important to note that infertility can occur just as equally in men as in women, with 30% of infertility attributable to men and 30% to women, while another 30% is attributed to both partners and the remaining 10% is related to unknown factors. Other statistics indicate that the annual incidence of male infertility is at least 2 million cases, which equates to an incidence rate of approximately 1 in 136 men, or 0.74% of the men in the United States.[1] In addition, more than 4.5 million couples in the United States do not conceive at their first attempt and more than one in two (50%) of the men involved have irreversible infertility and are not able to father children.

CAUSES

The reasons for infertility in men are numerous; the primary causes of male infertility entail problems with spermatozoa production or delivery that may result from certain types of hormonal dysfunction, whereas trauma or anatomical defects in the reproductive system and other illnesses can all lead to infertility. Recent research has shown that approximately one in four men over age 30 have low levels of testosterone.[2] Some additional causes of male infertility include:

Cryptorchidism—a failure of one or both testes to descend that can impair spermatogenesis
Cystic fibrosis—a condition associated with both an absence and=or blockage of the vas deferens
Ductal obstruction—an anatomical problem that may be caused by repeated infections, inflammations, or a developmental defect
Hemochromatosis—a metabolic disorder that causes iron deposition in the testes

Hormone dysfunction—a condition caused by dysregulation in the hypothalamic-pituitary-gonadal axis (See Chapter 2 on andropause)
Drugs and other substances—pharmaceuticals used to treat hypertension, arthritis, and digestive diseases; agents for chemotherapy; and recreational drugs (such as marijuana) that are associated with sperm-production problems and infertility as is alcohol use
Retrograde ejaculation—an anatomical defect that involves the muscles and nerves of the bladder neck
Sexually transmitted infections—diseases that may cause obstructions, infections, and scarring
Sickle-cell anemia—a condition that can cause hypogonadism
Systemic diseases—such as high fevers, infections, kidney diseases, or metabolic disorders that can impair spermatogenesis
Testicular cancer—a condition that may cause obstructions or dysfunctions or problems related to chemotherapy used to treat the disease
Testicular trauma—an event that causes damage to testes, impairing their ability to function
Varicocele—a condition that can alter testicular temperature affecting spermatogenesis

Spermatogenesis occurs in cycles composed of six stages; each one takes approximately 16 days to complete, and it takes 3 months to produce mature sperm. Development of sperm is ultimately controlled by the endocrine system via the hypothalamic-pituitary-gonadal axis. Because sperm production occurs over a relatively long period of time, an illness that occurs within that time period can affect sperm production; therefore, it is important to consider recent health history when exploring causes of infertility.

Environmental and Lifestyle Factors

Although the conditions mentioned previously are all contributors to infertility, there are many other factors that appear in the environment and=or that occur as a result of a person's lifestyle that may contribute to infertility. Among these are workplace hazards (chemical exposures), environmental toxins (endocrine disruptors), habits such as smoking or alcohol consumption, dietary factors (insufficient nutrition), oxidation, and even the type of underwear worn. Although these factors are not always indicated as causes of infertility, they must be considered to ascertain whether these factors contribute to a particular person's infertility.

Workplace Hazards

There are several chemicals commonly found in workplaces that are known to be reproductive hazards for men. The hazards come from plastic production, welding, and lead and other chemicals.[3] A complete list of reproductive hazards in the workplace is unavailable because this is an ongoing area of research. More than 1,000 different chemicals used in the workplace (of the 4 million chemical mixtures that are commercially used) have been shown to cause reproductive problems in animals: The majority of these chemicals' effects have not been studied in humans. Known workplace hazards affect reproduction by decreasing sperm counts, causing abnormally shaped sperm, altering sperm transfer, and altering hormones and sexual

function. Workplace exposures have been shown to affect the reproductive system in men; however, they do not affect each person in a similar way. Quantity, duration, and other factors determine whether someone is affected or not. These substances enter the body via inhalation, skin contact, or ingestion.

Other Environmental Toxins

There are several reports detailing the occurrence of decreased sperm counts in men who have resided in developed countries over the last 50 years. It has been suggested that the reason for this trend is increased environmental exposure to estrogen-like compounds as well as other chemicals that act as antiandrogens. This evidence has been repeated in a number of investigations.[4] A study investigating the effects of estrogenic substances (diethylstilbestrol, beta-estradiol [E2], daidzein, genistein, and nonylphenyl) on sperm was performed; the investigators found that the effects of these estrogenic substances caused similar negative effects as known reproductive toxins (lead sulfate, nitrate, and acetate, dibromochloropropane, ethylene glycol monoethyl ether, 1,2-epoxybutene, and 1,2,3,4-diepoxybutane). However, these in vitro studies using large amounts of single compounds have not been validated in human studies.[5] Additional studies have linked other environmental toxins to fertility problems. A study that examined the blood levels of organochlorines in men with either poor or normal semen quality revealed an inverse relationship between sperm count and progressive motility and polychlorinated biphenyl metabolite concentrations.[6] This study revealed a relationship between significantly decreased sperm counts and elevated organochlorine blood levels. In addition, a linear relationship was shown between organochlorine levels and the ages of the volunteers. These brief studies provide proof of the effects that environmental factors may have on male reproductive health.

A correlation exists between low prostate zinc levels and prostatic carcinoma.

Lifestyle Factors

Lifestyle factors, such as alcohol consumption and tobacco and marijuana smoking, are well-known causes of decreased sperm counts. In drinkers, alcohol has been shown to decrease sperm count, produce morphologic abnormalities, decrease sperm motility, and increase serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex-hormone-binding globulin levels. Patients who abused alcohol were found to be in a state of primary hypogonadism as a result of lifetime alcohol consumption.[7] Sperm count and motility were found to be lower in smokers compared to nonsmokers, and smokers had a higher incidence of oligospermia, higher levels of endogenous 17-beta-E2, and sperm counts below normal compared to nonsmokers.[8] Marijuana smoking has contributed to male infertility.[9] Other lifestyle factors, such as type of underwear worn by a man, appear to have an effect on fertility. Brief-style underwear holds the testes closely to the body and thus induces temperature elevations in the testicles that are not conducive to spermatogenesis. This technique was studied as a form of birth control; men enrolled in a study had their testicles kept in close apposition to their inguinal canals and as a result were unable to cause pregnancies for the duration of the study period.[10]

At the end of a 60-day study period, every subject who had taken vitamin C had impregnated his partner.

NUTRITIONAL SUPPORTS

Several steps can be taken to reverse infertility in some cases. Once a primary cause is treated or removed, then comes the task of enhancing the body's general health by using nutritional supports in order to assist recovery of spermatogenesis. Maintaining a state of fertility for some patients may require constant support; these methods can be used for patients who have suffered some type of damage to existing mature sperm to ensure that normal, healthy sperm production continues. Among the minerals, zinc is a key factor. (See Table 15–1 below.)

Zinc

Zinc is the second most abundant trace element in the human body, totaling nearly 2 g.[11] Found in more than 300 enzymes, zinc is a cofactor for multiple biologic processes including DNA, RNA, and protein synthesis. The mineral is used itself as a catalyst in 100 different enzymes.[12]

Male fertility is influenced by zinc in several different ways. Low zinc levels have a negative effect on serum testosterone concentration and seminal volume.[13] Seminal plasma zinc concentration has been significantly positively correlated with sperm density, possibly contributing a positive effect on spermatogenesis.[14,15] Other studies have shown the effects of zinc on sperm motility,[16] emphasizing the mineral's role in flagella function. Infertile males have been

Table 15–1. Dosing Guide for Supplements That Enhance Male Fertility

Supplements	Doses
Zinc[a]	45–60 mg per day
Selenium	200 mg per day
Glutathione	500 mg twice per day
Vitamin E	400–800 IU per day
Vitamin C	1,000–2,000 mg per day
Coenzyme Q10	100 mg per day
Arginine	3,000 mg per day
Carnitine	3,000 mg per day
Maca	1,500–3,000 mg per day, in 3 divided doses
Ginseng	200 mg standardized extract per day
Pygeum	200 mg per day
Supplements for increasing intracellular levels of glutathione	
Vitamin C	500 mg per day
N-acetylcysteine	800 mg per day

[a]When using zinc, also add a copper supplement. For long-term (three months) zinc use, 2 mg of copper should be taken per day.

shown to have lower levels of seminal plasma zinc that have been associated with reduced levels of zinc in their blood.[17] Treatment with zinc can improve sperm motility parameters in men with decreased motility, suggesting a relatively simple treatment for several factors that influence fertility.[18] In this study, men with asthenozoospermia (reduced sperm motility) were treated with 250 mg of zinc sulfate, twice per day, for three months. After six months of follow-up, the study subjects had significant improvements in sperm quality as measured by improved sperm counts, progressive motility, and fertilizing capacity; the men also had a reduced incidence of antisperm antibodies. Furthermore, the investigators hypothesized that zinc improves sperm parameters via a membrane-stabilizing effect as an antioxidant as well as affecting cellular and humoral immunity by decreasing antisperm antibody levels.

As a therapy, zinc has been suggested as a treatment for infertile male smokers by a study that investigated the mechanism of the zinc–cadmium relationship in the testes of laboratory animals.[19] Smokers had increased seminal cadmium levels, decreased sperm counts and motility, and poor sperm morphology. Therapy with zinc improved sperm quality and increased seminal levels of interleukin-4; yet the therapy also decreased tumor necrosis factor-alpha and interferon-gamma. When a zinc-deficient diet was fed to the animals, this allowed cadmium from cigarette smoke to accumulate in their testicles in similar amounts to that seen in animals that were given cadmium supplements.[19] The investigators of this study stated that, because of the ability of zinc to elevate Th-2 cytokines and down-regulate Th-1 cytokines, zinc may modulate the putative effects of cadmium on spermatogenesis.

In addition to the beneficial effects of zinc on fertility, the relationship of zinc in prostate health must also be mentioned. A correlation exists between low prostate (tissue and fluid) zinc levels and prostatic carcinoma. The concentration of zinc in the prostate is higher than that in any other tissue in the body. Prostatic zinc content decreases incrementally from normal prostate to benign prostatic hyperplasia (BPH) to cancer. Quantification of zinc levels in prostate biopsy samples has been proposed as an additional test in the differential diagnosing of BPH and cancer.[20] Investigators have reported the sensitivity and specificity of this test to be 98%. Zinc has been shown to play an important part in male reproductive health. The relationship between zinc and both seminal and prostate health is interesting; the results of inadequate amounts of zinc appear to have rather detrimental effects on the male reproductive system and, thus, zinc supplements should be considered for every man.

ANTIOXIDANTS

The role of reactive oxygen species (ROS) in male fertility has come under increasing speculation with regard to their physiologic and pathologic effects. Elevated levels of ROS are known to compromise sperm function and viability (damage of spermatic nuclear DNA). This oxidative stress is derived from excessive production of ROS and=or impaired antioxidant defense mechanisms in the semen.[21] The use of antioxidant nutrients, such as selenium, glutathione, vitamin E, and vitamin C, has produced benefits in relation to sperm health.

Selenium

A study of selenium and vitamins involved 69 infertile men who were treated with placebo, selenium, or selenium in combination with vitamins A, C, and E for three months. At the end of the study, both selenium-treated groups had significant improvements in sperm motility.[22] In addition, 11% of the men impregnated their partners during the three-month study period.

Another study utilizing selenium supplementation in a group of infertile men provided a dose of 200 mg per day for 12 weeks.[23] Selenium concentrations were increased in the men's seminal fluid and one form of supplemental selenium (selenium-rich yeast) significantly increased glutathione peroxidase activity in the subjects' seminal fluid.

Glutathione

Glutathione is an important part of sperm antioxidant defense and has been repeatedly shown to have a positive effect on sperm motility when subjects took supplements with this antioxidant.[24–26] In one interesting study, 600 mg of glutathione was administered intramuscularly to subjects, every other day for two months. Compared to subjects in a placebo group, men in the treatment group experienced a statistically significant effect on sperm motility, specifically in the percentage of sperm with forward mobility.[27] Glutathione and selenium are essential for producing a specific protein in sperm that is responsible for motility. The phospholipid enzyme hydroperoxide glutathione peroxidase is converted to a structural protein that comprises approximately 50% of the mitochondrial capsule in the midpiece of mature spermatozoa.[28] A deficiency of either nutrient leads to impaired motility of the spermatozoa. Deficiencies of either substance can lead to instability of the midpiece, resulting in defective motility.[29]

Vitamin E

Another well-known antioxidant, vitamin E, plays a role in protecting the lipid layer of human cells against ROS.[30] There are several studies in the literature documenting this effect as well as showing the benefits of vitamin E supplementation on spermatic fertility. A study on men with low sperm counts with decreased motility showed that subjects who were given vitamin E experienced increases in both of these parameters after six months of supplementation with vitamin E combined with selenium.[31] Another study estimated the amount of lipid peroxidation in the seminal plasma and spermatozoa via malondialdehyde (MDA) concentrations.[32] Supplementation with vitamin E was shown to decrease MDA concentration significantly. Sperm motility was improved as well, which led to a 21% pregnancy occurrence during the course of the study. A final study showed that 600 mg per day of vitamin E improved sperm function as demonstrated in the zona binding assay, a measurement that assesses sperms' egg penetration ability.[33]

Vitamin C

Seminal plasma levels are reflective of daily dietary intake, and decreased levels of vitamin C have been shown to be related to infertility and increased oxidative damage to spermatic DNA.[34] This was demonstrated in an experiment that reduced vitamin C intake in normal healthy men to a level of 5 mg per day—a decrease from 250 mg.[35] Seminal levels of vitamin C were reduced by 50% and were accompanied by a 91% increase in spermatic DNA damage in this study. In another study on the effects of vitamin C on sperm quality, smokers were given placebo, 200 mg, or 1,000 mg of vitamin C per day. The two vitamin C– treated groups had improvements in sperm quality related to increased vitamin C intake while the placebo group had no improvement whatsoever.[36] Another important study on the use of vitamin C and its effects on male fertility demonstrated that supplementation with this vitamin could reverse some aspects of infertility.[37] A group of infertile men were given placebo, 200 mg, or 1,000 mg of

vitamin C per day. After only one week of supplementation, the group who took the 1,000 mg of vitamin C had a 140% increase in sperm count, and the group who took 200 mg of the vitamin had a 112% increase in sperm count. The placebo group had no changes. In addition, the vitamin C–treated groups had decreased sperm agglutination and, at the end of the 60-day study period, every subject who had taken vitamin C had impregnated his partner while no placebo subjects were able to cause their partners to become pregnant.

Coenzyme Q10

As the final electron acceptor in the synthesis of adenosine triphosphate, coenzyme Q10 (CoQ10) is most concentrated in the mitochondria of the midpiece of spermatozoon, where flagella propulsion is initiated. CoQ10 has demonstrated antioxidant capabilities as well and protects the spermatic membranes against ROS. One study analyzed samples (from asthenospermic men) that were incubated with 50 micromoles of CoQ10; significant increases in motility were observed. In addition, 60 mg of CoQ10 was given to infertile men for approximately 100 days, producing improved fertilization rates for this group.[38] Another study produced increased sperm counts and motility in the sperm of infertile men after they were given 10 mg per day of coenzyme Q7, an analogue derivative of CoQ10.[39]

Amino Acids: Arginine and Carnitine

Arginine is a precursor of several compounds (putrescine, spermidine, and spermine) that are thought to play a role in sperm motility. An older study showed that 74% of subjects (178 total) had significant improvements in sperm counts and motility after being given 4 g per day of these nutrients for three months.[40] In a more recent study, arginine (administered as 80 mL of a 10% HCl solution) was given each day to men with normal sperm counts but whose sperm had decreased motility.[41] The sperm of these subjects increased as a result of the treatment and no side effects were noted.

Carnitine plays several roles in the development of healthy spermatozoa. Carnitine serves as a source of energy in the epididymis, helps to boost sperm motility, and is thought to be involved with sperm maturation.[42] Studies of infertile patients have shown a direct correlation between sperm motility and semen carnitine content as well as demonstrating a positive correlation between carnitine levels and sperm counts and number of motile sperm.[43] Another large trial supplied patients with 3 g per day of carnitine for four months. After assessing sperm parameters before, during, and following the study, the subjects' percent of motile sperm had increased by approximately 10% and the actual number of sperm per ejaculate was increased as well.[44]

BOTANICAL MEDICINES

Maca

Grown exclusively in the central Andes at an elevation of 4,000–4,500 m, maca (Lepidium meyenii) has traditional uses in the Andean region because of this herb's aphrodisiac and fertility-enhancing properties. Maca has several interesting applications for promoting male sexual health. Used for increasing energy, stamina, and athletic performance, maca has effects on impotence as well. Maca has been administered at doses of 1,500 mg and 3,000 mg in order

to determine its effects on male sexual function in relation to serum testosterone levels.[45] After eight weeks in a study, maca-treated subjects reported improvements in sexual desire while it was determined that serum testosterone and E2 levels were unaffected (compared to a placebo group). In addition, the researchers determined that the effects of maca were not the result of any effect on depression levels, which can influence sexual desire negatively. Another study was conducted to determine the effects of maca on seminal parameters in healthy men.[46] After giving the men 1,500 or 3,000 mg of maca per day for four months, researchers determined that this treatment caused an increase in seminal volume, sperm counts, motile sperm numbers, and sperm motility. The researchers noted no changes in hormone levels in this study as well. Serum LH, FSH, prolactin, testosterone, and E2 were measured before and after treatment. This herb has shown definitive effects on male sexual function, as a libido-enhancing agent, and as an enhancer of spermatozoa-related fertility functions. Studies have shown no side effects of maca and, just as importantly, its beneficial effects do not appear to be mediated via hormonal manipulation.

Ginseng

Ginseng (Panax ginseng) is well-known for its energy enhancing effects; it appears to have some impact on sexual function as well. A group of patients treated with an extract of ginseng had increased numbers of sperm and improved motility.[47] Also noted in this study was an increase in total and free testosterone, dihydrotestosterone, LH, and FSH, while prolactin was decreased. The active constituents in ginseng (ginsenosides) are known to have effects on the hypothalamic-pituitary-adrenal axis. More research in the area of male fertility is needed on ginseng.

Pygeum

Pygeum (Pygeum africanum) seems to have an effect on male fertility as a result of this herb's effects on prostatic secretions. An important part of the ejaculate, these secretions are designed to assist spermatic survival outside of the body. Sperm motility is affected by the pH of prostatic fluid, and some studies have demonstrated a beneficial effect of pygeum on prostatic fluid pH.[48,49] In addition to this effect, pygeum has been shown to be useful for treating prostatitis and BPH. A study of men with these conditions who also had additional sexual disturbance as a result showed that subjects who were treated with an extract of 200 mg per day of pygeum had improvements. At the study's two-month mark, analysis showed improvement of urinary parameters and sexual activity.[50]

CONCLUSIONS

There are many causes of infertility among men. Although many of these factors are related to specific structural anomalies or diseases, many infertility problems may be resolved by removing negative influences, such as environmental exposures or alcohol, drug, and cigarette intake. Most interestingly, there are numerous nutritional and botanical supplements that have provided fairly dramatic results in assisting the body to produce more viable spermatozoa. Table 15–1 summarizes these supports and provides guidelines for dosages. Although not cure-alls, adopting these measures can greatly increase a man's chance of achieving successful reproduction.

REFERENCES

[1]Online document at: www.wrongdiagnosis.com=m=male_infertility =prevalence.htm.
[2]Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, Clark RV, McKinlay JB. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab. 2007 Nov;92(11): 4241–4247. Epub 2007 Aug 14.
[3]Online document at: www.cdc.gov=niosh=malrepro.html.
[4]Luconi M, Bonaccorsi L, Forti G, Baldi E. Effects of estrogenic compounds on human spermatozoa: Evidence for interaction with a nongenomic receptor for estrogen on human sperm membrane. Mol Cell Endocrinol. 2001;178(1–2):39–45.
[5]Anderson D, Dobrzynska MM, Basaran N. Effect of various genotoxins and reproductive toxins in human lymphocytes and sperm in the Comet assay. Teratog Carcinog Mutagen. 1997;17:29–43.
[6]Dallinga JW, Moonen EJ, Dumoulin JC, Evers JL, Geraedts JP, Kleinjans JC. Decreased human semen quality and organochlorine compounds in blood. Hum Reprod. 2002;17:1973–1979.
[7]Villalta J, Ballesca JL, Nicolas JM, Martinez de Osaba MJ, Antunez E, Pimentel C. Testicular function in asymptomatic chronic alcoholics: Relation to ethanol intake. Alcohol Clin Exp Res. 1997;21:128–133.
[8]Ochedalski T, Lachowicz-Ochedalska A, Dec W, Czechowski B. Evaluating the effect of smoking tobacco on some semen parameters in men of reproductive age. Ginekol Pol. 1994;65:80–86.
[9]Buchanan JF, Davis LJ. Drug-induced infertility. Drug Intell Clin Pharm. 1984;18:122–132.
[10]Mieusset R, Bujan L. The potential of mild testicular heating as a safe, effective and reversible contraceptive method for men. Int J Androl. 1994;17:186–191.
[11]Grahn BH, Paterson PG, Gottschall-Pass KT, Zhang Z. Zinc and the eye. J Am Coll Nutr. 2001;20:106–118.
[12]Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academy Press, 2002; Online document at: www.nap.edu=books=0309072794=html.
[13]Hunt CD, Johnson PE, Herbel J, Mullen LK. Effects of dietary zinc depletion on seminal volume and zinc loss, serum testosterone concentrations, and sperm morphology in young men. Am J Clin Nutr. 1992;56:148–157.
[14]Chia SE, Ong CN, Chua LH, et al. Comparison of zinc concentrations in blood and seminal plasma and the various sperm parameters between fertile and infertile men. J Androl. 2000;21:53–57.
[15]Fuse H, Kazama T, Ohta S, Fujiuchi Y. Relationship between zinc concentrations in seminal plasma and various sperm parameters. Int Urol Nephrol. 1999;31:401–408.
[16]Henkel R, Bittner J, Weber R, et al. Relevance of zinc in human sperm flagella and its relation to motility. Fertil Steril. 1999;71:1138–1143.
[17]Mohan H, Verma J, Singh I, et al. Inter-relationship of zinc levels in serum and semen in oligospermic infertile patients and fertile males. Indian J Pathol Microbiol. 1997;40:451–455.
[18]Omu AE, Dashti H, Al-Othman S. Treatment of asthenozoospermia with zinc sulphate: Andrological, immunological and obstetric outcome. Eur J Obstet Gynecol Reprod Biol. 1998;79:179–184.
[19]Al-Bader A, Omu AE, Dashti H. Chronic cadmium toxicity to sperm of heavy cigarette smokers: Immunomodulation by zinc. Arch Androl. 1999;43:135–140.
[20]Zaichick VYE, Sviridova TV, Zaichick SV. Zinc in the human prostate gland: Normal, hyperplastic and cancerous. Int Urol Nephrol. 1997;29:565–574.
[21]Agarwal A, Saleh RA. Role of oxidants in male infertility: Rationale, significance, and treatment. Urol Clin North Am. 2002;29:817–827.
[22]Scott R, MacPheroson A, Yates RW, et al. The effect of oral selenium on human sperm motility. Br J Urol. 1998;82:76–80.
[23]Iwanier K, Zachara BA. Selenium supplementation enhances the element concentration in blood and seminal fluid but does not change the spermatozoal quality characteristics in subfertile men. J Androl. 1995;16:441–447.
[24]Lenzi A, Lombardo F, Gandini L, et al. Glutathione therapy for male infertility. Arch Androl. 1992; 29:65–68.
[25]Lenzi A, Picardo M, Gandini L, et al. Glutathione treatment of dyspermia: Effect on the lipoperoxidation process. Hum Reprod. 1994;9:2044–2050.
[26]Irvine DS. Glutathione as a treatment for male infertility. Rev Reprod. 1996;1:6–12.
[27]Lenzi A, Culasso F, Gandini L, et al. Placebo-controlled, double blind, cross-over trial of glutathione therapy in male infertility. Hum Reprod. 1993;8:1657–1662.
[28]Ursini F, Heim S, Kiess M, et al. Dual function of the selenoprotein PHGPx during sperm maturation. Science. 1999;285:1393–1396.

[29]Hansen JC, Deguchi Y. Selenium and fertility in animals and man—a review. Acta Vet Scand. 1996;37: 19–30.
[30]Aitken RJ, Clarkson JS, Hargreave TB, et al. Analysis of the relationship between defective sperm function and the generation of reactive oxygen species in cases of oligozoospermia. J Androl. 1989;10:214–220.
[31]Vezina D, Mauffette F, Roberts KD, Bleau G. Selenium–vitamin E supplementation in infertile men: Effects on semen parameters and micronutrient levels and distribution. Biol Trace Elem Res. 1996;53: 65–83.
[32]Suleiman SA, Ali ME, Zaki ZM, et al. Lipid peroxidation and human sperm motility: Protective role of vitamin E. J Androl. 1996:17:530–537.
[33]Kessopoulou E, Powers HJ, Sharma KK, et al. A double-blind randomized placebo cross-over controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated with male infertility. Fertil Steril. 1995;64:825–831.
[34]Dabrowski K, Ciereszko A. Ascorbic acid protects against male infertility in a teleost fish. Experientia. 1996;52:97–100.
[35]Fraga CG, Motchnik PA, Shigenaga MK, et al. Ascorbic acid protects against endogenous oxidative DNA damage in human sperm. Proc Natl Acad Sci USA. 1991;88:11003–11006.
[36]Dawson EB, Harris WA, Teter MC, Powell LC. Effect of ascorbic acid supplementation on the sperm quality of smokers. Fertil Steril. 1992;58:1034–1039.
[37]Dawson EB, Harris WA, Rankin WE, et al. Effect of ascorbic acid on male fertility. Ann NY Acad Sci. 1987;498:312–323.
[38]Lewin A, Lavon H. The effect of coenzyme Q-10 on sperm motility and function. Mol Aspects Med. 1997;18(suppl.):S213–S219.
[39]Tanimura J. Studies on arginine in human semen: 3. The influence of several drugs on male infertility. Bull Osaka Med Sch. 1967;13:90–100.
[40]Schachter A, Goldman JA, Zukerman Z. Treatment of oligospermia with the amino acid arginine. J Urol. 1973;110:311–313.
[41]Scibona M, Meschini P, Capparelli S, et al. L-arginine and male infertility. Minerva Urol Nefrol. 1994;46:251–253.
[42]Goa KL, Brodgen RN. L-carnitine: A preliminary review of its pharmacokinetics and its therapeutic use in ischemic cardiac disease and primary and secondary carnitine deficiencies in relationship to its role in fatty acid metabolism. Drugs. 1987;34:1–24.
[43]Menchini-Fabris GF, Canale D, Izzo PL, et al. Free L-carnitine in human semen: Its variability in different andrologic pathologies. Fertil Steril. 1984;42:263–267.
[44]Costa M, Canale D, Filicori M, et al. L-carnitine in idiopathic asthenozoospermia: A multicenter study. Italian Study Group on Carnitine and Male Infertility. Andrologia. 1994;26:155–159.
[45]Gonzales GF, Cordova A, Vega K, et al. Effect of Lepidium meyenii (MACA) on sexual desire and its absent relationship with serum testosterone levels in adult healthy men. Andrologia. 2002;34:367–372.
[46]Gonzales GF, Cordova A, Gonzales C, Chung A, Vega K, Villena A. Lepidium meyenii (maca) improved semen parameters in adult men. Asian J Androl. 2001;3:301–303.
[47]Salvalti G, Genovesi G, Marcellini L, et al., Effect of Panax ginseng, CA Meyer saponins on male fertility. Panminerva Med. 1996;38:249–254.
[48]Clavert A, Cranz C, Riffaud JP, et al. Effects of an extract of the bark of Pygeum africanum (V.1326) on prostatic secretions in the rat and in man. Ann Urol. 1986;20:341–343.
[49]Lucchetta G, Weill A, Becker N, et al. Reactivation of the secretion from the prostatic gland in cases of reduced fertility: Biological study of seminal fluid modifications. Urol Int. 1984;39:222–224.
[50]Carnini C, Salvioli V, Scuteri A, et al. Urological and sexual evaluation of treatment of benign prostatic disease using Pygeum africanum at high doses. J Arch Ital Urol Nefrol Androl. 1991;63:341–345.

16

FEMALE HORMONAL HEALTH— SO MUCH MORE THAN PMS OR MENOPAUSE

A Look at Whole Body Wellness

Even in the new millennium, with all the technology and broad dissemination and free flow of information, many busy clinicians are still performing the same diagnostic hormonal workups that have been conducted for decades. Frequently, a few specific data points are targeted, such as follicle stimulating hormone (FSH) and luteinizing hormone (LH) or estradiol and progesterone. Yet, primary care practitioners have all been trained to realize that hormonal pathways are dependent upon homeostasis of other pathways to promote and sustain optimal health.[1] Thus, it makes sense that examining the bigger hormonal picture, the "lay of the land," so to speak, yields facts needed to maximize clinical outcomes. The common practice of examining select and narrow hormonal indices is akin to looking at a few trees within a forest and making a judgment on the ecology of the entire forest. Until recently, affordable testing that provided a truly comprehensive look at a patient's hormonal profile was not readily available. Yet, by applying mass spectrometry more broadly in the clinical sciences, a few laboratories in the United States are providing comprehensive and affordable hormonal profiles at a fraction of the cost of previously used methods. These tests typically provide at least 20 data points, including measures of estrogen metabolites; progesterone metabolites; and adrenal hormones, testosterone, and each of their respective metabolites. Many labs are also providing saliva and blood tests that are affordable, easy to use, and provide similar data. In addition, newer testing is available to evaluate genetic variations (SNPs) that modulate hormone metabolism including SNPs in the phase 1 and 2 enzymes that metabolize endogenous estrogens along with xenoestrogens. A steroid-hormone metabolism-profile chart illustrates, quite clearly, the clinical relevance of identifying potential highs and lows within the greater unidirectional and bidirectional pathways and the clinical relevance of using more comprehensive hormonal profiling to clarify diagnostic hypotheses. By correlating the biochemical trends of each pathway and the resultant metabolite levels, added clinical insights and understanding are gained that otherwise would require a less well-informed assumption by a treating clinician. With such insights, dietary and nutritional interventions can be prescribed more easily and have greater specificity. There are numerous clinical considerations that come into play when one attempts to promote hormonal wellness. Many of these variables, when properly controlled, can minimize the risk of disease states, including breast cancer relative to hormonal modulation.[2]

ANDROGENS AND BREAST CANCER

Although menopause is a normal physiological process, the symptoms that are so commonly associated with this hormonal transition, such as hot flashes, night sweats, and many other symptoms, are only clinical indicators of a deeper problem, merely clues reflecting an underlying state of hormonal imbalance. Current research studies are clearly demonstrating that other hormones besides estrogen potentially contribute to health problems and are, themselves,

clear independent risk factors that must be measured and controlled directly and intentionally. Postmenopausal women, for instance, can have increased risks for developing breast cancer, not only from having elevated estrogen but also from high levels of testosterone being converted to estrogen, low levels of sex hormone binding globulin (SHBG), and the consequential higher levels of free steroid sex hormones.[2] Numerous other risk factors are also linked to this enhanced risk, including elevated adrenal secretions and chronic hyperinsulinemia.

A woman with elevated androgen levels is at a higher risk for developing breast cancer and other hormone-dependent diseases. Specific correlations with deleterious androgenic effects have been associated with increased levels of dehydroepiandrosterone (DHEA), DHEA sulfate,[3] androstenedione,[4] and testosterone concentrations. However, the correlation of DHEA and breast cancer has not been substantiated in other research, and it appears that testosterone has an indirect effect on breast cancer risk, via its influence on the amount of bioavailable estrogen.[5] Hyperandrogenism is associated with decreased SHBG, polycystic ovary syndrome, and insulin resistance.[6] (See Chapter 29 on polycystic ovary syndrome.)

There is a significantly lower prevalence of cancer risk in Asian populations whose diets are high in soy products.

Testing actively for levels of each of these specific hormones and metabolites provides the opportunity to correlate clinical presentations better and perform more focused interventions to modify hormonal dysregulation. Elevated androstenedione can arise from either ovarian or adrenal sources or from peripheral conversion of DHEA. However, increased testosterone levels are more likely to be a result of increased ovarian secretion of androstenedione and=or DHEA or peripheral conversion. Once again, seeking the source and addressing the global impact of such hormonal fluctuations is of paramount clinical significance. When hydroxyandrostenedione (11b OHA) is elevated and the androstenedione:11b OHA ratio is depressed, the adrenal glands are the primary source of the elevated androstenedione. If the androstenedione: 11b OHA ratio is elevated, the primary source of the problem is ovarian in nature. These ratios, again, illustrate that a comprehensive examination of hormonal balance and prevalence is crucial. Research findings reveal that women who experience a hyperandrogenic effect frequently have mixed adrenal and ovarian androgen production that has been correlated with adrenal cortical hyperplasia and ovarian stroma hyperplasia as determined by autopsies conducted on patients with breast cancer.[7–9]

SEX–HORMONE BINDING GLOBULIN

Levels of sex–hormone binding globulin, as previously mentioned, play a role in numerous conditions. Low levels are associated with hormone-related conditions such as breast cancer, polycystic ovary syndrome, and insulin resistance. Furthermore, decreased levels of this protein are associated with cardiovascular risk factors as well. A recent study showed that low SHBG is significantly associated with metabolic syndrome, increased triglycerides, and decreased high-density lipoprotein (HDL) in men and women. In women, decreased SHBG was also associated with elevated apolipoprotein B and diabetes.[10] SHBG has also been shown to inhibit the estradiol-induced proliferation of breast cancer cells.[11]

DIET, LIFESTYLE, HORMONES, AND BREAST CANCER

Chronic hyperinsulinemia is intimately linked to diet, lifestyle, and the development of a hormonal profile that correlates with increased breast cancer and hormone-related disease risk. What is noteworthy is the ability of insulin to inhibit hepatic synthesis of SBHG and enhance ovarian production of androgens.[12–14] Addressing the cause of hyperinsulinemia is a significant clinical intervention, thus lowering the adverse risk associated with this hormonal disturbance. Overweight women with high intra-abdominal fat stores have a particular risk for developing breast cancer as a result of hormone-modifying factors, including insulin resistance, increased insulin levels and insulin-like growth factor-I, low serum levels of SBHG, and high sex-hormone levels.[15–18]

> Clinicians are challenged daily when diagnosing hormonally related disease states.

Consuming a low-carbohydrate diet, while focusing on high-fiber and antioxidant-abundant vegetables, is a must for these patients. Increased fiber intake helps to ensure more regular bowel movements, with the goal being two to three bowel movements per day to increase elimination of toxic digestive products, hormones, and deleterious metabolites. Equally important is the ability of fiber-rich foods to prevent reabsorption of hormonal metabolites back into circulation.

DIETARY INTERVENTIONS FOR HORMONE MODULATION

Isoflavone- and Indole-Rich Foods

Dietary interventions, particularly phytoestrogen-rich foods,[19,20] can help to control and modulate the availability of sex hormones. These plant-derived diphenolics have both estrogenic and antiestrogenic properties that can help to diminish breast-cancer risk.[21,22] Classical phytoestrogen sources include soy (Glycine soja) isoflavones, lignans from flax (Linum usitatissimum) and other seeds and fiber-rich vegetables, and coumestrol from legumes and alfalfa sprouts.[23–25] (See the box on page 192 entitled ''Phytoestrogen-Rich Foods.'') Indole-3-carbinol (I3C)–abundant foods, such as cruciferous vegetables, are equally worth integrating into a hormone-modifying regimen because of these foods' estrogen-modulating activity.[26] It is advisable for patients to consume organic produce (and organic food in general) whenever this is possible, to minimize exposure to lipid-soluble pesticides and herbicides that can have numerous adverse effects in the body. What is noteworthy is that several agricultural chemicals, such as polychlorinated biphenyls (PCBs) and other organochlorines, can affect hormone function within the body, thus introducing another risk factor into the health equation.

There is a significantly lower prevalence of cancer risk in Asian populations.[27] The main risk factor for the Caucasian women, as opposed to the Oriental women, may be their higher estrogen levels that result from a higher-fat diet, higher estrogen production, and lower fecal estrogen excretion. In approximately 50% of the current studies available on this topic, Asian women have higher serum levels of SBHG. As mentioned previously, low levels of SHBG are associated with increased risk of breast cancer.

Maintaining and restoring intestinal microflora can augment the effects of isoflavone consumption.

Fats and Fatty Acids

One of the most intriguing studies, commonly referred to as the DIANA study, was conducted by Berrino et al.[1] This study demonstrated that the plasma insulin-lowering effects of low-fat intake decreased insulin resistance as a result of reduced body mass index and waist circumference.[1,28,29] Additional benefits were obtained by increasing omega-3 fatty acid and monounsaturated fatty acids while decreasing refined carbohydrate intake, with the goal of improving insulin sensitivity.[30–32]

Low-fat diets have been thoroughly tested. Diets that limit fat intake to 10%–25% of total calories significantly reduce plasma estradiol concentrations. Nine studies showed a mean 7.4% estradiol decrease in premenopausal women and, in four of the studies, a dramatic 23% after menopause.[33] However, these studies did not distinguish between the types of dietary fats. Most participants in these studies also had increased intakes of fiber-rich foods. In the DIANA study, a serum estradiol reduction of 18% was achieved with fat reduction from 37%–31% of total calories as a result of shifting consumption from animal to vegetable fats and focusing on low glycemic-index foods.[1]

Fiber

Supplemental fiber may be of clinical value in the absence of sufficient dietary intake; yet, it is not a substitute for a diet that is rich in fiber. Studies that have examined specific types of fiber supplements found no significant increases in plasma SBHG levels, although estradiol levels

A Typical Profile Yielded by Mass Spectrometry

Estrone (E1)
2-Hydroxyestrone
16-a-Hydroxyestrone
2 OH:16 OH estrone ratio
Estradiol (E2)
Estriol (E3)
Estrogens ratio
Total estrogens
Testosterone
Androstanediol
Androstenedione
Dehydroepiandrosterone (DHEA)
Androstenetriol
Androsterone
Etiocholanolone
Prenanediol[a]
5-Pregnenetriol
Pregnenolone
Cortisone
Cortisol
Tetrahydrocortisone
Tetrahydrocorticosterone
5-a-Tetrahydrocorticosterone
Tetrahydro-11-dehydrocorticosterone
Tetrahydrocortisol
5-a-Tetrahydrocortisol

[a]This metabolite is a marker used to measure progesterone levels indirectly because progesterone is not typically excreted via the urine. Adapted from Rhein Consulting Laboratories, Portland, Oregon.

Phytoestrogen-Rich Foods

- Berries
- Cruciferous vegetables
- Flax (Linum usitatissimum) seed (lignan-rich)
- Legumes
- Miso soup
- Seaweed
- Seeds
- Soybeans (Glycine soja)
- Soy milk
- Tempeh
- Tofu
- Whole-grain cereals

Note: Organic foods are recommended to minimize exposure to organotoxins.

were frequently lower and attributable to fiber inhibition of steroid reabsorption from the gut.[34–36] Measurement of postprandial and fasting plasma insulin levels has consistently shown that specific single-fiber supplementation has less effect on plasma SHBG than consumption of whole-grain food.[37] In short, consuming fiber-rich foods provides broader health benefits than swallowing fibers via supplements.

NUTRACEUTICAL INTERVENTIONS

Calcium D-glucarate

This unique calcium nutraceutical is derived from fruits and vegetables. Within the liver, hormone residues and other fat-soluble toxins are bound by glucuronic acids so that they are increasingly eliminated by means of glucuronidation via the beta-glucuronidase enzyme pathway. Conjugation with glucuronic acid is the process by which many fat-soluble hormones and xenobiotics are converted into polar compounds so they can be excreted in the bile. Beta-glucuronidase is made by intestinal flora, mainly from unhealthy bacteria associated with dysbiosis. When glucuronidated compounds are excreted into the gut, via the bile ducts, beta-glucuronidase cleaves the glucuronic acid, which allows the compound to be reabsorbed back into the bloodstream, thus beta-glucuronidase reverses the body's efforts at detoxification. Calcium D-glucarate has been shown to inhibit b-glucuronidase activity and prevent enterohepatic recirculation.

Chromium

This critical trace mineral can be particularly helpful for balancing insulin response directly and for reducing body fat and weight, thereby reducing the hyperinsulinemia and elevated sex-steroid levels that are associated with an increase risk for developing diseases.[38,39]

Glucosinolates

Men and women should be told to add cruciferous vegetables to their diets, but consistent dietary intake of these vegetables can be hard to achieve. Extracted indole-3-carbinol can provide significant protection by shunting estrogen metabolism away from the 16-alpha-hydroxylation pathway to the 2-hydroxylation pathway. This shunting produces a predominance

Table 16–1. Specific Nutraceuticals for Promoting Hormonal Health

Calcium D-glucarate	1,000 mg, 2–3 times per day
Indole (3¨3¨-di-indolymethane; DIM)	100 mg, 1–3 times per day
Isoflavones	1,000 mg, 2–3 times per day

of 2-hydroxy and 2-methoxy estrogens. The 2-methoxy estrogens are only produced when there is an abundant source of methyl groups, such as from folic acid, and a functional COMT enzyme. These active ''good'' metabolites serve as antioxidants and decrease the likelihood of cell division, whereas 16-alpha-hydroxy and 4-hydroxy compounds promote cellular division and, thus, can enhance cancer risk. Cruciferous vegetables, which are high in glucosinolates, have significant amounts of folic acid, a vitamin that is also essential for the methylation of estrogen metabolites. When cruciferous vegetables are chewed or macerated, glucobrassicin is hydrolyzed with the assistance of myrosinase to create indole-3-carbinol. In turn, IC3 is transformed in the stomach into various indole compounds, including indole (3¨3¨-di-indolymethane; DIM). Research has shown, however, that I3C can act as a cancer promoter when given after exposure to carcinogens. In addition, I3C activates the CYP1B1 enzyme to convert estradiol and estrone into 4-hydroxy derivatives, which are then converted into the genotoxic quinines and semiquinones. For this reason, supplementation with DIM is recommended because it has not shown this procarcinogenic effect. Typical supplemental dosing of DIM is in the range of 100–300 mg per day. (See Table 16–1 above.) Sulforaphane, a non-indole isothiocyanate from brassica vegetables, has also been shown to increase detoxification of both endogenous estrogens and xenoestrogens by up-regulating phase 2 enzymes, including glucuronsyltransferases, glutathione-transferases, and quinine reductases.

Examining a patient's full hormonal picture provides the basic foundation needed to achieve rapid, clear, and specific diagnosis and treatment for patients with hormonal imbalances.

Isoflavones

Isoflavones, such as genistein and daidzein, are abundant in soy and numerous other botanicals including red clover (Trifolium pratense). There are numerous isoflavones in soybeans and soy products, such as tofu and tempeh, including genistein and daidzein. Genistin, glycitin, glycitein, and daidzin are the glycoside forms of genistein, glycitein, and diadzein, which are the predominant forms found in the plant. These flavones are potent antioxidants that help to support immune function and help to protect DNA integrity from exogenous and endogenous stressors. The phytoestrogen properties of isoflavones produce weaker estrogenic activity than human estrogens. The isoflavones compete with the human estrogens for the same cell receptor sites, thus decreasing the total estrogenic effect on the body. These phytoestrogens have been shown to increase growth hormone while decreasing LH and cholesterol.[40] Additionally, the phytoestrogens found in red clover, biochanin A, and formononetin may provide benefit as they are metabolized to the isoflavones genistein and daidzein and may act as selective estrogen-receptor modulators.

Probiotics

Maintaining and restoring intestinal microflora can augment the effects of isoflavone consumption. The DIANA study suggested that the bioavailability of phytoestrogens may have been higher as a result of the enhanced microflora balance produced by a more vegetarian diet that promoted beneficial flora growth. Phytoestrogens are in foods, in the form of glycosides that must be hydrolyzed by gut bacteria to produce aglycones. Studies comparing Western microflora versus the flora of vegetarians or people who consume macrobiotic diets demonstrate that the latter subjects typically have more lactobacilli and bifidobacteria, which hydrolyzes glycosides to aglycones.[41] Thus, diets emphasizing plant foods are recommended. Probiotics, themselves, have not been shown to directly affect phytoestrogen metabolism, although they can decrease beta-glucuronidase activity.

General Herbals

Other herbal products that may modulate hormone function include Angelica sinensis (dong quai), Glycyrrhiza glabra (licorice root), Leonurus cardiaca (motherwort), Vitex agnus-castus (chaste tree), Dioscorea villosa (wild yam), Cimicifuga racemosa (black cohosh), Tribulus terrastris (tribulus), Medicago sativa (alfalfa), and many more. The key is understanding how each herb acts on hormonal pathways; how it can be applied best relative to a given patient's comprehensive hormonal profile and induce specific modulation of hormonal pathways. Licorice, for instance, can affect estrogen directly via the herb's isoflavone content and can also help to support adrenal function and its resultant hormonal production, illustrating the versatility of potential botanical interventions and the need to understand how each pathway is functioning to avoid creating disturbances in an otherwise balanced pathway.

CASE DISCUSSION

As a physician in family practice, my patient base is comprised of approximately 70% adult women who experience the spectrum of hormonal wellness. Over the years, certain common clinical patterns have emerged from these patients, providing increased clinical insight that has helped to yield improved patient outcomes.

Recently, a 57-year-old menopausal patient presented with numerous hormone-related symptoms, including hot flashes, night sweats, irritability, and vaginal dryness, that had not responded to standard hormonal treatment provided by her previous physician. After having the patient complete a 24-hour urine collection for a hormone-profile analysis, her clinical picture became substantially clearer. Her laboratory values reflected low progesterone metabolites, pointing to low progesterone levels. She had low normal testosterone and androgen levels and substantially lower-than-optimal cortisone and cortisol levels. This correlated well with her previous experience, when she had taken progesterone, either orally or transdermally, and felt better. However, her severe atopic vaginitis with ulcerations strongly correlated with an effect caused by lower-than-normal estrogen. Thus, she had taken a preparation consisting of estradiol, estrone, and estriol. However, she experienced symptoms of estrogen dominance even with small and varied dosing regimens. Her comprehensive steroid-hormone profile helped to solve the riddle by showing that her adrenal pathways reflected dramatic

adrenal-insufficiency trends. She had a history of experiencing improved energy, decreased aches and pains, less irritability, and improved sleep=wake cycles when she took a progesterone supplement alone. This made sense because her body was probably shunting progesterone via 17-hydroxyprogesterone to cortisol. And the estrogen-dominance symptoms she experienced when she took the triple-hormone preparation probably were the result of shunting her insufficient dose of progesterone to the cortisol pathway and, thus, producing symptoms of relative estrogen dominance. Considering these factors, her treatment protocol was adjusted, and her short- and long-term health goals were accomplished successfully. These extra data points, thus, were the key to solving this patient's problem.

CONCLUSIONS

Clinicians are challenged daily when diagnosing hormonally related disease states. Often preceding actual pronounced signs of hormonal imbalance, symptoms arise that can alter the quality of a patient's life dramatically. These symptoms can be typical premenstrual syndrome, menopausal problems, or more subtle conditions, such as depression, anxiety, and fatigue. Examining a patient's full hormonal picture provides the basic foundation needed to achieve rapid, clear, and specific diagnosis and treatment for patients with hormonal imbalances.

REFERENCES

[1]Berrino F, Bellati C, Secreto G, et al. Reducing bioavailable sex hormones through comprehensive change in diet: The diet and androgens (DIANA) randomized trial. Cancer Epidemiol Biomarkers Prev. 2001;10(1): 25–33.

[2]Hankinson SE, Willet WC, et al. Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 1995;87:190–197.

[3]Dorgan JF, Stanczyk, FZ, et al. Relationship of serum dehydroepiandrosterone (DHEA), DHEA sulfate, and 5-androstene-3-b, 17 beta-diol to risk of breast cancer in postmenopausal women. Cancer Epidemiol Biomark Pre. 1997;6:177–181.

[4]Berrino F, Muti P, et al. Serum sex hormone levels after menopause and subsequent breast cancer. J Natl Cancer Inst. 1996;88:290–296.

[5]Zeleniuch-Jacquotte A, Bruning PF, Bonfrer JM, Koenig KL, Shore RE, Kim MY, Pasternack BS, Toniolo P. Relation of serum levels of testosterone and dehydroepiandrosterone sulfate to risk of breast cancer in postmenopausal women. Am J Epidemiol. 1997 Jun 1;145(11):1030–1038.

[6]Kajaia N, Binder H, Dittrich R, Oppelt PG, Flor B, Cupisti S, Beckmann MW, Mueller A. Low sex hormone-binding globulin as a predictive marker for insulin resistance in women with hyperandrogenic syndrome. Eur J Endocrinol. 2007 Oct;157(4):499–507.

[7]Escobar-Morreale H, Garcia-Robles R, et al. Ovarian suppression with triptorelin and adrenal stimulation with adrenocorticotropin in functional hyperandrogenism: Role of adrenal and ovarian cytochrome p450c17a. Fertil Steril. 1994;62:521–530.

[8]Gonzales F, Chang L, et al. Adrenal dynamic responses to physiologic and pharmacological adrenocorticotropic hormone stimulation before and after ovarian steroid modulation in women with polycystic ovary syndrome. Fertil Steril. 1999;71:439– 444.

[9]Sommers SC. Endocrine abnormalities in women with breast cancer. Lab Invest. 1955;4:160–174.

[10]Onat A, Hergenç G, Karabulut A, Albayrak S, Can G, Kaya Z. Serum sex hormone-binding globulin, a determinant of cardiometabolic disorders independent of abdominal obesity and insulin resistance in elderly men and women. Metabolism. 2007 Oct;56(10):1356–1362.

[11]Catalano MG, Frairia R, Boccuzzi G, Fortunati N. Sex hormone-binding globulin antagonizes the antiapoptotic effect of estradiol in breast cancer cells. Mol Cell Endocrinol. 2005 Jan 31;230(1–2):31–37.

[12]Kaaks R. Nutrition, hormones and breast cancer: Is insulin the missing link? Cancer Causes Control. 1996;7:605–625.

[13]Preziosi P, Barret-Connor E, et al. Interrelation between plasma sex hormone-binding globulin and plasma insulin in healthy adult women: The Telecom study. J Clin Endocrinol Metab. 1993;76:283–287.
[14]Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome p450c17a activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. N Eng J Med. 1996;335: 617–623.
[15]Peiris AN, Sothmann MS, et al. Relative contribution of obesity and body fat distribution to alteration in glucose insulin homeostasis: Predictive values of selected indices in premenopausal women. Am J Clin Nutr. 1989;49:758–764.
[16]Evans DJ, Hoffmann RG, et al. Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberrations in premenopausal women. J Clin Endocrinol Metab. 1983;57: 304–310.
[17]Bruning PF, Bonfrer JM, et al. Insulin resistance and breast cancer risk. Int J Cancer. 1992;52:511–516.
[18]Hankinson SE, Willet WC, et al. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet. 1998;351:1393–1396.
[19]Loukovaara M, Carson M, et al. Refulation of sex hormone binding globulin production by isoflavonoids and patterns of isoflavonoids conjugation in Hep G2 cell cultures. Steroids. 1995;60:656–661.
[20]Makela S, Poutenen M, et al. Estrogen specific 17b-hydroxysteroid oxidoreductase type 1 as a possible target for the action of phytoestrogens. Proc Soc Exp Biol Med. 1995;208:51–259.
[21]Wang C, Makela T, et al. Lignans and flavonoids inhibit aromatase enzyme in human preadipocytes. J Steroid Biochem Mol Biol. 1998;50:205–212.
[22]Adlercreutz H. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect. 1995;103(suppl.7):103–112.
[23]Reinli K, Block G. Phytoestrogen content of foods—a compendium of literature values. Nutr Cancer. 1996;26:123–148.
[24]Thompson LU, Robb P, et al. Mammalian lignan production from various foods. Nutr Cancer. 1991;16:43–52.
[25]Pillow PC, Duphrone CM, et al. Development of a database for assessing dietary phytoestrogen intake. Nutr Cancer. 1999;33:3–19.
[26]Michnovicz JJ, Adlercreutz H, et al. Changes in levels of urinary estrogen metabolites after oral indole-3-carbinol treatment in humans. J Natl Cancer Inst. 1997;89:718–723.
[27]Adelercreutz H, Gorbach SL, et al. Estrogen metabolism and excretion in Oriental and Caucasian women. J Natl Cancer Inst. 1994;86:1076–1082.
[28]Flatt JP. Dietary fat, carbohydrate balance and weight maintenance. Ann NY Acad Sci. 1993;683: 122–140.
[29]Hannah JS, Howard BV. Dietary fats, insulin resistance and diabetes. J Cardiovasc Risk. 1994;1:31–37.
[30]Liu S, Baracos VE, et al. Dietary omega-3 and polyunsaturated fatty acids modify acyl composition and insulin biding in skeletal-muscle sarcolemma. Biochem J. 1994;299:831–837.
[31]Feskens EJ, Virtanen SM, et al. Dietary factors determining diabetes and impaired glucose tolerance: A 20-year follow-up of the Finnish and Dutch cohorts of the Seven Countries Study. Diabetes Care. 1995;18:1104–1112.
[32]Frost G, Keogh B, et al. The effect of low-glycemic carbohydrate on insulin and glucose response in vivo and in vitro in patients with coronary heart disease. Metabolism. 1996;45:669–672.
[33]Wu AH, Pike MC, et al. Meta-analysis dietary fat intake, serum estrogen levels and risk of breast cancer. J Natl Cancer Inst. 1999;91:529–534.
[34]Rose DP, Goldman M, et al. High fiber diet reduces serum estrogens concentrations in premenopausal women. Am J Clin Nutr. 1991;54:520–525.
[35]Stark AH, Switzer BR, et al. Estrogen profiles in postmenopausal African-American women in a wheat bran fiber intervention study. Nutr Cancer. 1998;31:138–142.
[36]Bagga D, Ashley JM, et al. Effects of a very low fat, high fiber diet on serum hormones and menstrual function: Implications for breast cancer prevention. Cancer. 1995;76:2491–2496.
[37]Jenkins DJ, Wesson V, et al. Whole meal versus whole grain breads: Proportions of whole or crack grain and glycemic response. Br Med J. 1988;297:958–960.
[38]Kaats GR, Blum K, et al. Effects of chromium picolinate supplementation on body composition: A randomized, double-masked, placebo-controlled study. Curr Ther Res. 1996;57:747–756.
[39]Kaats GR, Blum K, et al. A randomized, double-masked, placebo-controlled study of the effects of chromium picolinate supplementation on body composition: A replication and extension of a previous study. Curr Ther Res. 1998;59:379–388.
[40]Ingram D, et al. Case control study of phyto estrogens and breast cancer. Lancet. 1997;350(9083): 990–994.
[41]Xu X, Harris KS, et al. Bioavailability of soy bean isoflavones depends upon gut microflora in women. J Nutr. 1995;125:307–2315.

17

DELAYED FOOD SENSITIVITIES AND ALLERGIES

In 1906, Clemens Von Pirquet, M.D., the noted Austrian pediatrician, coined the term allergy from the Greek allos (meaning changed or altered state) and ergon (meaning reaction or reactivity) to describe patients with excessive physiologic responses to substances in their environment. Currently, 50 million Americans suffer from allergies on a yearly basis, with allergy ranking as the fifth leading cause of chronic disease, and more than half of U.S. citizens test positive for one or more allergens.[1] In fact, 16.7 million office visits to health care providers are attributed to allergic rhinitis alone.[2] At all ages, allergic rhinitis without asthma is reported by nearly 90 people of every 1,000.[3] In 1996, estimated U.S. health care expenditures attributable to sinusitis were more than $5.8 billion.[4] Two recent estimates of allergy prevalence in the United States were 9% and 16%,[5] while the prevalence for specific allergic conditions, such as allergic rhinitis and atopic dermatitis, have increased over the last 15 years.[6,7] What is even more alarming is the fact that these numbers continue to increase at a rapid rate. These statistics reflect the prevalence of clinically diagnosed, commonly established allergic conditions. Food allergy is one type of condition that is not always easy to recognize and, therefore, treat appropriately.

Food allergy is a complex of clinical syndromes resulting from sensitization to one or more foods whereby symptoms manifest locally in the gastrointestinal (GI) tract or elsewhere in the body as a result of immunologic reactions. Numerous food-based allergic syndromes with manifestations other than classical allergic symptoms are misdiagnosed and are, therefore, medically mismanaged. Delayed patterns of food allergy are not always clinically obvious and are generally unrecognized, because of the delay in symptom onset of hours to days. The relative neglect of food as an allergenic factor in conventional medical practice has led to a gap in the management of patients with these allergies and a void in the understanding of the disease process involved. Because of this, food allergies other than type I, immediate-onset allergies, are often unacknowledged in clinical medicine and research. Yet, food allergies that are attributable to type III, delayed-onset allergies, have been implicated in numerous medical conditions, ranging from childhood hyperactivity to migraine headaches. The concept of delayed-onset food allergies is not new. In the 1920s, reactions to food were linked, via experiments, to such physical symptoms as colitis, diarrhea, bladder pain, and Meniere's syndrome.[8,9] Other experiments were performed, demonstrating the ability of ingested food antigens to penetrate the GI barrier and become affixed to dermal mast cells.[10,11] Food allergies other than type I were described in the 1930s, with reports of delayed symptoms of hours to days following the ingestion of suspect foods.[12]

A REVIEW OF IMMUNITY AND ALLERGY

The two types of acquired immunity, depending on the primary immune-cell response, are:

1. The humoral response primarily involves production of antibodies from B cells. Of the five major classes of immunoglobulin (Ig)—IgA, IgD, IgE, IgG, and IgM. IgE

typically responds to parasitic infections and is the prime antibody that provokes immediate hypersensitivity allergic reactions (the majority of clinically diagnosed food allergies). IgA, IgD, IgG, and IgM antibodies are typically involved in longer-term immunologic processes; IgG is the largest portion of the 80% of total circulating antibodies. Of the five classes of immunoglobulins, IgG, IgM, and IgE are known to be involved in hypersensitivity reactions.

2. Cell-mediated immune responses typically involve destruction of infected cells by cytotoxic T cells or destruction of intracellular pathogens by macrophages activated by Th1 cells. Th1 and Th2 cells can also contribute to humoral immunity by up-regulating production of IgA, IgE, and the four subclasses of IgG.

The mechanisms of immune-mediated tissue injury and disease fall into four major categories:

1. Type I immediate hypersensitivity—These IgE-mediated reactions (e.g., allergic rhinitis, asthma, anaphylaxis, in the clinical subgroups atopy and anaphylaxis) occur within minutes with late-phase inflammatory responses that may occur hours later. The reactions involve vasodilation, smooth-muscle contractions, and mucous-gland secretions.
2. Type II antibody-mediated (cytotoxic) hypersensitivity—These reactions (e.g., hemolytic anemia, Rh-factor hemolytic disease) involve specific reactions of IgG or IgM to cellular antigens and include activation of a complement cascade and cell destruction.
3. Type III immune complex–mediated hypersensitivity—These reactions (e.g., serum sickness, Arthus reactions) involve IgG or IgM forming complexes with allergens to activate a complement, resulting in a rise in inflammatory mediators.
4. Type IV T-cell–mediated hypersensitivity (delayed hypersensitivity)—These reactions (e.g., contact dermatitis, tuberculin reactions) are mediated by T-helper lymphocytes and cytotoxic T cells, not by antibodies, and occur when contact with an allergen leads to dermal inflammation, with a latency period of one to two days after contact.

THE COMPLEX ROLES OF IMMUNOGLOBULINS

Food allergies, including immediate hypersensitivity reactions involving IgE and other, delayed hypersensitivity reactions involving other immunoglobulins, contribute to immune-mediated tissue injury and disease. IgE antibodies are thought to trigger allergic reactions when cross-linking occurs on GI mast cells, resulting in a cascade of histamines and leukotrienes. Histamine-receptor activation is one possible mechanism for underlying cellular pathways that cause the barrier function of the intestinal epithelium to break down.[13] The onslaught of previously mentioned inflammatory allergic molecules and their alteration of intestinal permeability permit food macromolecules to pass through the mucosal serosa. Once food antigens are in circulation, they may predispose other organs and systems of the body to allergic reactions.

In addition, IgG antibodies have been shown, experimentally, to increase the permeability of the intestinal wall.[14] Increased intestinal permeability has been indicated as a precipitating factor in allergic diseases, such as chronic urticaria.[15] The majority of food allergies are IgE-mediated, and the amount of evidence on this immunoglobulin as a marker for food allergy is

extremely large and is increasingly more common. However, the significance of food-specific serum IgG4 antibody in food allergy is unclear, although concomitant elevations of both IgE and IgG are found in various food allergies.[16] This does not imply, necessarily, that these IgG levels are causing the allergy symptoms, but rather that IgG is somehow involved in the allergy process.

Although IgGs are present in the food-allergy reaction, it is unknown if these antibodies are contributing to the allergic process and concomitant symptomatology or if they provide a type of blocking mechanism against IgE antibodies involved in the allergic process. For example, two common food allergens, peanut and ovalbumin, elicit specific IgG antibody responses that are measured using enzyme-linked immunosorbent assays (ELISAs) as well as testing for IgE responses.[17] It has been suggested, however, that IgG is responsible for long-term reactivity to allergens because of the extended life of IgG antibodies in the serum. IgE has a half-life of only 1 to 2 days (in circulation) while mast-cell-committed IgE has an approximate half-life of 14 days. Alternatively, IgG has a half-life of approximately 21 days in circulation, with a half-life on bound mast cells of 2 to 3 months.[18] The conventional radioallergosorbent test (RAST) and skin testing of food allergies are not wholly adequate for diagnosing an IgG-related allergy because these tests mainly reveal the presence of IgE-related allergies.

> Once food antigens are in circulation, they may predispose other organs and systems of the body to allergic reactions.

THE ETIOLOGY OF FOOD ALLERGIES

The GI tract plays a pivotal role in the mucosal immune response. While permitting the absorption of nutrients from the intestinal lumen to the systemic circulation, the GI tract also protects the body against invasion from microbes and other antigens by inducing an immune response. Loss of oral tolerance—the decrease or down-regulation of the immune response—can result in increased local inflammation in the gut. These inflammatory reactions cause increased intestinal permeability that allows more dietary antigens access to the systemic circulation, which can lead to the development of food allergen reactivity.[19] Some scientists say that this dysfunction may be caused by exposure to high doses of antigens, which override the protective mechanisms; but other scientists question if this is, indeed, a matter of dysfunction, suggesting instead that the body might normally react to high levels of exposure to antigens. Allergic reactivity to food is the result of both IgE and non–IgE-mediated mechanisms. Non–IgE-mediated allergic responses tend to involve a T-cell–mediated delayed hypersensitivity reaction, with released cytokines determining the immune response. Serum analysis of patients with immediate-type food-allergy symptoms have revealed a significant correlation between titers of antiallergen antibodies of both isotypes, indicating that immune stimulation from allergenic foods is not limited only to IgE but also affects IgG-producing antibody systems as well.[20]

GI symptoms in food allergy have been explained by alterations in transport across the intestinal wall (increased secretory and=or decreased absorptive functions), increased permeability, and motility of the intestine.[21] In addition, repeated intestinal infections, coupled with reduced secretory IgA levels, can alter intestinal permeability and result in increased food antigen access to the systemic circulation. Such an increased antigenic load, combined with a

patient's allergic predisposition, may foster immunologic responses to food proteins. It is commonly acknowledged that food comprises the largest pool of antigenic challenges to the immune system.[22] Food allergy is, indeed, an important and common health issue that warrants the need to identify and characterize the sensitizing potential of food proteins.

Current approaches to identify food allergy include consideration of amino acid sequence homology with known human allergens, sequence homology with human cell-surface antigens (as is the case with numerous cereal grains and connective-tissue antigens), serologic cross-reactivity with known allergens, and quantifying resistance to proteolytic digestion. Although these concepts do not explain the ability of a protein to cause allergic sensitization, they do provide information regarding the pathogenesis of allergy. What does explain the increasing incidence of allergic symptoms? A primary cause may be repetitive consumption of high doses of similar foods such as processed wheat and corn on a long-term basis, along with ingesting food additives, such as preservatives, coloring, flavor-enhancing agents, and antibiotics.[23] In addition, it has been speculated that infrequent food rotation predisposes patients toward developing hypersensitivities. Coupled with inadequate digestion of proteins into requisite amino acids, dipeptides, and short-chain polypeptides, partial proteins are able to retain their antigenic properties thereby provoking the immune system once they are allowed into systemic circulation. Early introduction of antigenic proteins may also contribute. Researchers have shown that exposure to cow's milk during the first three months of life is associated with high IgG4 subclass antibody levels to beta-lactoglobulin up to eight years of age, particularly in children with maternal atopy.[24]

FOOD ALLERGIES AND ILLNESSES

Food allergies cause a number of conditions that have often been attributed to other causes. These conditions include asthma, eczema, urticaria, migraine headaches, and irritable bowel syndrome (IBS).

Allergy Detection Tests

The enzyme linked immunosorbent assay (ELISA)

The ELISA is a useful and powerful method for estimating ng=mL to pg=mL ordered materials in the solution, such as serum, urine, and culture supernatants (i.e., any cell-derived material that is used in the test, depending on the ELISA that is being run). This is the most reliable test for detecting antibodies and is commonly used in diagnostic testing for allergies. Antibodies to various antigens are detected easily by this test. Extracted and purified antigens are fixed to a surface to which the patient's serum is added. After washing and centrifugation, adherent immunoglobulin is then detected when a second antibody couple to an enzyme is added to the original surface. The last stage of the test involves adding the enzyme's substrate, causing a color reaction that is then measured by a spectrophotometer. This test is also performed by placing the antibody on the plate surface. ELISA assays are very sensitive and can measure IgA, IgE, IgG, and IgG4 antibodies, yielding disclosure of both immediate and long-term hypersensitivity reactions.

(continued)

Allergy Detection Tests (continued)

The radioallergosorbent test (RAST)

For the RAST, possible allergens are affixed to a plate that is then saturated with a sample of serum from the patient. If the patient's serum contains an antibody that is specific to an affixed antigen, it will link to the antigen. Next, a small amount of radioactive, polyclonal antireagenic antibody is then added to the plate. Following a reaction and washing period, residual radiation is measured to determine what percentage of the radioactive antibody is bound to the linked antigen-antibody complex. Higher amounts of radioactive bonding equate to a greater amount of reactive antibody that is specific to tested allergens in the patient's serum. The RAST primarily measures IgE-mediated allergies, that is, immediate hypersensitivity. Being that a growing body of evidence cites IgG in food allergies, the RAST may not detect all food allergen reactions accurately.

The radioallergosorbent procedure (RASP)

The RASP is similar in nature to RAST, but follows a different protocol. The RASP is a mild variant of the RAST that identifies IgG results in a meaningful and reproducible way. The RASP also has greater sensitivity and specificity for detecting food allergens than the RAST, which may be the result of ability of this test to detect IgG complexes in addition to IgE.

Skin tests

Epicutaneous or cutaneous allergen testing produces a localized pruritic wheal and erythema that is maximal at 15–20 minutes post-introduction. It is used most commonly for diagnosing of allergic respiratory diseases in patients with symptoms of pruritis, congestion, sneezing, and chronic coughs with wheezing. Skin testing for allergy is appropriate only if a patient has symptoms that are consistent with IgE-mediated allergy within two hours of eating a suspected food.

The elimination-challenge diet

Oral provocation with suspected allergenic foods administered in a double-blinded, placebo-controlled test is widely considered to be the definitive test for food allergy. This type of testing is not performed in patients with suspected food-induced anaphylaxis. Testing via this method will reveal immediate hypersensitivity to foods that cause symptomology. However, the relationship between certain foods ingested and resulting symptoms is not entirely clear-cut. In such cases, patients are placed on limited diets that involve the removal of commonly allergenic foods (e.g., foods with corn, wheat, soy, and dairy products) and the addition of hypoallergenic foods or foods that are rarely consumed by patients.

Patients are maintained on the diet for several weeks, on the theory that allergy symptoms that have been caused by previously removed allergenic foods will be reduced or removed and that reintroduction of such foods at a later date will cause significant clinical symptoms that are reportable by patients. This type of testing for food allergies is advisable because singular tests are unable to identify specific triggers for patients who experience a wide array of symptoms (such as nausea, abdominal pain, vomiting, cramping, and diarrhea), which may be the result of various mediators of allergy, such as mast cells, eosinphils, IgE, and IL-4. To achieve specificity, however, more testing may be required.

Asthma

Atopy is a major predisposing factor for asthma, and environmental allergens are a causal factor for producing asthma. Food allergy is frequently underestimated in association with asthma, despite having been shown to trigger or exacerbate broncho-obstruction in 2%–8.5% of children with asthma.[25] Sensitization of food can occur early in life, involving a T-cell response of the Th2 phenotype in addition to the commonly cited IgE-mediated hypersensitivity. Diagnosis of asthma-associated food allergy is important for children with respiratory symptoms, especially when asthma symptoms begin early on in life and when they are associated with other manifestations of food allergies. Elimination of food allergens early in infancy have resulted in improved clinical asthma manifestations as well as exerting a protective effect on the progression of allergic tendencies later in life, as evidenced by decreased production of both total and specific IgE.[26]

Eczema

Atopic disease prevalence is increasing worldwide. Atopic eczema affects nearly 18% of infants in the first two years of life. It has been widely speculated that food allergies are the main cause of atopy. Strong associations between atopic eczema and IgE-mediated allergies to milk, eggs, and peanuts have been demonstrated. However, nearly two-thirds of patients with food allergies display no IgE sensitization to the instigating food proteins and symptoms either returned or were exacerbated upon administration of food-challenge tests.[26,27] These patients with allergic reactions to the ingestion of specific foods did not display sensitized IgE to the foods, yet still had allergic reactions when the foods were reintroduced in their diets. Thus, such patients can be said to be allergic to the foods with no identifiable IgE antibodies, in essence, having ''hidden food allergies.''

Urticaria

In one study, patients with chronic idiopathic urticaria were placed on oligoantigenic and histamine-free diets for 21 days followed by systematic food reintroduction over the next 70 days. These patients developed histamine levels that diminished to control levels as well as experiencing significant reductions of symptoms during the test phase, indicating that histamine plays a large role in chronic idiopathic urticaria.[27,28] Another study of patients with chronic urticaria suggested that the symptoms of a group of patients with chronic urticaria indicated increased intestinal permeability, which was concordant with joint complaints, high titers of IgG, and the absence of specific IgE.[15]

Migraine Headaches

The link between food allergy and migraine has long been dismissed by many general practitioners, who do not tend to treat their patients' migraine headaches as having food-allergy-based etiologies. However, various foods have been cited as causative agents including citrus fruits, tea, coffee, pork, chocolate, milk, nuts, vegetables, and cola drinks.[28,29] In general, higher IgE incidence is no greater among people with migraine headaches than among the general population. However, this does not rule out food allergy as a cause of migraine headaches. There are various causes of migraines that are more appropriately labeled as food sensitivities to tyramine, phenylalanine, phenolic flavonoids, alcohol, and caffeine. In addition,

food additives, such as sodium nitrate, monosodium glutamate, and aspartame, are thought to induce migraine headaches by modifying vascular tone. Each patient must be individually assessed for various causes and relationships to foods prior to establishing an allergic causation of the headaches.

Irritable Bowel Syndrome

Allergic reactions in the gut have an estimated prevalence of approximately 1%–2% in adults. Clinical symptoms include abdominal pain, nausea, vomiting, cramping, and diarrhea. Intestinal mast cells and intestinal eosinophils have been shown to be involved in the pathogenesis of food-allergy-related enteropathy. In addition to classical IgE-dependent degranulation, other agonists, such as interleukin (IL)-4, have been demonstrated to activate mast cells.[29,30] Because low-grade mucosal inflammation predominates in IBS, undiagnosed food allergies may play a role in the promotion and perpetuation of the low-grade inflammatory process.[30,31] Food products have variously been reported as causing, perpetuating, or being used to treat IBS, and many patients with IBS report histories of food intolerance concomitant with IBS symptoms.[31,32] A study with 150 IBS patients were ELISA tested and were randomized to receive either a diet excluding all foods to which they had tested positive or a placebo diet. At 12 weeks, the true elimination diet resulted in a 10% greater reduction in symptom score than the placebo diet, and increasing to 26% in the fully compliant patients. Additionally, relaxing the elimination diet led to a 24% greater deterioration in symptoms.[33] Given the high prevalence of gluten-enteropathy (approximately 1:200 patients) and the overlap between symptoms of celiac disease and IBS, many gastroenterologists believe that every patient with IBS-like symptoms should be tested for this (e.g., with antitransglutaminase IgA titers).

Other Physical Manifestations

Numerous additional conditions and symptoms have been empirically attributed to food allergies and sensitivities, including:

Dermatologic conditions—acne, unexplained pruritis, and rashes
Musculoskeletal conditions—bursitis, joint pain, and low-back pain
Immunologic conditions—chronic infections
Genitourinary conditions—enuresis and chronic cystitis
Gastrointestinal conditions—Apthous ulcers, chronic diarrhea, ulcers, gastritis, and colitis
Respiratory conditions—coughing
Cardiovascular conditions—dysrhythmia, edema, and syncope
Head, eyes, ears, nose, and throat (collectively, HEENT)—headaches, sinusitis, palate pruritis, postnasal dripping, and ''black circles around the eyes.''

IDENTIFYING FOOD ALLERGENS

For determining the food antigens to which a patient is susceptible, food-allergy tests are performed to determine a patient's allergies sensitively and specifically. Modern serum testing,

used with detailed history taking and analysis of a patient's symptomatology, can expedite a diagnosis of food allergy. This approach is helpful because symptoms of such allergies are typically quite difficult to isolate and explain via food-ingestion-related causes and effects, because of the delayed reactions that are typically involved. Laboratory and challenge tests can provide reliable information to help identify both suspected and unsuspected food allergens. Although standard laboratory tests, such as the RAST and ELISA are simple for a patient, tests that entail challenging a patient with antigenic foods, either orally or dermally, are much more difficult or may not provide adequate specificity to identify offending food allergens. For example, the two common offenders, wheat and soy, are so prevalent in foods (under different names), that in recalcitrant cases, it is necessary to utilize laboratory tests to identify additional reactive foods. This is especially true because some patients have allergies to food other than the most common culprits that might not be removed in elimination diets. A study was carried out to compare the efficacy of the ELISA versus the skin-prick test to cow's milk proteins in 41 children with suspected allergy. The patients were simultaneously evaluated by skin-prick testing with scratch test antigen to whole CMP. Although only 13 (32%) of the 41 patients were positive by the skin-prick test, 25 (61%) were positive by the IgE ELISA. Of the 25 IgE ELISA-positive patients, 20 were also positive by the IgG ELISA. There was concordance of positive results between skin testing and the IgE ELISA in 9 patients (22%), and there was concordance of negative results in 12 patients (29%). Discordant results were found in 20 patients (49%). These results indicate that the ELISA is more sensitive than skin-prick testing in the identification of individuals with elevated levels of IgE to CMP.[34] An additional study examined RASTs testing with elimination diets based on the results of the test in 114 patients. The results demonstrated a 71% success rate for all symptoms achieving at least a 75% improvement of symptoms. In the group of patients with chronic, disabling symptoms that were unresponsive to other intensive treatments, 70% obtained 75% or more improvement of symptoms and 20% of these patients obtained 100% relief.[35] See the box on pages 200–201 entitled ''Allergy Detection Tests'' for more information about the different tests that are available, how they are performed, and their utility.

THE ALTERNATIVE APPROACH

In general, alternative medical practitioners do not attempt to suppress allergy symptoms. An M.D. might attempt to achieve suppression by down-regulating the body's response to the antigen protein that is being treated by the body as a foreign substance. Instead, allergic reactions—watery eyes, mucus production, sneezing, coughing, and other symptoms—are considered to be protective warning signs that allergens have invaded the body. Thus, patients are encouraged to take supplements, such as methylsulfonylmethane, quercetin, vitamin C, and others, to support the body's ability to deal with the allergens.

Probiotics

There are more than 400 strains of bacteria inhabiting the human intestinal tract. These microbes perform many important functions such as preserving mucosal integrity, decreasing intestinal permeability, metabolizing food, absorbing nutrients, inducing growth factor, and preventing colonization by pathogenic bacteria.[36,37]

Lactobacillus. This group of microflora is named due to its ability to produce lactic acid. Common species include Lactobacillus acidophilus, Lactobacillus reuteri, Lactobacillus

rhamnosus, Lactobacillus sporenges, and Lactobacillus fermentum. Lactobacillus binds to the mucosal lining in the intestines. Here, they inhibit pathogenic bacteria by lactic acid and hydrogen peroxide synthesis, as well as preventing pathogenic bacteria from binding to the mucosal lining by competing for mucosal binding sites.[38–40] Research has also suggested that Lactobacillus has immune-modulating effects, and is helpful in many GI conditions such as Crohn's disease, irritable bowel syndrome, food allergy, antibiotic-induced diarrhea, and pouchitis.[41–43]

Bifidobacteria. This strain of bacteria also produces lactic acid, but generally resided lower in the intestinal tract than Lactobacillus. Common strains include Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium longum, and Bifidobacterium infantis. Studies suggest that low levels of lactic-acid producing intestinal microflora in children increases the incidence of allergies and atopy. Also, studies indicate that these bacteria can regulate immune function by providing signals to pro-T helper cell 1 (TH1.) This can correct the TH2 bias seen in allergies.[44]

Glutamine

Glutamine is an amino acid produced primarily in skeletal muscle and is the most abundant amino acid in the body. Glutamine can be considered a ''conditionally essential'' amino acid because, although the body can make glutamine, in times of severe stress it cannot meet the demand. It is important for immune function, intestinal health, and amino acid synthesis. This amino acid provides food for cells such as intestinal enterocytes, macrophages, lymphocytes and fibroblasts. It affects the activity and proliferation of many cells in the immune system. Studies indicate that glutamine supplementation stimulates proliferation and differentiation of intestinal cells, increases intestinal villous height, and maintains mucosal integrity. It also prevents intestinal hyperpermeability and bacterial translocation.[45] Glutamine also plays a role in the regulation of intestinal IgA.[46] It has been shown that glutamine supplementation normalized the cytokines that promote the TH2 allergenic phenotype.[47] Studies have demonstrated that glutamine decreases intestinal permeability, and is useful in the treatment of diarrhea and other gastrointestinal complaints.[48–50]

Digestive Enzymes

Supplementation with digestive enzymes will help the natural enzymes secreted by the pancreas to properly digest carbohydrates, proteins, and fats. Natural digestive enzymes are often missing or inadequately secreted in patients with food allergies.[51] Supplementation of these enzymes can decrease absorption of inappropriately large macromolecules from the intestines. These enzymes are often supplemented as combinations including lactase, sucrase, lipase, amylase, protease, maltase, phytase, and cellulase. Betaine hydrochloride supplementation may also be beneficial.

CONCLUSIONS

The diagnosis of food allergens requires extensive detective work. Detecting delayed-onset food allergies is becoming more acceptable among physicians because conventional food-allergy testing does not completely uncover food-allergy reactions other than immediate-onset IgE- and IgG-mediated symptoms. Although cutaneous testing remains the ''gold standard'' in

allergy diagnosis according to the majority of allergists, some allergists do believe that this method of testing is indeed inaccurate and outdated. However, it is still not easy to find allergists who are willing to explore the possibility of food allergies with etiologies other than IgE or those allergies that have already been researched and localized to the gut (e.g., IBS, urticaria, Crohn's disease), in addition to pursuing links among other body symptoms and food allergy. While an array of testing possibilities exists, much work is needed in order to elicit fully the far-reaching effects of delayed food-allergy reactions.

REFERENCES

[1]American Academy of Allergy, Asthma and Immunology. Allergy Statistics. Available at www.aaaai.org=media=resources=media_kit=allergy_statistics.stm. Accessed on November 11, 2007.

[2]Centers for Disease Control and Prevention (CDC). Fast Stats A–Z: Vital and Health Statistics, Series 10, no. 13. Atlanta Georgia: CDC, 1999.

[3]Centers for Disease Control and Prevention (CDC). Fast Stats A–Z: Vital and Health Statistics, Series 10, no. 200, Table 57. Atlanta, GA: CDC, 1996.

[4]Ray NF, et al. Healthcare expenditures for sinusitis in 1996: Contributions of asthma, rhinitis, and other airway disorders. J Allergy Clin Immunol. 1999;103(3[pt.1]):408–414.

[5]The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet. 1998;351:1225–1232.

[6]Linneberg A, et al. The prevalence of skin-test–positive allergic rhinitis in Danish adults: Two cross-sectional surveys 8 years apart. The Copenhagen Allergy Study. Allergy. 2000;55:767–772.

[7]Rudikoff D, Lebwohl M. Atopic dermatitis. Lancet. 1998;351:1715–1721.

[8]Duke WW. Food allergy as a cause of abdominal pain. Arch Intern Med. 1921;28:151.

[9]Duke WW: Meniere's syndrome caused by allergies. JAMA. 1923;81:2179.

[10]Brunner M, Walzer M. Absorption of undigested protein in human beings: The absorption of unaltered eff protein in infants. Arch Intern Med. 1928;42:173–179.

[11]Wilson SJ, Walzer M. Absorption of undigested protein in human beings: IV. Absorption of unaltered eff protein in infants. Am J Dis Child. 1935;50:49–54.

[12]Rinkel HJ. Food allergy. J Kansas Med Soc. 1936;37:177.

[13]Groot J, Bijlsma P, Van Kalkeren A, Kiliaan A, Saunders P, Perdue M. Stress-induced decrease of the intestinal barrier function: The role of muscarinic receptor activation. Ann NY Acad Sci. 2000;915:237–246.

[14]Quinti I, Papetti C, D'Offizi G, Cavagni G, Panchor ML, Lunardi C, Paganell. IgG subclasses to food antigens. Allerg Immunol (Paris). 1988;20:41:43–44.

[15]Paganelli R, Fagiolo U, Cancian M, Scala E. Intestinal permeability in patients with chronic urticaria–angioedema with and without arthralgia. Ann Allergy. 1991;66:181–184.

[16]Sheah-Min Y, Choon-Kook S. The relevance of specific serum IgG, IgG4 and IgE in the determination of shrimp and crab allergies in Malaysian allergic rhinitis patients. Asian Pac J Allergy Immunol. 2001;19:7–10.

[17]Atherton KT, Dearman RJ, Kimber I. Protein allergenicity in mice: A potential approach for hazard identification. Ann NY Acad Sci. 2002;964:163–171.

[18]El Rafei A, Peters SM, Harris N, Bellanti JA. Diagnostic value of IgG4 measurements in patients with food allergy. Ann Allergy. 1989;62:94–99.

[19]Shah U, Walker WA Pathophysiology of intestinal food allergy. Adv Pediatr. 2002;49:299–316.

[20]Berrens L, Homedes IB. Relationship between IgE and IgG antibodies in type I allergy. Allerg Immunol (Leipzig). 1991;37:131–137.

[21]Ahmed T, Fuchs GJ. Gastrointestinal allergy to food: A review. J Diarrhoeal Dis Res. 1997;15:211–223.

[22]Buckley RH, Metcalfe D. Food allergy. JAMA. 1982;248:2627–2631.

[23]Andre F, Andre C, Colin L, Cacaraci F, Cavagna S. Role of new allergens and of allergens consumed in the increased incidence of food sensitizations in France. Toxicology. 1994;93:77–83.

[24]Jenmalm MC, Björkstén B. Exposure to cow's milk during the first 3 months of life is associated with increased levels of IgG subclass antibodies to beta-lactoglobulin to 8 years. J Allergy Clin Immunol. 1998 Oct;102(4 Pt 1):671–678.

[25]Baena-Cagnani CE, Teijeiro A. Role of food allergy in asthma in childhood. Curr Opin Allergy Clin Immunol. 2001;1:145–149.

[26]Ito S, Mikawa H. Immunological aspects of asthma (prophylaxis). Acta Paediatr Jpn. 1990;32:192–196.

[27]Turjanmaa K. ''Atopy patch tests'' in the diagnosis of delayed food hypersensitivity. Allerg Immunol (Paris). 2002;34:95–97.
[28]Guida B, De Martino CD, De Martino SD, Tritto G, Patella V, Trio R, D'Agostino C, Pecoraro P, D'Agostino L. Histamine plasma levels and elimination diet in chronic idiopathic urticaria. Eur J Clin Nutr. 2000;54:155–158.
[29]Leira R, Rodriguez R. Diet and migraine. Rev Neurol. 1996;24:534–538.
[30]Bischoff SC, Mayer JH, Manns MP. Allergy and the gut. Int Arch Allergy Immunol 2000;121:270–283.
[31]Barbara G, De Giorgio R, Stanghellini V, Cremon C, Corinaldesi R. A role for inflammation in irritable bowel syndrome? Gut. 2002;51(suppl.1)41–44.
[32]Zar S, Kumar D, Benson MJ. Food hypersensitivity and irritable bowel syndrome. Aliment Pharmacol Ther. 2001;15:439–449.
[33]Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: A randomised controlled trial. Gut. 2004 Oct;53(10):1459–1464.
[34]Campbell DE, Ngamphaiboon J, Clark MM, Harris MC, Kolski GB, Douglas SD. Indirect enzyme-linked immunosorbent assay for measurement of human immunoglobulins E and G to purified cow's milk proteins: Application in diagnosis of cow's milk allergy. J Clin Microbiol. 1987 Nov;25(11):2114–2119.
[35]Dixon HS. Treatment of delayed food allergy based on specific immunoglobulin G RAST testing. Otolaryngol Head Neck Surg. 2000 Jul;123(1 Pt 1):48–54.
[36]Madsen KL, Doyle JS, et al. Lactobacillus species prevents colitis in interleukin 10 gene-deficient mice. Gastroentrology. 1999;116:1107–1114.
[37]Casas IA, Dobrogosz WJ. Validation of the probiotic concept: Lactobacillus reuteri confers broad-spectrum protection against disease in humans and animals. Microbial Ecology in Health and Disease. 2000;12:247–285.
[38]deRoos NM, Katan MB. Effects of probiotic bacteria on diarrhea, lipid metabolism, and carcinogenesis: A review of papers published between 1988 and 1998. Am J Clin Nutr. 2000;71:405–411.
[39]Mack DR, Michail S et al. Probiotics inhibit enteropathogenic E. coli adherence in vitro by inducing intestinal mucin gene expression. Clin Exp Immunol. 1999;116:276–282.
[40]McGroarty JA. Probiotic use of lactobacilli in the human female urogenital tract. FEMS Immunol Med Microbiol. 1993;6:251–264.
[41]Schultz M, Sartor RB. Probiotics and inflammatory bowel diseases. Am J Gastroenterol. 2000;95:S19–S21.
[42]Goldin BR. Health Benefits of probiotics. Br J Nutr. 1998;80:S203–S207.
[43]Pelto L, Ioslauri E et al. Probiotic bacteria down-regulate the milk-induced inflammatory response in milk-hypersensitive subjects but have an immunostimulatory effect in healthy subjects. Clin Exp Allergy. 1998 Dec;28(12):1474–1479.
[44]Cross ML, Gill HS. Can immunoregulatory lactic acid bacteria be used as dietary supplements to limit allergies? Int Arch Allergy Immunol. 2001 Jun;125(2):112–119.
[45]Miller AL. Therapeutic considerations of L-glutamine: a review of the literature. Altern Med Rev. 1999;4:239–248.
[46]Fukatsu K, Kudsk KA, et al. TPN decreases IL-4 and IL-10 mRNA expression in lipopolysaccharide stimulated intestinal lamina propria cells but glutamine supplementation preserves the expression. Shock. 2001 Apr;15(4):318–322.
[47]Kudsk KA, Wu Y et al. Glutamine-enriched total parenteral nutrition maintains intestinal interleukin-4 and mucosal immunoglobulin A levels. JPEN J Parenter Enteral Nutr. 2000 Sep–Oct;24(5):270–274; discussion 274–275.
[48]Basuroy S, Sheth P, et al. Acetaldehyde disrupts tight junctions and adherens junctions in human colonic mucosa: Protection by EGF and L-glutamine. Am J Physiol Gastrointest Liver Physiol. 2005 Feb 17.
[49]Yalcin SS, Yurdakok K et al. Effect of glutamine supplementation on diarrhea, interleukin-8 and secretory immunoglobulin A in children with acute diarrhea. J Pediatr Gastroenterol Nutr. 2004 May;38(5):494–501.
[50]Li J, Langkamp-Henken B, et al. Glutamine prevents parenteral nutrition-induced increases in intestinal permeability. JPEN J Parenter Enteral Nutr. 1994 Jul–Aug;18(4):303–307.
[51]Anonymous. The Life Extension Foundation's Disease Prevention and Treatment, 4th Edition. Segala M, ed. Life Extension Media. 2003;44.

18

NATURAL APPROACHES FOR GASTROESOPHAGEAL REFLUX DISEASE AND RELATED DISORDERS

Gastroesophageal reflux disease (GERD) is a chronic recurrent condition affecting millions of Americans. A recent study investigating the economic and social burden of gastrointestinal (GI) disease in the United States indicated that GERD was the most common GI-related diagnosis given at office visits in 2006. This study also showed that sales of proton pump inhibitors (PPIs) exceeded $10 billion per year, and the number of prescriptions for PPIs per year has doubled since 1999.[1] Numerous environmental and genetic risk factors have been implicated in the pathogenesis of GERD. GERD commonly presents with heartburn and acid regurgitation, although there are numerous atypical presentations, such as chronic cough, noncardiac chest pain, laryngitis, and poor sleep quality. This disease is associated with several other conditions, including Barrett's esophagus, esophageal carcinoma, gastritis, esophagitis, respiratory conditions, sleep disorders, and various ear-nose-throat (ENT) conditions. Conventional treatment often includes the use of PPIs and other acid blockers. Natural therapies and lifestyle interventions are important to consider, owing to the chronic nature of GERD.

PREVALENCE

Studies attempting to assess the prevalence of GERD widely vary in their results, depending on criteria used for diagnosis. A large survey performed by the National Heartburn Alliance in 2000 estimated that 60 million Americans have GERD symptoms at least once per month, and 25 million adults have daily symptoms. This survey revealed that 95% of these individuals have had symptoms for more than one year, and 54% have had symptoms for more than five years. Forty percent of these individuals reported symptoms two to four times per week, and 33% reported symptoms five times per week or more.[2] This survey also showed that GERD symptoms greatly affect activities of daily living, as more than 80% of the respondents reported decreased enjoyment of food, more than 60% reported that symptoms affected their ability to sleep well, and approximately 40% reported that their symptoms affect concentration at work and family activities.[2]

RISK FACTORS

Both genetic and environmental factors appear to influence the presence of GERD. Numerous studies have shown that obesity, weight gain, and increasing body mass index (BMI) are associated with GERD. Hiatal hernia is also a risk factor for GERD symptoms. Studies indicate that individuals with large hiatal hernias have shorter and weaker lower esophageal sphincters (LES), increased amount of reflux, less-efficient acid clearance, less-effective peristalsis, and increased severity of esophagitis compared with individuals with small or no hiatal hernia.[3] Research also indicates that smoking, excess alcohol consumption, irritable bowel syndrome, and a family history of upper GI disease are risk factors. Pharmaceutical usage such as

anticholinergics, antidepressants, and inhaled bronchodilators are also related to the disease. This study also associated lack of education and manual work with the presence of GERD.[4]

Additional studies have suggested that increased intake of table salt, sweets, or white bread is also a risk factor. Exercise and diets high in fruit and dietary fiber appear to be protective against the condition.[5,6] However, high-intensity exercise has been shown to decrease LES pressure and induce GERD symptoms in otherwise asymptomatic individuals.[7] Caffeine ingestion also decreases LES pressure and decreases distal esophageal mean amplitude of contractions and peristaltic velocity, which can increase reflux.[8] Ingestion of carbonated beverages has also been observed in a study to decrease the resting pressure, overall length, and abdominal length of the LES in healthy individuals temporarily. This study showed that 62% of individuals who drank carbonated beverages had significant decreases in these parameters to meet the criteria for incompetence of the LES.[9]

GERD may present with atypical symptoms of esophageal and extraesophageal origin.

In addition, persistent wheezing, asthma, and airway hyper-responsiveness in childhood and adolescence have been shown to significantly increase risk for GERD symptoms at age 26 independent of BMI.[10] A study with a Spanish population indicated that long-term GERD symptoms of 10 years or longer are associated with obesity and having a direct family member with GERD symptoms. GERD symptoms of 1 year or less were more closely correlated with having a spouse with GERD symptoms or taking 1–5 aspirins per week.[11]

DIAGNOSIS

Diagnosis of GERD is often based on symptoms. It is characterized by chronic intermittent heartburn as a burning sensation in the chest and throat as well as acid regurgitation presenting as a sensation of acid in the throat or mouth. GERD may also present with atypical symptoms of esophageal and extra-esophageal origin such as chronic cough, sleep disturbance, chest pain, asthma, and hoarseness.[12] In fact, one study showed that 50% of individuals with noncardiac chest pain had abnormal pH tests or positive endoscopy confirming the presence of GERD.[13] A positive response to PPI therapy is frequently used to confirm the diagnosis of GERD. Additional diagnostic tests are performed for an individual with an atypical presentation, a high risk for complications, or a poor response to initial therapy. Initially, a barium swallow and upper GI series are commonly performed. Esophageal pH monitoring is an important diagnostic tool for GERD. Ambulatory pH monitoring detects abnormal levels of acid in the esophagus and can be used to correlate esophageal acid exposure with symptoms. The Bravo capsule is a wireless pH monitoring device that has been shown to be more tolerable, accurate, and sensitive than the catheter-based pH monitoring. The Bilitec system measures duodenogastroesophageal reflux by evaluating bilirubin absorbance; this system is useful particularly for the subset of patients that may be affected by duodenogastroesophageal reflux. These patients report reflux symptoms with normal acid exposure in the esophagus on high-dose PPI therapy. Intraluminal impedance monitoring detects the composition, distribution, and clearing of both acid and nonacid esophageal reflux. Combined esophageal pH-impedance monitoring

allows detection of nearly all gastroesophageal reflux episodes, acid as well as nonacid, which provides better diagnostics, particularly with patients on acid-suppression therapy.[14] Esophageal manometry is also performed to measure the pressure at the LES. Esophagoscopy, more commonly called endoscopy, is used to diagnose esophagitis, and a biopsy can differentiate esophageal strictures from cancer. Endoscopy should be performed on patients with chronic GERD symptoms to rule out Barrett's esophagus.

PATHOPHYSIOLOGY AND ASSOCIATED CONDITIONS

Transient LES relaxation is the primary mechanism of GERD. It results from a vaso-vagal reflex triggered by stretch receptors of the proximal stomach. Studies have indicated that most reflux episodes are acidic. However, according to one study, 28% of episodes were only weakly acidic and 10% of episodes were weakly alkaline.[15] Numerous factors may influence the symptoms of GERD. Delayed gastric emptying, volume of gastric content, quantity and acidity of refluxed contents, ability of the esophagus to clear this material, LES function, and the resistance of the esophageal tissue can influence reflux symptoms.[16] Some researchers have proposed that patients with GERD can be categorized further as having erosive esophagitis, nonerosive reflux disease, and Barrett's esophagus.[17]

Gastritis

There is conflicting evidence regarding the role that Helicobacter pylori may play in GERD pathology. There are various studies that have looked at treatment of gastritis by eradicating H. pylori and the effects of treatment on concurrent GERD symptoms. The results of these studies vary from showing improvement to showing worsening of GERD symptoms.[18] Research regarding inflammation in the gastroesophageal junction, or cardia, has indicated that the presence of erosive GERD or H. pylori gastritis is associated with the inflammation.[19] In addition, GERD and carditis are associated with intestinal metaplasia at the gastroesophageal junction.[20]

Esophagitis

Esophagitis is common with GERD and may be classified as erosive or nonerosive with the severity based on the number and location of mucosal breaks. Other types of esophagitis, such as eosinophilic esophagitis, present with similar symptoms as GERD and are commonly misdiagnosed. The common presentation of eosinophilic esophagitis is dysphagia and food impaction. Additional symptoms may include epigastric pain, emesis, weight loss, and failure to thrive.[21] The diagnosis is based on a histologic finding of greater than 20 eosinophils per high-powered field in the esophageal squamous mucosa. This condition also presents with motor disturbances that may cause food impaction in the absence of strictures. Manometry shows high amplitude long-duration waves in the distal esophagus particularly at night. The symptoms often respond to elimination or elemental dietary regimens and antiallergy treatment.[22] Standard skin-prick tests measure type 1 hypersensitivity reactions, which are typically mediated by immunoglobulin E (IgE). (It is possible to have a positive skin test but normal blood levels of IgE on a radioallergosorbent test [RAST].) However, these tests do not diagnose many food-allergy reactions, which are frequently IgG-mediated. Thus, IgG testing can offer additional insights that are frequently missed with standard skin-prick tests.

Respiratory Conditions

GERD is associated with numerous respiratory conditions. Approximately 10% of patients presenting to ENT specialists have conditions that may be attributed to GERD.[23] One study revealed that GERD is present in 75% of individuals with refractory ENT symptoms, and PPI therapy provided symptom relief or reduction in the majority of these individuals.[24] Asthma is associated with the presence of GERD symptoms, and although the relationship has not been well-studied. It is estimated that prevalence of GERD in people with asthma is between 60%–80% in adults and 50%–60% in children. Although the direct correlation is unknown, researchers have suggested that reflux aggravates asthma, which in turn induces further reflux.[25] GERD is associated with a chronic nonproductive cough in some individuals; the cough occurs primarily during the day and while these patients are in an upright position. One study demonstrated that chronic cough was caused by reflux in 21% of cases. In addition, the researchers showed that chronic cough was the sole presenting symptom in GERD 43% of the time.[26]

Otitis media may also be linked to GERD.[27] A study examining otitis media with effusion in adults demonstrated that pepsinogen concentration was higher in middle-ear effusion in patients who reported GERD symptoms. In addition, treatment for GERD with PPIs provided some patients with GERD symptom relief as well as decreasing the concentration of pepsinogen in the effusion. Additionally, research has indicated that patients with chronic rhinosinusitis have an increased prevalence of GERD. These chronic rhinosinusitis symptoms in many patients are reduced when their GERD is treated.[28] Laryngeal symptoms may be associated with GERD. Often, they present as hoarseness, frequent throat clearing, a postnasal drip, excess phlegm, sore throat, dysphagia, a globus sensation, or cough. Chronic laryngitis and chronic sore throat are associated with GERD in as many as 60% of patients.[29] In addition, one study showed that at least 50% of patients presenting with laryngeal and voice disorders had laryngopharyngeal reflux.[30] Less-common GERD-related laryngopharyngeal disorders include paroxysmal laryngospasm, subglottic stenosis, vocal-cord granuloma, and laryngeal and pharyngeal carcinoma.[31]

Oral Health

GERD has been shown to affect overall oral health. One study showed that children with GERD have increased dental erosion, salivary yeast, and salivary Mutans streptococci compared with healthy children.[32] In addition, research indicates that children with GERD have more dental caries and more severe erosion compared with healthy children.[33]

Sleep Apnea

Sleep disturbance is common in individuals with GERD. Patients with obstructive sleep apnea (OSA) have GERD symptoms significantly higher than the general population.[34] Studies have indicated that the severity of GERD symptoms is correlated positively to the severity of OSA.[35] One study showed that treatment with continuous positive airway pressure (CPAP) in individuals with GERD and OSA reduced supine esophageal-acid contact time to within normal levels in 81% of the study patients.[36] In addition, researchers have shown that treatment of GERD in patients who have OSA decreases the number of arousals during sleep.[37]

Barrett's Esophagus and Cancer

Barrett's esophagus is a precancerous condition showing intestinal metaplasia of the lower esophagus and mucosecretory cells on histologic examination. It is the precursor to esophageal

adenocarcinoma. Approximately 8%–10% of individuals with GERD have Barrett's esophagus.[38] In fact, the cancer risk for an individual with Barrett's esophagus is 30 times higher than in the general population. Risk factors for Barrett's esophagus include GERD for at least five years' duration, male gender, Caucasian race, and age over 50.[39] A study with U.S. veterans showed that GERD increases the risk of both laryngeal and pharyngeal cancers independent from other risk factors.[40]

CONVENTIONAL TREATMENT

Pharmaceuticals

Pharmaceutical acid blockers are usually the initial recommendation for both diagnosis and treatment. Treatment recommendations are usually based on a step-up or step-down approach depending on the severity of symptoms. Step-up treatment typically involves an eight-week trial of a histamine H_2-receptor antagonist taken two times per day as needed, changing to a PPI if symptoms are not controlled. The step-down approach begins with an eight-week trial of a PPI taken 30 to 60 minutes before the first meal of the day and then decreasing to the lowest possible dosage that provides relief. Studies have indicated that both PPI therapy and H_2 blockers provide symptom relief for the majority of patients. One study showed that eight weeks of therapy with the PPI omeprazole relieved symptoms in 74%, and eight weeks of the H_2 blocker ranitidine relieved symptoms in 50% of individuals with reflux esophagitis.[41] Low-dose antacids have also been shown to decrease reflux symptoms better than a placebo.[42]

Long-term therapy with acid blockers has not been well-studied. Some research has indicated that nutrient deficiencies may arise with these treatments. Research has also suggested that long-term therapy with both PPI and H_2 blockers increases the risk of vitamin B_{12} deficiency significantly in elderly adults.[43] In fact, one study demonstrated that therapy with H_2 blockers caused a 53% decrease in absorption of protein-bound vitamin B_{12}.[44] H_2 blockers have also been associated with decreased absorption of folic acid, iron, and zinc.[45–47] Research has demonstrated that treatment with the H_2 blocker cimetidine significantly decreases intestinal calcium transport as well as altering vitamin D metabolism.[48,49] There is also evidence that long-term use of PPIs increases the risk of hip fracture significantly.[50]

Baclofen is a gamma-aminobutyric acid (GABA) receptor B agonist currently being investigated as a possible treatment for GERD symptoms. Studies have indicated that baclofen reduces the rate of transient LES relaxations significantly, reduces the rate of gastroesophageal acid-reflux episodes, increases basal LES pressure, and increases gastric pH. Studies have also suggested that the drug is well-tolerated by patients.[51] Atropine has also been studied as a

Commonly Prescribed Pharmaceuticals for GERD

Histamine H_2-receptor antagonists	Proton pump inhibitors
Cimetidine (Tagamet)	Lansoprazole (Prevacid)
Famotidine (Pepcid)	Esomeprazole (Nexium)
Ranitidine (Zantac)	Omeprazole (Prilosec)
Nizatidine (Axid)	Pantoprazole (Protonix)
	Rabeprazole (Aciphex)

treatment for GERD symptoms. Evidence suggests that administration of atropine decreases transient relaxation in the LES and significantly decreases the number of reflux episodes.[52] However, atropine can only be administered short-term, via intramuscular injections or intravenously.

Surgery

Surgery is considered based on severity of disease, response to pharmaceutical treatment, risk of complications, and individual patient needs. The most frequent antireflux procedure performed is laparoscopic fundoplication, although surgery can also be done to correct hiatal hernias and other anatomical causes of GERD. Laparoscopic fundoplication places a gastric wrap around the gastroesophageal junction, strengthening the barrier function. Research has indicated that fundoplication relieves heartburn and typical symptoms in 93% of patients, yet only 56% of individuals had relief of their atypical symptoms.[53] This procedure does not appear to replace the use of acid-blocking medication or decrease the incidence of carcinoma over standard medication therapy.[54]

Lifestyle Modification

Lifestyle modifications can have a great impact on GERD symptoms. Diet recommendations include avoiding foods that trigger symptoms. Common culprits include acidic foods, such as tomatoes, coffee, tea, and citrus foods. Additionally, avoidance of foods that decrease LES pressure, such as high-fat foods, chocolate, peppermint, and alcohol, may be necessary. Research has shown that diets high in the antioxidant vitamin C are associated with less risk of GERD symptoms, Barrett's esophagus, and esophageal adenocarcinoma.[55] In addition, a small study showed that very-low-carbohydrate diets reduce GERD symptoms and decrease lower esophageal acid exposure in obese individuals with GERD. In fact, this study showed that diets containing less than 20 g of carbohydrates per day significantly reduced symptoms in less than six days.[56] Another study demonstrated that chewing sugar-free gum for one half-hour after a meal reduced postprandial esophageal reflux possibly by increasing the frequency of swallowing.[57] A study with children who had GERD symptoms that were unresponsive to treatment showed that feeding an elemental formula reduced or resolved all patients' GERD symptoms as well as improving histologic changes in the esophagus.[58] Commonly, it is suggested to patients to sleep with the head of the bed elevated as well as sleeping in the left-lateral decubitus position.[59] Numerous studies have investigated the effect of weight loss on GERD symptoms. Research has indicated that weight loss and decreased visceral fat mass correlated significantly with decreased esophageal-acid exposure.[60] Smoking cessation is also recommended.

Alternative Supplements for Treating GERD

- Vitamin C
- Melatonin
- Fish oil
- D-limonene
- Glycyrrhiza glabra (licorice)
- Digestive enzymes
- Atropa belladonna (belladonna)
- Calcium
- Magnesium

ALTERNATIVE TREATMENT

Antioxidants

Antioxidants have been shown to be protective in numerous diseases, such as GERD, gastric ulcers, and GI cancers. Oxidative stress of the esophageal mucosa is a contributing factor in the pathology of GERD. A study was performed with individuals with both erosive and nonerosive GERD pre- and post-antireflux surgery measuring oxidative stress. This study showed that individuals with GERD have lower glutathione levels in the distal esophagus compared with controls. In addition, myeloperoxidase activity in the distal esophagus decreased after antireflux surgery but never returned to levels found in the control group.[61] Supplementation to increase glutathione levels with the precursors N-acetyl-cysteine and selenium may be beneficial. Additional studies have shown that oxygen-free radicals measured by arachidonic acid peroxidation metabolites are significantly higher in patients with GERD compared with controls.[62] Studies have also indicated that free-radical oxidative damage plays a role in gastric and duodenal ulcers as well in as gastric carcinoma.[63]

Although studies directly supporting antioxidant supplementation with GERD are lacking, substantial evidence supports using antioxidant therapy for patients with gastric ulcers and cancer, and shows that the therapy may also provide benefit for patients who have GERD. Research has shown that the hormone and potent antioxidant melatonin prevented gastric ulceration and reduced endogenous hydroxyl radicals by 88%. In fact, melatonin was shown to be more effective than ranitidine for preventing stress-related ulcers in animal models.[64]

Fish oil supplementation has also been shown to protect gastric mucosa and decrease the severity of gastric ulceration in animal studies. Fish oil increased antioxidant enzyme activity, decreased acid-pepsin secretion, increased mucin secretion, and decreased lipid peroxidation in the gastric mucosa.[65]

A study was performed with an antioxidant dietary supplement containing melatonin, L-tryptophan, vitamin B_6, folic acid, vitamin B_{12}, methionine, and betaine. The supplement or omeprazole was given to individuals with GERD. In this study, 100% of individuals who took the supplement had complete regression of their GERD symptoms within 40 days compared with less than 66% of individuals who had regression of symptoms treated with omeprazole.[66]

D-Limonene

D-limonene is a monoterpene in citrus oil. Numerous studies have shown that D-limonene exerts anti-cancer, antimicrobial, and anti-inflammatory effects. In particular, studies have shown that this constituent of citrus oil is protective against GI cancers, including cancers of the stomach and colon, decreasing both growth and metastasis.[67] Although direct evidence of D-limonene's effects on esophageal cancer is lacking, it is certainly possible that this monoterpene may be protective against Barrett's esophagus and esophageal adenocarcinoma. Alternative practitioners often recommend D-limonene for treatment of GERD with generally good results, although studies are lacking.

Licorice

Glycyrrhiza glabra (licorice) root has historically been used as a demulcent and anti-inflammatory botanical for treating conditions such as gastric and duodenal ulcers. Studies have shown that ingestion of deglycyrrhizinated licorice (DGL) may increase mucous production

Tell Your Patients

Lifestyle Modifications for GERD

- Lose weight.
- Avoid eating large meals.
- Avoid consuming acidic foods, such as citrus foods, tomatoes, coffee, and tea.
- Avoid caffeine and chocolate.
- Avoid consuming food allergens.
- Eat a diet high in fiber and antioxidants.
- Eat a low-carbohydrate diet.
- Avoid pharmaceuticals that aggravate GERD.
- Elevate the head of the bed 4–8 inches.
- Sleep in left-lateral decubitus (lying down) position.
- Avoid lying down 2–3 hours after a meal.
- Stop smoking.

and accelerate healing of duodenal and gastric ulcers.[68,69] In addition, a small study showed that DGL also accelerates healing of aphthous ulcers.[70] Although studies that correlate DGL with GERD directly are lacking, it is reasonable to assume that DGL may provide symptom relief in patients with GERD. Clinically, alternative health care providers often prescribe additional demulcent herbs for their healing and soothing properties, including such herbs as Aloe vera (aloe), Ulmus fulva (slippery elm), and Althaea officinalis (marshmallow).

Mastic

Pistacia lentiscus (mastic) resin is used medicinally for treating duodenal and gastric ulcers. Animal studies show that it decreased H. pylori colonies thirtyfold.[71] Research has also indicated that mastic resin oral supplementation protects gastric mucosa from experimentally induced damage as well as decreasing free acidity.[72] In addition, a small study showed that mastic supplementation provided symptomatic relief of duodenal ulcers in 80% of individuals who were treated with the supplement, and 70% experienced healing with endoscopy.[73] The antisecretory and cytoprotective activity of mastic may provide benefit for individuals with GERD, although direct evidence is lacking.

Minerals

Calcium carbonate, magnesium, aluminum, and phosphate salts are frequently used in over-the-counter antacids. Studies have indicated that antacids are effective for treating GERD symptoms, reducing acid regurgitation, and relieving both daytime and nighttime heartburn.[74] Mineral supplementation, using calcium and magnesium, may reduce GERD symptoms, although direct evidence is lacking.

Digestive Enzymes

Supplemental digestive enzymes may reduce GERD symptoms. Delayed gastric emptying and a large volume of food in the stomach are associated with GERD symptoms, and

Figure 18–1. Aloe vera (aloe).

supplementation using digestive enzymes may reduce these factors. Digestive enzymes are commonly included in combination products, including lipase, amylase, protease, maltase, lactase, sucrase, phytase, and cellulase. Clinically, some patients actually benefit from hydrochloric acid and pepsin supplementation, including individuals who have low levels of stomach acid and delayed gastric emptying.

ALLERGY TREATMENT

Eosinophilic esophagitis is frequently misdiagnosed as GERD. Allergy treatment may be indicated in individuals who are not responsive to typical GERD therapies. Allergy testing to measure both IgE and IgG antibodies is indicated. In addition, dietary supplementation, using products to treat allergic reactions directly may also be necessary. Quercitin is a bioflavonoid often used in allergies because it has antihistamine, anti-inflammatory, and antioxidant effects. Vitamin C has been shown to be protective against GERD and to have antioxidant and some antihistamine properties.

Zinc Carnosine

Zinc carnosine has been shown to speed healing in many types of gastrointestinal lesions. Many studies refer to polaprezinc, a chelate compound consisting of zinc and L-carnosine. Studies show that polaprezinc has antioxidant activity and decreases the gastric inflammation caused by H. pylori infection.[75] Polaprezinc has been shown to protect gastric mucosa from damaging free radicals as well as speed healing of gastric lesions in animal models.[76] Additionally, studies show that zinc carnosine improves intestinal integrity and decreased lab-induced gastric and small-intestine injury.[77]

L-Glutamine

L-Glutamine is an amino acid utilized as an energy source by intestinal epithelium. Research has shown that supplementation with glutamine prevented the development in chemical-

induced gastric lesions in stressed rats.[78] Also, glutamine has been shown to decrease duration and severity of mucosal lesions induced by chemotherapy.[79]

Belladonna

Atropa belladonna (belladonna) is a botanical often used for its anticholinergic activity. One of the constituents of belladonna is atropine. Although anticholinergics have been shown to aggravate GERD, atropine has been shown to be beneficial. It is possible that belladonna may be useful for treating GERD owing to the herb's atropine component.

CONCLUSIONS

GERD is a chronic recurring condition that makes a great impact on the quality of life of individuals who have this condition. As a result of the economic and social burdens of GERD in the United States, it is important for patients to have access to alternative therapies and lifestyle modifications. Currently, research in this area is minimal.

REFERENCES

[1]Shaheen NJ, Hansen RA, Morgan DR, et al. The burden of gastrointestinal and liver diseases, 2006. Am J Gastroenterol. 2006;101:2128–2138.

[2]National Heartburn Alliance. Survey 2000 Results: A Community Perspective. 2000. Online document at: www.heartburnalliance.org/survey 2000.pdf. Accessed January 16, 2007.

[3]Patti MG, Goldberg HI, Arcerito M, et al. Hiatal hernia size affects lower esophageal sphincter function, esophageal acid exposure, and the degree of mucosal injury. Am J Surg. 1996;171:182–186.

[4]Mohammed I, Nightingale P, Trudgill NJ. Risk factors for gastro-oesophageal reflux disease symptoms: A community study. Aliment Pharmacol Ther. 2005;21:821–827.

[5]Nocon M, Labenz J, Willich SN. Lifestyle factors and symptoms of gastro-oesophageal reflux—a population-based study. Aliment Pharmacol Ther. 2006;23:169–174.

[6]Nilsson M, Johnsen R, Ye W, et al. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux. Gut. 2004;53:1730–1735.

[7]Maddison KJ, Shepherd KL, Hillman DR, Eastwood PR. Function of the lower esophageal sphincter during and after high-intensity exercise. Med Sci Sports Exerc. 2005;37:1728–1733.

[8]Lohsiriwat S, Puengna N, Leelakusolvong S. Effect of caffeine on lower esophageal sphincter pressure in Thai healthy volunteers. Dis Esophagus. 2006;19:183–188.

[9]Hamoui N, Lord RV, Hagen JA, et al. Response of the lower esophageal sphincter to gastric distention by carbonated beverages. J Gastrointest Surg. 2006;10:870–877.

[10]Hancox RJ, Poulton R, Taylor DR, et al. Associations between respiratory symptoms, lung function and gastro-oesophageal reflux symptoms in a population-based birth cohort. Respir Res. 2006;7:142.

[11]Diaz-Rubio M, Moreno-Elola-Olaso C, Rey E, et al. Symptoms of gastro-oesophageal reflux: Prevalence, severity, duration and associated factors in a Spanish population. Aliment Pharmacol Ther. 2004;19:95–105.

[12]Hungin AP, Raghunath AS, Wiklund I. Beyond heartburn: A systematic review of the extra-oesophageal spectrum of reflux-induced disease. Fam Pract. 2005;22:591–603.

[13]Dekel R, Martinez-Hawthorne SD, Guillen RJ, Fass R. Evaluation of symptom index in identifying gastroesophageal reflux disease–related noncardiac chest pain. J Clin Gastroenterol. 2004;38:24–29.

[14]Hirano I. Review article: Modern technology in the diagnosis of gastrooesophageal reflux disease—Bilitec, intraluminal impedance and Bravo capsule pH monitoring. Aliment Pharmacol Ther. 2006;23(suppl1):12–24.

[15]Zerbib F, des Varannes SB, Roman S, et al. Normal values and day-today variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. Aliment Pharmacol Ther. 2005;22:1011–1021.

[16]Castell DO, Murray JA, Tutuian R, et al. Review article: The pathophysiology of gastro-oesophageal reflux disease—oesophageal manifestations. Aliment Pharmacol Ther. 2004;20(suppl9):14–25.

[17]Fass R, Ofman JJ. Gastroesophageal reflux disease—should we adopt a new conceptual framework? Am J Gastroenterol. 2002;97: 1901–1909.

[18]Malfertheiner P, Peitz U. The interplay between Helicobacter pylori, gastrooesophageal reflux disease, and intestinal metaplasia. Gut. 2005;54(suppl.1):i13–i20.
[19]Voutilainen M, Farkkila M, Mecklin JP, et al. Chronic inflammation at the gastroesophageal junction (carditis) appears to be a specific finding related to Helicobacter pylori infection and gastroesophageal reflux disease. The Central Finland Endoscopy Study Group. Am J Gastroenterol. 1999;94:3175–3180.
[20]Voutilainen M, Farkkila M, Juhola M, et al. Complete and incomplete intestinal metaplasia at the oesophagogastric junction: Prevalences and associations with endoscopic erosive oesophagitis and gastritis. Gut. 1999;45:644–648.
[21]Pasha SF, Sharma VK, Crowell MD. Current concepts and treatment options in eosinophilic esophagitis. Curr Opin Investig Drugs. 2006;7:992–996.
[22]Luis AL, Rinon C, Encinas JL, et al. Non stenotic food impaction due to eosinophilic esophagitis: A potential surgical emergency. Eur J Pediatr Surg. 2006;16:399–402.
[23]Drug VL, Cobzeanu D, Papaghiuc C, et al. Gastroesophageal reflux involvement in ENT disorders [in Romanian]. Rev Med Chir Soc Med Nat Iasi. 2005;109:220–222.
[24]Poelmans J, Feenstra L, Tack J. Determinants of long-term outcome of patients with reflux-related ear, nose, and throat symptoms. Dig Dis Sci. 2006;51:282–288.
[25]Sontag SJ. Gastroesophageal reflux disease and asthma. J Clin Gastroenterol. 2000;30(3 suppl.):S9–S30.
[26]Irwin RS, Curley FJ, French CL. Chronic cough. Am Rev Respir Dis. 1990;141:640–647.
[27]Sone M, Yamamuro Y, Hayashi H, et al. Otitis media in adults as a symptom of gastroesophageal reflux. Otolaryngol Head Neck Surg. 2007;136:19–22.
[28]Loehrl TA, Smith TL. Chronic sinusitis and gastroesophageal reflux: Are they related? Curr Opin Otolaryngol Head Neck Surg. 2004;12:18–20.
[29]Poelmans J, Tack J. Extraoesophageal manifestations of gastrooesophageal reflux. Gut. 2005;54:1492–1499.
[30]Koufman JA, Amin MR, Panetti M. Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders. Otolaryngol Head Neck Surg. 2000;123:385–388.
[31]Franco RA Jr. Laryngopharyngeal reflux. Allergy Asthma Proc. 2006;27:21–25.
[32]Ersin NK, Oncag O, Tumgor G, et al. Oral and dental manifestations of gastroesophageal reflux disease in children: A preliminary study. Pediatr Dent. 2006;28:279–284.
[33]Linnett V, Seow WK, Connor F, Shepherd R. Oral health of children with gastro-esophageal reflux disease: A controlled study. Aust Dent J. 2002;47:156–162.
[34]Ing AJ, Ngu MC, Breslin AB. Obstructive sleep apnea and gastroesophageal reflux. Am J Med. 2000;108(suppl.4a):120S–125S.
[35]Demeter P, Visy KV, Magyar P. Correlation between severity of endoscopic findings and apnea-hypopnea index in patients with gastroesophageal reflux disease and obstructive sleep apnea. World J Gastroenterol. 2005;11:839–841.
[36]Tawk M, Goodrich S, Kinasewitz G, Orr W. The effect of 1 week of continuous positive airway pressure treatment in obstructive sleep apnea patients with concomitant gastroesophageal reflux. Chest. 2006;130: 1003–1008.
[37]Zanation AM, Senior BA. The relationship between extraesophageal reflux (EER) and obstructive sleep apnea (OSA). Sleep Med Rev. 2005;9:453–458.
[38]Stoltey J, Reeba H, Ullah N, et al. Does Barrett's oesophagus develop over time in patients with chronic gastro-oesophageal reflux disease? Aliment Pharmacol Ther. 2007;25:83–91.
[39]Pascu O, Lencu M. Barrett's esophagus. Rom J Gastroenterol. 2004;13:219–222.
[40]El-Serag HB, Hepworth EJ, Lee P, Sonnenberg A. Gastroesophageal reflux disease is a risk factor for laryngeal and pharyngeal cancer. Am J Gastroenterol. 2001;96:2013–2018.
[41]Festen HP, Schenk E, Tan G, et al. Omeprazole versus high-dose ranitidine in mild gastroesophageal reflux disease: Short- and long-term treatment. The Dutch Reflux Study Group. Am J Gastroenterol. 1999;94:931–936.
[42]Weberg R, Berstad A. Symptomatic effect of a low-dose antacid regimen in reflux oesophagitis. Scand J Gastroenterol. 1989;24:401–406.
[43]Valuck RJ, Ruscin JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. J Clin Epidemiol. 2004;57:422–428.
[44]Salom IL, Silvis SE, Doscherholmen A. Effect of cimetidine on the absorption of vitamin B12. Scand J Gastroenterol. 1982;17:129–131.
[45]Russell RM, Golner BB, Krasinski SD, et al. Effect of antacid and H2 receptor antagonists on the intestinal absorption of folic acid. J Lab Clin Med. 1988;112:458–463.
[46]Sturniolo GC, Montino MC, Rossetto L, et al. Inhibition of gastric acid secretion reduces zinc absorption in man. J Am Coll Nutr. 1991;10: 372–375.
[47]Aymard JP, Aymard B, Netter P, et al. Haematological adverse effects of histamine H2-receptor antagonists. Med Toxicol Adverse Drug Exp. 1988;3:430–448.

[48]Ghishan FK, Walker F, Meneely R, et al. Intestinal calcium transport: Effect of cimetidine. J Nutr. 1981;111:2157–2161.
[49]Odes HS, Fraser GM, Krugliak P, et al. Effect of cimetidine on hepatic vitamin D metabolism in humans. Digestion. 1990;46:61–64.
[50]Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006;296:2947–2953.
[51]Ciccaglione AF, Marzio L. Effect of acute and chronic administration of the GABA B agonist baclofen on 24 hour pH metry and symptoms in control subjects and in patients with gastro-oesophageal reflux disease. Gut. 2003;52:464–470.
[52]Lidums I, Checklin H, Mittal RK, Holloway RH. Effect of atropine on gastro-oesophageal reflux and transient lower oesophageal sphincter relaxations in patients with gastro-oesophageal reflux disease. Gut. 1998;43:12–16.
[53]So JB, Zeitels SM, Rattner DW. Outcomes of atypical symptoms attributed to gastroesophageal reflux treated by laparoscopic fundoplication. Surgery. 1998;124:28–32.
[54]Spechler SJ, Lee E, Ahnen D, et al. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: Follow-up of a randomized controlled trial. JAMA. 2001;285:2331–2338.
[55]Veugelers PJ, Porter GA, Guernsey DL, Casson AG. Obesity and lifestyle risk factors for gastroesophageal reflux disease, Barrett esophagus and esophageal adenocarcinoma. Dis Esophagus. 2006; 19:321–328.
[56]Austin GL, Thiny MT, Westman EC, et al. A very low–carbohydrate diet improves gastroesophageal reflux and its symptoms. Dig Dis Sci. 2006;51:1307–1312.
[57]Moazzez R, Bartlett D, Anggiansah A. The effect of chewing sugarfree gum on gastro-esophageal reflux. J Dent Res. 2005;84:1062–1065.
[58]Kelly KJ, Lazenby AJ, Rowe PC, et al. Eosinophilic esophagitis attributed to gastroesophageal reflux: Improvement with an amino acid-based formula. Gastroenterology. 1995;109:1503–1512.
[59]Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. Arch Intern Med. 2006;166:965–971.
[60]Mathus-Vliegen EM, Tygat GN. Gastro-oesophageal reflux in obese subjects: Influence of overweight, weight loss and chronic gastric balloon distension. Scand J Gastroenterol. 2002;37:1246–1252.
[61]Rantanen TK, Rasanen JV, Sihvo EI, et al. The impact of antireflux surgery on oxidative stress of esophageal mucosa caused by gastroesophageal reflux disease: 4-yr follow-up study. Am J Gastroenterol. 2006;101:222–228.
[62]Modzelewski B. Effect of arachidonic acid peroxidation products on the development of gastroesophageal reflux disease [in Polish]. Pol Merkur Lekarski. 2004;16:532–535.
[63]Tandon R, Khanna HD, Dorababu M, Goel RK. Oxidative stress and antioxidants status in peptic ulcer and gastric carcinoma. Indian J Physiol Pharmacol. 2004;48:115–118.
[64]Bandyopadhyay D, Bandyopadhyay A, Das PK, Reiter RJ. Melatonin protects against gastric ulceration and increases the efficacy of ranitidine and omeprazole in reducing gastric damage. J Pineal Res. 2002;33: 1–7.
[65]Bhattacharya A, Ghosal S, Bhattacharya SK. Effect of fish oil on offensive and defensive factors in gastric ulceration in rats. Prostaglandins Leukot Essent Fatty Acids. 2006;74:109–116.
[66]Pereira R de S. Regression of gastroesophageal reflux disease symptoms using dietary supplementation with melatonin, vitamins and amino acids: Comparison with omeprazole. J Pineal Res. 2006;41:195–200.
[67]Lu XG, Zhan LB, Feng BA, et al. Inhibition of growth and metastasis of human gastric cancer implanted in nude mice by D-limonene. World J Gastroenterol. 2004;15;10:2140–2144.
[68]Larkworthy W, Holgate PF. Deglycyrrhizinized liquorice in the treatment of chronic duodenal ulcer: A retrospective endoscopic survey of 32 patients. Practitioner. 1975;215:787–792.
[69]Khayyal MT, el-Ghazaly MA, Kenawy SA, et al. Antiulcerogenic effect of some gastrointestinally acting plant extracts and their combination. Arzneimittelforschung. 2001;51:545–553.
[70]Das SK, Das V, Gulati AK, Singh VP. Deglycyrrhizinated liquorice in aphthous ulcers. J Assoc Physicians India. 1989;37:647.
[71]Paraschos S, Magiatis P, Mitakou S, et al. In vitro and in vivo activities of Chios mastic gum extracts and constituents against Helicobacter pylori. Antimicrob Agents Chemother. 2007;51:551–559.
[72]Al-Said MS, Ageel AM, Parmar NS, Tariq M. Evaluation of mastic, a crude drug obtained from Pistacia lentiscus for gastric and duodenal antiulcer activity. J Ethnopharmacol. 1986;15:271–278.
[73]Al-Habbal MJ, Al-Habbal Z, Huwez FU. A double-blind controlled clinical trial of mastic and placebo in the treatment of duodenal ulcer. Clin Exp Pharmacol Physiol. 1984;11:541–554.
[74]Weberg R, Berstad A. Symptomatic effect of a low-dose antacid regimen in reflux oesophagitis. Scand J Gastroenterol. 1989;24:401–406.

[75]Handa O, Yoshida N, Tanaka Y, Ueda M, Ishikawa T, Takagi T, Matsumoto N, Naito Y, Yoshikawa T. Inhibitory effect of polaprezinc on the inflammatory response to Helicobacter pylori. Can J Gastroenterol. 2002 Nov;16(11):785–789.

[76]Nishiwaki H, Kato S, Sugamoto S, Umeda M, Morita H, Yoneta T, Takeuchi K. Ulcerogenic and healing impairing actions of monochloramine in rat stomachs: effects of zinc L-carnosine, polaprezinc. J Physiol Pharmacol. 1999 Jun;50(2):183–95.

[77]Mahmood A, FitzGerald AJ, Marchbank T, Ntatsaki E, Murray D, Ghosh S, Playford RJ. Zinc carnosine, a health food supplement that stabilises small bowel integrity and stimulates gut repair processes. Gut. 2007 Feb;56(2):168–175. Epub 2006 Jun 15.

[78]Anderson PM, Schroeder G, Skubitz KM. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. Cancer. 1998 Oct 1;83(7):1433–1439.

[79]Okabe S, Hung CR, Takeuchi K, Takagi K. Effects of L-glutamine of acetylsalicylic acid or taurocholic acid-induced gastric lesions and secretory changes in pylorus-ligated rats under normal or stress conditions. Jpn J Pharmacol. 1976 Aug;26(4):455–460.

19

TAMING HIGH BLOOD PRESSURE NATURALLY

Hypertension is one of the greatest health care problems facing today's world with 50 million North Americans suffering from this often-silent killer. According the American Heart Association, one in three U.S. adults has hypertension, and one-third are unaware that they have it.[1] Elevated blood pressure is a known risk factor for heart attacks and strokes along with excess wear and tear throughout the body, and hypertension is the foremost cause of unexpected death. Hypertension also contributes to comorbidity in individuals with diabetes: More than 73% of people with diabetes also have elevated blood pressure.[2] One of the most challenging aspects of treating a patient with hypertension is that the majority of cases of hypertension are categorized as essential hypertension, that is, the condition's cause is not readily identifiable. Thus, clinically deciding which of the multiple drug therapies that are most apt to help a given patient is as much art as it is clinical protocol. The numerous conventional options to help a patient control hypertension include the following well-known interventions: diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and beta-blockers. Alternative approaches that use natural therapies are equally as varied, and they include botanicals, nutraceuticals, diet, and lifestyle interventions.

The first intervention for hypertensive treatment common to all fields of medicine is to incorporate diet and lifestyle changes, such as increased exercise, increased consumption of magnesium and potassium, and a low-sodium diet. Beyond these first steps to set the foundation, the realm of specific supplementation protocols are individually customized and frequently include coenzyme Q10 (CoQ10), hawthorn (Crataegus spp.) berry extract, olive (Olea europaea) leaf extract, garlic (Allium sativum), coleus (Coleus forskohlii), omega-3 fatty acids, and L-arginine. Clinical practice routinely demonstrates that a multifactorial approach of lifestyle changes combined with appropriate supplements can make a significant impact on hypertension. The ''bottom line'' when creating a therapeutic intervention for a patient who has hypertension is to achieve a normotensive state safely with as few side effects as possible, while supporting overall cardiovascular health in a manner that is sustainable for a lifetime.

DIET AND LIFESTYLE CHANGES

Dietary and lifestyle interventions, without question, are the most challenging with regard to compliance for all patients. However, tackling the very patterns of behavior that have contributed to onset of a disease state is essential when reestablishing a health-promoting homeostasis. The maintenance and protection of the 60,000 miles of blood vessels that include 18,000 miles of capillaries are governed by what a person eats and how much that person exercises. Both a healthy diet and a consistent exercise routine are important keys to preventing and controlling hypertension. In a randomized and multicenter study published in 2004 of more than 800 patients, the group that was involved in increased physical activity, weight loss, and decreased sodium and alcohol intake had its baseline rate of hypertension cut by more than half.[3] Moreover, a recent epidemiologic study assessing the contribution of Western society's common risk factors in hypertension found that physical inactivity makes the largest

contribution to risk of developing hypertension, though high sodium and low potassium intake each contributed a significant risk, as did low magnesium intake.[4] A study has also shown that supplementation with soy protein and psyllium fiber decreased 24-hour systolic blood pressure by 5.9 mmHg in hypertensive individuals.[5]

As difficult as it is to help patients change their behavior, the time practitioners invest in constructing specific exercise plans, discussing particular fruits and vegetables that patients find appetizing and would be likely to incorporate into their diets, and recommending salt restriction is all time well-spent. Frequently, the role of an effective practitioner is that of a ''motivational health coach,'' providing powerful treatment tools to share with patients and combining these tools with educational facts that can empower patients to change. Thus, as a patient learns about the consequences, both good and bad parts, of personal life choices, the more likely he or she is to make changes. For example, illustrating the importance of achieving an optimal lean body mass with facts and figures can make a goal more tangible. When a patient comes to realize that the capillary beds within the body while at rest contain a mere 5% of the blood volume yet contribute to 27% of peripheral resistance (explained in intelligent lay terms), this can serve a motivational pivot because the loss of 1 pound can equate to the loss of 250 miles of blood vessels, thus, lowering the resistance that the heart must pump against and the resultant blood-pressure change. In addition, a patient with an average heart rate of 72 beats per minute can be educated on the importance of properly fueling the cardiovascular system by learning that the heart weighs a mere 10 ounces yet contracts approximately 100,000 times per day.

COENZYME Q10

Coenzyme Q10 (CoQ10), one of the better-studied supplements with regard to hypertension, also plays a crucial role in energy protection and performance of the myocardium. The clinical literature reports on the hypertensive benefits of CoQ10 go back as early as the mid 1970s, with an early study on five patients with essential hypertension who also had deficient activity of the CoQ10-dependent enzyme, succinate dehydrogenase-CoQ10 reductase.[6] Four of the five patients experienced significant reductions in blood pressure when given CoQ10 for three to five months. In a more recent trial, 26 patients with essential hypertension were given 50 mg of CoQ10, two times per day for 10 weeks.[7] At the end of the 10 weeks, the subjects' average systolic blood pressure had dropped from 164 mmHg to 146 mmHg, and their average diastolic blood pressure had decreased from 98 mmHg to 86 mmHg, a significant and relevant decrease. As an indication of this supplement's effect on total heart health, total cholesterol decreased from about 223 mg=dL to 213 mg=dL, while their average high-density lipoprotein (HDL) increased from approximately 41 mg=dL to 43 mg=dL. Several other studies corroborate the effectiveness of CoQ10 for reducing blood pressure.

In an observational study of 109 patients seen in a private cardiology practice and who had essential hypertension, the patients added an average of 225 mg per day of CoQ10 to the antihypertensive medications they were already taking.[8] The dose of CoQ10 was adjusted individually according to the subjects' responses and, as needed, the pharmaceuticals in the patients' hypertensive regimens were altered. In this study, not only was the New York Heart Association functional class significantly improved in these patients—51% were able to discontinue from one to three of their other antihypertensive medications over the course of several months. Furthermore, a randomized, double-blind trial on 59 patients already receiving antihypertensive medications also showed reductions in systolic and diastolic blood pressures when they received CoQ10 supplementation.[9] In this study's CoQ10 group there

Figure 19–1. Hawthorn (Crataegus spp.).

were also reductions in plasma insulin, glucose, and triglyceride levels, as well as an increase in HDL, suggesting the appropriateness of CoQ10 for patients with diabetes and metabolic syndrome who also have hypertension. Finally, researchers who did a randomized, double-blinded, placebo-controlled trial on CoQ10 in 82 patients with isolated systolic hypertension found that, over 12 weeks, subjects who consumed 60 mg of CoQ10 twice daily had an average drop of 17.8 7.3 mmHg.[10] What is clinically noteworthy is that, although CoQ10 frequently works well as an isolated therapy, combining it with allopathic regimens often provides synergistic benefits as well. In addition, CoQ10 and L-carnitine have also produced improved clinical benefit for patients with a number of cardiovascular maladies, which was likely, in part, the result of their combined role in supporting adenosine triphosphate production and myocardial energy performance.

HAWTHORN

There are several other supplements that may well be useful for controlling hypertension, although the level of research evidence may not yet be as great as the level of their use among alternative and complementary medicine practitioners. Several species of hawthorn (Crataegus spp.) have garnered some research interest. In a recent double-blinded study of Iranian C. curvisepala, 92 subjects took either the hawthorn extract or a placebo for more than four months, and these produced significant drops in both systolic and diastolic blood pressure three months into the study.[11] An additional pilot study showed a favorable trend toward reduced hypertension for hawthorn extract but the results did not reach statistical significance.[12] Traditionally, this herb has been used as a heart tonic, and is used extensively for patients with chronic heart failure. What is important to note is that, in the practice setting, the full benefits of hawthorn in the proper dosages may take approximately six to eight weeks to be clinically observable.

OLIVE LEAF EXTRACT

Olive leaf (Olea europaea) extract is another of several botanicals with antihypertensive effects. Given orally to rats predisposed to hypertension and exposed to a hypertensive drug, olive leaf extract prevented rises in blood pressure over eight weeks in a dose-dependent manner.[13]

Figure 19–2. Garlic (Allium sativum).

The antihypertensive effects from this plant or its subspecies are probably the result of triterpenoids that have been demonstrated to act as beta-adrenergic antagonists.[14] Because of this potential action, it is possible for an interaction with pharmaceutically produced beta-blockers.

GARLIC

Garlic (Allium sativum) is another food botanical with mild antihypertensive effects. A meta-analysis of studies using dried garlic powder does suggest that this form of garlic supplementation may lead to a significant drop in both systolic and diastolic pressures, although larger studies would be welcome.[15] One specific study on 47 patients over 12 weeks showed that the subjects who took the garlic powder had a drop in supine diastolic pressure from an average of 102 mmHg to 91 mmHg over 12 weeks.[16] In addition to a drop in blood pressure, there were also significant reductions in cholesterol and triglyceride levels. Thus, it appears that garlic, like CoQ10, may lead to an overall improvement in cardiovascular function that results in lowered blood pressure.

COLEUS

Another herb, traditionally used in India for its antihypertensive effects is coleus (Coleus forskohlii). Coleus contains diterpenes that may have antihypertensive actions.[17] One of these, forskolin, is a molecule that acts directly on adenyl cyclase and leads to increased intracellular levels of the second messenger cyclic adenosine monophosphate (cAMP).[18] This, in turn, may lead to a cAMP-induced vasodilation and result in lower blood pressure. Some clinical experience with this herb indicates that about 540 mg per day of an extract standardized to 10% forskolin may have an antihypertensive effect in some people; at this dose, it is also not unusual for loose bowel movements to occur.

L-ARGININE

The amino acid L-arginine is gaining interest as an antihypertensive agent, because of its ability to increase nitric oxide production when taken as a nutritional supplement. In one study

on 13 patients with hypertension and angina, L-arginine, taken at 2 g, three times per day led to improvement of resting systolic blood pressure, reduction of angina symptoms, and better quality of life; all were considered to be significant.[19] In another study on patients with both hypertension and diabetes, patients were given 3 g of L-arginine every hour for 10 hours over two days, and this produced a drop in systolic blood pressure of about 12 mmHg and a drop in diastolic blood pressure of about 6 mmHg.[20] These effects were reversed within hours of L-arginine cessation. As it is impractical to take L-arginine orally every hour, a three times per day dosing schedule of 2–5 g may be attempted, or a time-release product utilized. An additional benefit of L-arginine therapy is that its ability to vasodilate can also help support better erectile functioning that often becomes compromised with long-term circulatory disease.

POMEGRANATE JUICE

Pomegranate (Punica granatum) juice has shown several cardio-protective properties. In one study, consumption of 50 ml of pomegranate juice (1.5 mmol of total polyphenols) per day for two weeks in hypertensive individuals showed a decrease in angiotensin converting enzyme (ACE) activity by 36%. Additionally, there was a 5% reduction in systolic blood pressure.[21] A similar study examined the effect of pomegranate juice consumption for one to three years in atherosclerotic patients with carotid artery stenosis. The results showed that, after one year, systolic blood pressure was reduced by 21%.[22] Animal studies suggest that pomegranate juice inhibits the CYP3A4 enzyme comparable to the inhibition with grapefruit juice, which may alter the metabolism of pharmaceuticals metabolized with this pathway.[23]

OMEGA-3 FATTY ACIDS

Fish oils from fatty fish such as salmon, mackerel, and herring are especially high in the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-3 fatty acids from fish oils have anti-inflammatory and antithrombotic effects because they compete with arachidonic acid in the cyclooxygenase and lipoxygenase pathways. Omega-3 fatty acids suppress COX-2 expression and the inflammatory cytokines interleukin (IL)-1 alpha and tumor necrosis factor-alpha (TNF-a).[24] A study with highly purified eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) ethyl esters at a dose of 4 g per day was shown to significantly decrease both systolic and diastolic blood pressure in mildly hypertensive individuals.[25] Additional studies have shown that 4 g per day of fish oil reduced systolic and diastolic blood pressure, as well as decreased triglycerides and very low density lipoprotein (VLDL) cholesterol.[26]

MINERALS

Calcium, magnesium, and potassium have all shown some efficacy in the management of hypertension. In a double-blind, randomized crossover study, patients with mild to moderate primary hypertension were supplemented with 600 mg per day of magnesium for six weeks. Oral magnesium significantly reduced the systolic, diastolic, and mean blood pressure.[27] In another double-blind crossover study of magnesium supplementation ranging from 15–40 mmol

per day, a significant decrease in the mean systolic blood pressure was recorded from while the mean diastolic blood pressure decreased from 100.2 = 4.2 mmHg to 92.0 = 6.6 mmHg.[28]

A study examined calcium carbonate supplementation at a dosage of 1.5 g per day in hypertensive patients for eight weeks. The results showed that the salt-sensitive hypertensive individuals had a significant blood pressure decrease.[29] Another study showed that there was a significant linear decrease in systolic and diastolic blood pressure with increasing dairy calcium intake, and conversely with increasing blood pressure, there was a significant linear decrease in age-adjusted calcium intake from dairy sources.[30] Additional analysis has shown that calcium supplementation (mean daily dose of 1,200 mg) reduced systolic BP by –1.86 mmHg and diastolic BP by 0.99 mmHg with a more profound impact in patients with a relatively low calcium intake.[31]

Potassium is also important in the prevention of hypertension. A meta-analysis of the studies performed showed that potassium supplementation is associated with a significant reduction in mean systolic blood pressure by –3.11 mmHg and diastolic blood pressure by –1.97 mmHg. The beneficial effects are more pronounced in individuals with low potassium and high sodium intake.[32]

CONCLUSIONS

There are numerous natural medicine therapeutics that can be particularly effective to help control mild to moderate hypertension. It is noteworthy that combined allopathic and naturopathic approaches can often help lessen the need for high-dose conventional drug therapy, and=or can help offset some of the side effects of such therapy. While no option in itself may be completely sufficient, several of the previously reviewed supplements used together and combined with consistent lifestyle changes, such as increased exercise, increased potassium and magnesium intake, and lowered sodium intake, will often lead to substantial reductions in hypertension.

Studies have shown that over 80% of all doctor visits and hospital admissions can be attributed directly or indirectly to stress, thus proving that stress has clear and devastating physical consequences well beyond the mental anguish. It is paramount to remember throughout the day:

> It is better to de-stress (lose stress) before you experience dis-stress (bad stress); for when we experience stress, it robs us of our existence in a state of “ease” or health, thus, we enter the realm of dis-ease (disease).

REFERENCES

[1]American Heart Association. High Blood Pressure Statistics. Available at: www.americanheart.org=presenter.jhtml?identifier 212. Accessed November 13, 2007.

[2]French MT, Mundt MP, Fleming M, Zavala SK. The cost of medical care for patients with diabetes, hypertension and both conditions: Does alcohol use play a role? J Intern Med. 2005;258:45–54.

[3]McGuire HL, Svetkey LP, Harsha DW, et al. Comprehensive lifestyle modification and blood pressure control: A review of the PREMIER trial. J Clin Hypertens (Greenwich). 2004;6:383–390.

[4]Geleijnse JM, Kok FJ, Grobbee DE. Impact of dietary and lifestyle factors on the prevalence of hypertension in Western populations. Eur J Public Health. 2004;14:235–239.

[5]Burke V, Hodgson JM, Beilin LJ, Giangiulioi N, Rogers P, Puddey IB. Dietary protein and soluble fiber reduce ambulatory blood pressure in treated hypertensives. Hypertension. 2001 Oct;38(4):821–826.

[6]Yamagami T, Shibata N, Folkers K. Bioenergetics in clinical medicine: VIII. Administration of coenzyme Q10 to patients with essential hypertension. Res Commun Chem Pathol Pharmacol. 1976;721–727.

[7]Langsjoen P, Langsjoen P, Willis R, Folkers K. Coenzyme Q10 in essential hypertension. Mol Aspects Med. 1994;15(suppl.):S257–S263.

[8]Langsjoen P, Langsjoen P, Willis R, Folkers K. Treatment of essential hypertension with coenzyme Q10. Mol Aspects Med. 1994;15(suppl.):S265–S272.

[9]Singh RB, Niaz MA, Rastogi SS, et al. Effect of hydrosoluble coenzyme Q10 on blood pressures and insulin resistance in hypertensive patients with coronary artery disease. J Hum Hypertens. 1999;13:203–208.

[10]Burke BE, Neuenschwander R, Olson RD. Randomized, double-blind, placebo-controlled trial of coenzyme Q10 in isolated systolic hypertension. South Med J. 2001; 94:1112–1117.

[11]Asgary S, Naderi GH, Sadeghi M, et al. Antihypertensive effect of Iranian Crataegus curvisepala Lind: A randomized, double-blind study. Drugs Exp Clin Res. 2004;30(5–6):221–225.

[12]Walker AF, Marakis G, Morris AP, Robinson PA. Promising hypotensive effect of hawthorn extract: A randomized double-blind pilot study of mild, essential hypertension. Phytother Res. 2002;16:48–54.

[13]Khayyal MT, el-Ghazaly MA, Abdallah DM, et al. Blood pressure lowering effect of an olive leaf extract (Olea europaea) in L-NAME induced hypertension in rats. Arzneimittelforschung. 2002;52:797–802.

[14]Somova LI, Shode FO, Mipando M. Cardiotonic and antidysrhythmic effects of oleanolic and ursolic acids, methyl maslinate and uvaol. Phytomedicine. 2004;11(2–3):121–129.

[15]Silagy CA, Neil HA. A meta-analysis of the effect of garlic on blood pressure. J Hypertens. 1994;12: 463–468.

[16]Auer W, Eiber A, Herrkorn E., et al. Hypertension and hyperlipidaemia: Garlic helps in mild cases. Br J Clin Pract. 1990;69(suppl.):S3–S6.

[17]Dubey MP, Srimal RC, Nityanand S, Dhawan BN. Pharmacological studies on coleonol, a hypotensive diterpene from Coleus forskohlii. J Ethnopharmacol. 1981;3:1–13.

[18]Ishikawa Y. Isoform-targeted regulation of cardiac adenylyl cyclase. J Cardiovasc Pharmacol. 2003; 41(suppl.1):S1–S4.

[19]Palloshi A, Fragasso G, Piatti P, et al. Effect of oral L-arginine on blood pressure and symptoms and endothelial function in patients with systemic hypertension, positive exercise tests, and normal coronary arteries. Am J Cardiol. 2004;93:933–935.

[20]Huynh NT, Tayek JA. Oral arginine reduces systemic blood pressure in type 2 diabetes: Its potential role in nitric oxide generation. J Am Coll Nutr. 2002;21:422–427.

[21]Aviram M, Dornfeld L. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. Atherosclerosis. 2001 Sep;158(1):195–198.

[22]Aviram M, Rosenblat M, Gaitini D, Nitecki S, Hoffman A, Dornfeld L, Volkova N, Presser D, Attias J, Liker H, Hayek T. Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. Clin Nutr. 2004 Jun;23(3): 423–433.

[23]Hidaka M, Okumura M, Fujita K, Ogikubo T, Yamasaki K, Iwakiri T, Setoguchi N, Arimori K. Effects of pomegranate juice on human cytochrome p450 3A (CYP3A) and carbamazepine pharmacokinetics in rats. Drug Metab Dispos. 2005 May;33(5):644–648. Epub 2005 Jan 26.

[24]Curtis CL, Hughes CE, Flannery CR, Little CB, Harwood JL, Caterson B. n-3 fatty acids specifically modulate catabolic factors involved in articular cartilage degradation. J Biol Chem. 2000 Jan 14;275(2): 721–724.

[25]Prisco D, Paniccia R, Bandinelli B, Filippini M, Francalanci I, Giusti B, Giurlani L, Gensini GF, Abbate R, Neri Serneri GG. Effect of medium-term supplementation with a moderate dose of n-3 polyunsaturated fatty acids on blood pressure in mild hypertensive patients. Thromb Res. 1998 Aug 1;91(3):105–112.

[26]Toft I, Bønaa KH, Ingebretsen OC, Nordøy A, Jenssen T. Effects of n-3 polyunsaturated fatty acids on glucose homeostasis and blood pressure in essential hypertension. A randomized, controlled trial. Ann Intern Med. 1995 Dec 15;123(12):911–918.

[27]Sanjuliani AF, de Abreu Fagundes VG, Francischetti EA. Effects of magnesium on blood pressure and intracellular ion levels of Brazilian hypertensive patients. Int J Cardiol. 1996 Oct 11;56(2):177–183.

[28]Widman L, Wester PO, Stegmayr BK, Wirell M. The dose-dependent reduction in blood pressure through administration of magnesium. A double blind placebo controlled cross-over study. Am J Hypertens. 1993 Jan;6(1):41–45.

[29]Weinberger MH, Wagner UL, Fineberg NS. The blood pressure effects of calcium supplementation in humans of known sodium responsiveness. Am J Hypertens. 1993 Sep;6(9):799–805.

[30]Jorde R, Bonaa KH. Calcium from dairy products, vitamin D intake, and blood pressure: The Tromso Study. Am J Clin Nutr. 2000 Jun;71(6):1530–1535.

[31]van Mierlo LA, Arends LR, Streppel MT, Zeegers MP, Kok FJ, Grobbee DE, Geleijnse JM. Blood pressure response to calcium supplementation: A meta-analysis of randomized controlled trials. J Hum Hypertens. 2006 Aug;20(8):571–580. Epub 2006 May 4.

[32]Whelton PK, He J, Cutler JA, Brancati FL, Appel LJ, Follmann D, Klag MJ. Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. JAMA. 1997 May 28;277(20):1624–1632.

20

NATURAL APPROACHES TO CONTROLLING INFLAMMATORY DISEASE

Inflammation is simply a physiologic response generated by the body in response to injury, infection, or irritation. In acute stages, the inflammatory process is vital to the healing process; however, chronic inflammation can increase disease-associated morbidity. New insights into the chronic inflammatory process now provide evidence that this mechanism is a negative contributor to an ever-expanding list of chronic conditions, including Alzheimer's disease, cardiovascular diseases, diabetes, arthritis, asthma, cancer, and even depression.

As inflammation is increasingly acknowledged as a main precursor to morbidity in the pathology of chronic disease, medicine is elucidating both the effects of inflammation prior to clinical disease manifestation and preventative treatments geared toward reversal and attenuation of symptoms. Natural medical therapies directed toward anti-inflammatory effects have become more intensely researched in the last several years, providing significant insight into the role of inflammation in disease and offering options for effective preventative and symptomatic treatment.

We are a society plagued with countless inflammatory conditions or more aptly stated -itis. You name the body part and place the modifier -itis behind it, and the vast majority of the time the condition has walked through the local family practice clinic in the neighborhood. Whether it is arthritis, tendonitis, bursitis, cystitis, prostatitis, dermatitis, gingivitis, gastritis, esophagitis, colitis; the point is well-made. We are a society that is afflicted and ultimately dying with a great deal of inflamed parts. For example, according to the Centers for Disease Control and Prevention (CDC), the nation's number one cause of disability, arthritis, currently affects 46 million Americans and projections suggest that by 2030, 67 million Americans will be affected.[1]

INFLAMMATION AND THE DISEASE PROCESS

The inflammatory process is now being associated with several diseases in which an inflammatory component was previously unknown. Coronary artery disease, major depression, and cancer are associated with an increased level of interleukin-1 (IL-1), a pro-inflammatory cytokine, while elevated IL-1 levels and pro-inflammatory leukotriene (LT) B-4, most notably produced by omega-6 fatty acids, similarly characterize diseases such as arthritis, Crohn's disease, ulcerative colitis, and systemic lupus erythematosis.[2] In cell-mediated immune responses, cytokines released from T lymphocytes are important mediators of inflammation. CD4 T-helper cells are generally differentiated into Th1 and Th2 types. Th1 cells secrete predominantly pro-inflammatory cytokines such as interferon-gamma, IL-1, IL-6, IL-12, and tumor necrosis factor-alpha (TNF-a). Recent evidence indicates that inflammation plays a pivotal role in the origins and complications of atherosclerotic and type 2 diabetic disease, linked by C-reactive protein (CRP), plasminogen activator inhibitor-1, and homocysteine. These nonconventional risk factors are now known as markers indicative of general low-grade inflammation, vascular injury, and thrombotic processes.[3]

Chronic inflammation is believed to be an associated risk factor for cancer in the human body such as in the bowel and rectum. Localized inflammatory processes incite numerous pro-oxidative enzymes (e.g., the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, nitric oxide synthase) that react among themselves and with other reactive oxygen species to create an environment that is rich in highly reactive, pro-oxidative species. These oxidants damage DNA, leading to mutations, and may activate oncogenes and=or inactivate tumor-suppressor proteins, allowing carcinogenic processes to occur.

Other causes of localized chronic inflammatory-induced tumor growth that have been proposed include an oxidative process that inhibits cellular apoptosis, cellular switching to a glycolytic metabolism, and neovascular genesis and vasorelaxation that can inhibit recruitment of immune cells, all of which act collectively as an opposing force to the normally rapid cytotoxic response.[4] Studies on these topics lend credence to the concept of preventative cancer treatment via modulating chronic inflammatory conditions.

ANTI-INFLAMMATORY DIETS

The anti-inflammatory diet, although it is not a recent development in preventing and treating inflammatory diseases, serves as the cornerstone for mitigating the generalized, chronic inflammatory response. This treatment is applied in many forms, differing from practitioner to practitioner. What is consistent in the various forms of the anti-inflammatory diet is strict avoidance of foods that contain high amounts of arachidonic acid (AA), the main precursor of the negatively associated inflammatory cascade process. Metabolites of AA include prostaglandins (PGs), LTs, and thromboxanes, which are closely involved in both acute and chronic inflammatory responses. The rate-limiting step in the creation of these inflammatory metabolites is the release of AA from membrane phospholipids, which are catalyzed by the enzyme phospholipase A2. The clinical implications associated with imbalanced intake and metabolism of the two essential fatty acids (EFAs), linoleic and alpha-linolenic acids, are directly related to their by-product concentrations in the membrane phospholipid layer. Levels of these long-chain polyunsaturated fatty acids (arachidonic, eicosapentaenoic, and docosahexaenoic acids) may be affected by diet and disease and can alter the severity, character, and intensity of systemic inflammatory processes.[5]

An alteration or loss of regulation of the AA cascade leads to a chronic inflammatory state, which characterizes numerous physical disorders. A frequently indicated offender to be removed from the diet is conventionally raised red meat, a significant source of AA. It should be clarified that grass-fed beef has a higher omega-3 to omega-6 ratio than conventionally raised beef. Additionally, white meat from poultry and eggs may be high in AA depending on the type of feed. Another source of dietary inflammation is hydrogenated foods, which are high in the pro-inflammatory trans-fatty acids. Numerous studies highlight a link between foods that are high in omega-6 fatty acid and decreased intake of omega-3 fatty-acid-rich foods.[6] Dietary gluten and lectins are also recognized as common triggers of inflammation.

It is theorized that humans evolved on a diet consisting of a 1:1 ratio of omega-6 to omega-3 fatty acids. Today, the typical Western diet consists of a ratio between 10:1 and 25:1 and, in some cases, this ratio may be as high as 40:1. It is this imbalanced fatty-acid ratio that is linked to chronic inflammatory health problems.

A common misconception is that all commonly consumed omega-6 fatty acids (LA, AA, and gamma linolenic acid [GLA]) are unhealthy, when the reality is that only excessive intake of AA (combined with a decreased intake of omega-3 fatty acids) contributes to chronic in-

flammation, because these fatty acids are necessary for essential functions in the body. The delta-6-desaturase (D6D) enzyme is both the initial and rate-limiting enzyme in both the omega-6 and omega-3 fatty-acid pathways and shown to exhibit suboptimal activity in several diseases. In addition, if LA is not metabolized further, dihommo-gamma linolenic acid (DGLA), which is the precursor to GLA, is not formed. DGLA, in turn, is the precursor of a number of beneficial eicosanoids that are important for optimal cell functioning. GLA in combination with EPA-DHA has considerable health benefits and is not linked to the problems associated with an unbalanced fatty-acid profile.

POLYUNSATURATED FATTY ACIDS AND LYMPHOCYTE FUNCTIONS

The inflammatory mediators (PGs and LTs) that are produced via polyunsaturated fatty-acid (PUFA) metabolism can directly influence the behavior of inflammatory immunologic cells and their production and balance of cytokines. Increased consumption of omega-3 PUFAs displaces the amount of AA in cellular membranes and thereby limits the production of pro-inflammatory eicosanoids. It is believed that components of both natural and acquired immunity, including the production of key inflammatory cytokines, can be affected by omega-3 PUFA intake and that fatty acids may stimulate some immune activity by way of non-eicosanoid-dependent mechanisms.[7] Fish oil (a rich source of omega-3 PUFA) supplementation in animals results in positively associated improved lymphocyte function, decreased macrophage-borne pro-inflammatory cytokines, and pacification of autoimmune disease symptomatology. In human subjects, dietary additions of omega-3 PUFAs have led to decreased monocyte and neutrophil chemotaxis and production of pro-inflammatory cytokines.[8]

Suboptimal levels of vitamin B_6 are associated with increased risk for cardiovascular disease and rheumatoid arthritis.

Inflammatory-type diseases are amenable to fatty-acid replacement therapies because the composition of fatty acids in lymphocytes and other immune cells are modified by both bodily-fat amounts and types of fatty acids available for eicosanoid production. Fatty acids such as arachidonic, alpha-linolenic, eicosapentaenoic, oleic, linoleic, conjugated linoleic, gamma-linolenic, dihomo-gamma-linolenic, and docosahexaenoic all have the ability to influence inflammatory responses that are associated with lymphocyte proliferation and cytokine production, as well as natural-killer (NK) cell activity.[9] Pro-inflammatory cytokine production is reduced by omega-3 PUFAs, decreasing the severity of the inflammatory cytokine-related disease processes. Because cytokine production and function are part of a normal host defense, they are necessary. Consumption of PUFAs in excess of 3–4 g per day may lead to impairment of the immune response. Increased consumption of PUFAs may also lead to increased lipid peroxidation and resultant oxidative species causing a reduction in T-cell directed function, NK cell function, and macrophage activity.[10] Consuming other sources of antioxidants, such as vitamin E, may mitigate increased oxidation due to consumption of PUFAs.

VITAMIN B_6 AND INFLAMMATION

Vitamin B_6 (pyridoxine) plays several roles in the etiology and pathogenesis of chronic inflammation and inflammatory diseases. Pyridoxine is water-soluble and is preferentially absorbed in an acidic milieu in the proximal small intestine via simple diffusion. This vitamin's role in inflammation can be observed on a number of metabolic levels and in various pathologies. In one study, pyridoxine-deficient rats developed increased concentrations of thiobarbituric acid reactive substances (indicators of lipid peroxidation) up to 30%–43%, suggesting an enhanced inflammation response caused by pyridoxine deficiency.[11] In another study, median pyridoxine levels were significantly lower in human patients with inflammatory bowel disease (IBD) compared to controls and were even lower in patients with active IBD compared to those whose disease was quiescent. In addition, lower pyridoxine levels were positively correlated with CRP serum levels, and hyperhomocysteinemia occurred more frequently in patients with lower pyridoxine levels.[12] Suboptimal levels of vitamin B_6 are associated with increased risk for cardiovascular disease and rheumatoid arthritis. The reasons for this are not evident, and a clear pathophysiologic picture has not emerged for these two conditions, other than the inflammatory reaction shared by both diseases. In one study, decreased levels of plasma pyridoxal 5′-phosphate, the active form of vitamin B_6, were associated with higher levels of CRP independent of total plasma homocysteine. The researchers hypothesized that such evidence may indicate that vitamin B_6 deficiency contributes to chronic inflammatory processes.[13] Another aspect of inflammation in which vitamin B_6 is involved is fatty-acid metabolism. Inhibition of D6D, which is both the initial and rate-limiting enzyme in both the omega-6 and omega-3 fatty-acid pathways, can result from vitamin

Table 20–1. Anti-Inflammatory Supplements at a Glance

Supplements	Doses and Notes
Vitamin B_6	50 mg per day
Magnesium	600–800 mg per day, in divided doses (an adjustment for bowel tolerance maybe required)
Vitamin E	400–800 international units per day (in mixed or gamma-tocopherol form)
Fish oils	2–4 g per day, in a 1.5 EPA:DHA ratio (low peroxide levels are critical)
Cat's claw	75 mg of a standardized preparation (Uncaria tomentosa), 3 times per day
Propolis	500 mg, encapsulated, 3 times per day
Boswellia (Boswellia serrata)	300–500 mg, standardized for boswellic also known as frankincense acids, 3 times per day, not with food
Ginger (Zingiber officinalis)	250 mg 4 times per day
Holy basil (Ocimum sanctum)	250 mg 3 times per day, freeze-dried capsules
Green tea (Camellia sinensis)	240–400 mg per day, standardized for EGCG
Nettle leaf (Urtica dioica)	100–300 mg 3 times per day
Stephania tetrandra	300 mg 2 times per day
Serrapeptase	10–30 mg 3 times per day, away from food
Nattokinase	30–108 mg 1–2 times per day, away from food

EPA eicosapentaenoic acid, DHA docosahexaenoic acid.

B_6 deficiency.[14] In addition, because LA is not metabolized further, GLA, which is the precursor to DGLA, is not formed. DGLA, in turn, is the precursor for a number of beneficial eicosanoids that are important for optimal cell functioning and production of PGE1, an anti-inflammatory PG.

VITAMIN E, ZINC, AND MAGNESIUM

Other nutritional factors that are involved in positive up-regulation of D6D include zinc, magnesium, and vitamin E. In one study, the enzymatic activity of D6D was increased at twice that of baseline level in subjects when their vitamin E microsomal membrane concentrations were increased, reflecting the vitamin's role in controlling the membranous metabolism of PUFAs.[15] In addition, zinc has been shown to assist in converting LA to GLA via D6D, and a deficiency of zinc produced an EFA deficiency and down-regulation of D6D.[16] Magnesium deficiency contributed to decreased formation of D6D molecules, resulting in a less-rapid conversion of LA to GLA in liver microsomes.[17] By supplying patients with proper nutritional doses of these enzymatic cofactors, efficient activation of this D6D can induce complete fatty-acid metabolism and production of non-inflammatory fatty-acid products, helping to reducing chronic inflammatory patterns further.

Cat's Claw

Cat's claw (Uncaria tomentosa) is a medicinal plant that is native to the Amazon River basin, with a history of traditional use for inflammatory conditions. Two active compound groups, alkaloids and flavanols, are presumed to be the major effector compounds.[18] Studies of cat's claw have utilized two species, Uncaria guianensis and Uncaria tomentosa, and both are considered to be equiactive but, currently, Uncaria tomentosa has been more thoroughly researched. A pulverized bark fraction of Uncaria tomentosa inhibited tumor necrosis factor-alpha (TNF-a) production by approximately 65%–85% and has acted as a potent antioxidant.[19] These effects, immunomodulation of TNF-alpha and antioxidative abilities, are widely documented in the literature. What is more, the anti-inflammatory effects of this plant have been demonstrated recently. In test subjects with osteoarthritis of the knee, a comprehensive study was undertaken to determine the adverse-effect, pain, medical, and subject-assessment scores of patients who took a purified extract of the herb. The researchers noted an absence of negative effects on red-blood-cell indices and liver function or other side effects compared to a placebo. In the Uncaria-treated group, activity-associated pain, medical, and subjective assessment scores were "significantly" reduced within one week of therapy at doses that achieved a level of 13.6–21.7 mg per mL of each subject's blood and lipopolysaccharide-induced PGE2 synthesis was inhibited at a concentration higher than necessary to mitigate TNF-alpha production, as had been explained in previous studies.[20] In another study, an extract of Uncaria tomentosa was given to patients with active rheumatoid arthritis and who were undergoing sulfasalazine or hydroxychloroquine treatment in a 52-week, two-phase study. Twenty-four weeks of treatment with the cat's claw extract resulted in a decreased amount of painful joints in treated subjects compared to those who were on a placebo (53.2% versus 24.1%) with minor side effects, none of which were listed.[21]

Cat's claw is emerging as an effective botanical medicine that can be used for treating various inflammatory states and conditions, producing positive effects and few side effects. The anti-inflammatory properties of this herb are undergoing further investigation, and continued

Burns treated with propolis had less inflammation compared to those treated with silver sulfadiazine.

research promises to provide even more specific explanations of the herb's actions in inflammatory diseases.

Propolis

Propolis is a resinous substance derived from poplar and conifer buds and used by Apis mellifera bees for maintaining their hives. The pharmacologically active molecules in propolis are flavonoids and phenolic acids and their esters. These components have proven antibiotic effects on bacteria, fungi, and viruses.[22] New evidence suggests that propolis may suppress the lipoxygenase pathway thereby decreasing LT synthesis.[23] In studies using the rat paw edema model, it has been theorized that caffeic acid phenethyl ester (CAPE) is the constituent that is most responsible for the anti-inflammatory effects of propolis for reducing acute and chronic inflammation.[24]

One study investigated the effects of both CAPE and galangin (an ethanolic extract of propolis) on cyclo-oxygenase (COX) activity. Propolis inhibited COX activity significantly in a dose-dependent manner. Similar results were obtained independently with CAPE and galangin; however, the COX inhibitory effect of propolis containing galangin but not CAPE, was determined to be approximately 10 times less potent than the extract containing CAPE. Both CAPE and galangin contribute to the activity of propolis, although CAPE is the stronger-acting constituent.[25]

The anti-inflammatory effects of this plant medicine have also been studied in other models of inflammation, such as corneal injury and skin burns. It was shown to produce anti-inflammatory effects comparable to dexamethasone in treating experimentally induced chemical corneal injury.[26] Propolis was compared to silver sulfadiazine (SSD) for treating superficial second-degree burns. Burns treated with propolis had less inflammation and increased cicatrisation compared to those treated with SSD, and no significant differences in microbial-wound colonization were noted between the two treatment groups in one study.[27] The researchers hypothesized that, had the dressing been changed more frequently (fewer than every three days), the antimicrobial and healing effects may have been enhanced. The two previous studies exemplify the broad use of propolis as an anti-inflammatory agent that can be useful for treating a number of conditions with various medical therapies, many of which may yet be discovered.

Propolis is difficult to standardize leading to a variation in active ingredients. Using a reputable product is imperative with this treatment.

Boswellia

Boswellia (Boswellia serrata), also known as frankincense, is native to the Indian continent, North Africa, and the Middle East, and is used widely as a traditional herb in Ayurvedic medicine for treating inflammatory disease. The resin, or gum, from the plant contains pentacyclic triterpenes (boswellic acids) of which produce much of this plant's anti-inflammatory

activity. Nearly 16% of the resin is comprised of essential oil. The acids contained in boswellia inhibit the enzyme 5-lipoxygenase by binding to the enzyme, resulting in decreased LT production in neutrophilic granulocytes.

Several clinical trials have attributed beneficial effects of this herb in treating chronic inflammatory diseases, such as rheumatoid arthritis, chronic colitis, ulcerative colitis, Crohn's disease, asthma, and tumor-associated brain edema.[28] In a study of patients with colitis, a gum resin extract of Boswellia serrata was supplied at a dose of 900 mg, three times per day, for six weeks while a control group was maintained on 3 g per day of sulfasalazine for six weeks. Ninety percent of the boswellia-treated patients experienced improvements in stool properties; histopathology; and levels of hemoglobin, iron, calcium, phosphorus, proteins, and total leukocytes and eosinophils, with few side effects; while 60% of the sulfasalazine-treated patients experienced similar results. However, 14 of the 20 boswellia-treated patients experienced remissions, while only 4 of the 10 sulfasalazine-treated patients reached remission.[29] Boswellia has been proven to be effective for treating asthma also, and the beneficial effects are attributed to LT inhibition. Seventy percent of subjects who were treated with 300 mg of the herb, three times per day, for six weeks, experienced improvements in forced expiratory volume 1 (FEV_1), forced vital capacity (FVC), and peak expiratory flow rate (PEFR). What is more, these same subjects had decreased eosinophilic counts and erythrocyte sedimentation rates, plus subjective improvements. The placebo group experienced a 27% improvement overall.[30] Boswellia serrata can serve as a potent anti-inflammatory medicine and as a nonredox, noncompetitive specific inhibitor of the 5-lipoxygenase enzyme.

Stephania tetrandra

Stephania tetrandra is an herb traditionally used in Asia to treat various inflammatory conditions. Traditionally, it has been used for its anti-inflammatory, antioxidant, immune modulating, antifibrogenic, and antiallergy activity. Its main anti-inflammatory constituents are tetrandrine and fangchinoline. Studies show that the constituent tetrandrine suppressed the lipopolysaccharide (LPS) induction of nitric oxide (NO) release and prostaglandin E2 (PGE2) generation. It also significantly attenuated the LPS-induced transcription of the pro-inflammatory cytokines TNF-alpha, IL-4 and IL-8. Tetrandine also significantly blocked the LPS induction of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression.[31] Research has also alluded that tetrandine inhibits IL-1 and TNF-alpha release from monocytes, and inhibits intercellular adhesion molecule-1 (ICAM-1) expression, which may indicate a way in which it exerts its anti-inflammatory activity.[32] Tetrandine has been shown to be particularly beneficial in treating rheumatic conditions such as rheumatoid arthritis, which is believed to be due to inhibition of lymphocyte proliferation and inhibition of cyclo-oxygenase-1 (COX-1) activity.[33] Tetrandine has been shown to have anti-cancer activity, and work synergistically with chemotherapy to induce apoptosis in cancer cell lines.[34]

Nettle Leaf (Urtica dioica)

Stinging nettle (Urtica dioica) is an herb that traditionally has been used to treat inflammatory conditions such as asthma, eczema, and rheumatic conditions. Nettles have been shown to decrease numerous pro-inflammatory cytokines. Research suggests that part of the anti-inflammatory effect of nettles extract may be due to its inhibitory effect on NF-kappaB activation.[35] Studies also show that Urtica inhibits production of Th1-specific IL-2 and

IFN-gamma in peripheral blood mononuclear cells and stimulated the secretion of Th2-specific IL-4. This immune-modulating activity was suggested as the possible mechanism in which Urtica benefits autoimmune diseases such as RA.[36]

Holy Basil (Ocimum sanctum)

Holy basil (Ocimum sanctum) has numerous traditional uses including anti-inflammatory, antimicrobial, anti-cancer, and analgesic action. Holy basil blocks both the cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism, which may be responsible for the anti-inflammatory activity.[37] Studies also have shown that holy basil inhibits both COX-1 and COX-2 pathways. In fact, the constituent eugenol demonstrated 97% cyclooxygenase-1 inhibitory activity.[38]

Ginger (Zingiber officinalis)

Ginger root (Zingiber officinalis) has historically been used for its anti-inflammatory antipyretic, analgesic, sedative, and antibiotic activity. Ginger contains several active constituents such as gingerol, gingerdione, and shogaol. Evidence shows that ginger extract significantly inhibited the activation of TNF-alpha and COX-2 expression in human synoviocytes with suppression of NF-kappaB and IkappaB-alpha induction as well as suppressed the production of TNF-alpha and PGE-2.[39] In addition, ginger also suppresses leukotriene biosynthesis by inhibiting 5-lipoxygenase.[40] One study examined the effects of ginger supplementation with musculoskeletal pain and arthritis. Results showed that more than three-quarters of the arthritis, both osteoarthritis and rheumatoid arthritis, patients experienced, to varying degrees, relief in pain and swelling, and all of the patients with muscular discomfort experienced relief in pain.[41]

Green Tea (Camellia sinensis)

Green tea is a widely used botanical medicine for numerous conditions, particularly used for anti-inflammatory, anti-cancer, and antioxidant activity. Many of the benefits of green tea are attributed to the catechins epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC). Animal models show that green tea inhibits the production of leukotriene B4 and 5-lipooxygenase activity.[42] Also, a study demonstrated that human chondrocytes pretreated with EGCG showed a dose-dependent inhibition in the production of NO by 48% and PGE(2) by 24%, and correlated with the inhibition of iNOS and COX-2 activity. In addition, IL-1 beta-induced expression of iNOS and COX-2 was also markedly inhibited in human chondrocytes pretreated with EGCG. EGCG also inhibited the IL-1 beta-induced LDH release in chondrocytes cultures.[43] Another study found that EGCG inhibits TNF-alpha-mediated activation of the NF-kappaB pathway, with inhibition of IL-8 gene expression.[44]

Enzymes: Serrapeptase and Nattokinase

Nattokinase is a fibrinolytic enzyme derived from natto, a fermented soybean product. It acts by inactivating plasminogen activator inhibitor 1 (PAI-1).[45] Studies show that it has fibrinolytic activity four times more potent than plasmin.[46] Animal models demonstrate that nattokinase supplementation inhibits thickening of the intimal wall after vessel injury.[47] Research has also shown that nattokinase increases thrombolysis at the site of thrombus formation caused by endothelial injury.[48]

Serrapeptase is a proteolytic enzyme originally isolated from the silkworm. It has anti-inflammatory and fibrinolytic activity and decreases swelling. A double-blind, placebo-controlled study demonstrated that serrapeptase supplementation rapidly decreased inflammation and decreased symptoms in a group of patients suffering from ENT symptoms.[49]

Additional important therapies for inflammation include:

Turmeric (Curcuma longa, curcumin) and Willow bark (Salix spp.). (See Chapter 27 on pain management.)
Bromelain. (See Chapter 37 on therapeutic enzymes.)

CONCLUSIONS

Science is continually discovering an inflammatory link in many chronic diseases, revealing this process as both a precipitive and propagative factor in these conditions. Because of this new understanding, physicians must now, more than ever, use preventative medicine to treat their patients. Preventative anti-inflammatory treatments are numerous and may be applied at various levels of care. The most motivated patients can alter the course of their health positively and prevent chronic conditions, such as cardiovascular disease, cancer, or Alzheimer's disease, simply by manipulating the fatty acid ratios of their dietary intake.

In addition, patients with preexisting "chronic" disease conditions may also affect the outcomes of these disease processes by adhering to similar protocols. Natural medicines and nutritional cofactors also collectively play an important role in preventing and treating diseases in which inflammation is active. Greater understanding of these medicines and the benefits that they exert on various parts of the inflammatory process will allow practitioners to use such natural anti-inflammatories safely to treat chronic inflammation as well as for general preventative health care.

REFERENCES

[1]Arthritis Foundation. Arthritis Prevalence, Activity Limitations to Skyrocket. Online document at: http:= 216.205.93.140=media=newsroom=news-releases=Dc253.pdf. Accessed November 02, 2007.
[2]Simopoulos AP. Omega-3 fatty acids in inflammation and autoimmune diseases. J Am Coll Nutr. 2002; 21:495–505.
[3]Theuma P, Fonseca VA. Inflammation and emerging risk factors in diabetes mellitus and atherosclerosis. Curr Diab Rep. 2003;3:248–254.
[4]Schwartsburd PM. Chronic inflammation as inductor of pro-cancer microenvironment: Pathogenesis of dysregulated feedback control. Cancer Metastasis Rev. 2003;22:95–102.
[5]Tapiero H, Ba GN, Couvreur P, Tew KD. Polyunsaturated fatty acids (PUFA) and eicosanoids in human health and pathologies. Biomed Pharmacother. 2002;56:215–222.
[6]Ford F. Health benefits of omega-3s for the whole family. J Fam Health Care. 2002;12:91–93.
[7]Calder PC, Grimble RF. Polyunsaturated fatty acids, inflammation and immunity. Eur J Clin Nutr. 2002; 56(suppl.3):S14–S19.
[8]Calder PC. Polyunsaturated fatty acids, inflammation, and immunity. Lipids. 2001;36(9):1007–1024.
[9]Calder PC, Yaqoob P, Thies F, Wallace FA, Miles EA. Fatty acids and lymphocyte functions. Br J Nutr. 2002;87(suppl.1):S31–S48.
[10]Meydani SN. Effect of (n-3) polyunsaturated fatty acids on cytokine production and their biologic function. Nutrition. 1996;12(suppl.1):S8–S14.
[11]Lakshmi R, Lakshmi AV, Divan PV, Bamji MS. Effect of riboflavin or pyridoxine deficiency on inflammatory response. Indian J Biochem Biophys. 1991;28(5–6):481–484.

[12]Saibeni S, Cattaneo M, Vecchi M, Zighetti ML, Lecchi A, Lombardi R, Meucci G, Spina L, de Franchis R. Low vitamin B_6 plasma levels, a risk factor for thrombosis, in inflammatory bowel disease: Role of inflammation and correlation with acute phase reactants. Am J Gastroenterol. 2003;98:112–117.

[13]Friso S, Jacques PF, Wilson PW, Rosenberg IH, Selhub J. Low circulating vitamin B_6 is associated with elevation of the inflammation marker Creactive protein independently of plasma homocysteine levels. Circulation. 2001;12;103:2788–2791.

[14]Bordoni A, Hrelia S, Lorenzini A, Bergami R, Cabrini L, Biagi PL, Tolomelli B. Dual influence of aging and vitamin B_6 deficiency on delta-6-desaturation of essential fatty acids in rat liver microsomes. Prostaglandins Leukot Essent Fatty Acids. 1998;58:417–420.

[15]Despret S, Dinh L, Clement M, Bourre JM. Alteration of delta-6 desaturase by vitamin E in rat brain and liver. Neurosci Lett. 1992;145:19–22.

[16]Ayala S, Brenner RR. Essential fatty acid status in zinc deficiency: Effect on lipid and fatty acid composition, desaturation activity and structure of microsomal membranes of rat liver and testes. Acta Physiol Lat Am. 1983;33:193–204.

[17]Mahfouz MM, Kummerow FA. Effect of magnesium deficiency on delta 6 desaturase activity and fatty acid composition of rat liver microsomes. Lipids. 1989;24:727–732.

[18]Sandoval M, Okuhama NN, Zhang XJ, Condezo LA, Lao J, Angeles FM, Musah RA, Bobrowski P, Miller MJ. Anti-inflammatory and antioxidant activities of cat's claw (Uncaria tomentosa and Uncaria guianensis) are independent of their alkaloid content. Phytomedicine. 2002;9:325–337.

[19]Sandoval M, Charbonnet RM, Okuhama NN, Roberts J, Krenova Z, Trentacosti AM, Miller MJ. Cat's claw inhibits TNFa production and scavenges free radicals: Role in cytoprotection. Free Radic Biol Med. 2000;29:71–78.

[20]Piscoya J, Rodriguez Z, Bustamante SA, Okuhama NN, Miller MJ, Sandoval M. Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: Mechanisms of action of the species Uncaria guianensis. Inflamm Res. 2001;50:442–448.

[21]Mur E, Hartig F, Eibl G, Schirmer M. Randomized double blind trial of an extract from the pentacyclic alkaloid—chemotype of Uncaria tomentosa for the treatment of rheumatoid arthritis. J Rheumatol. 2002;29:678–681.

[22]Foster S, Tyler VE. Tyler's Honest Herbal: A Sensible Guide to the Use of Herbs and Related Remedies, 3rd Edition. Binghamton, NY: Haworth Herbal Press, 1993.

[23]Mirzoeva OK, Calder PC. The effect of propolis and its components on eicosanoid production during the inflammatory response. Prostaglandins Leukot Essent Fatty Acids. 1996;55:441–449.

[24]Borrelli F, Maffia P, Pinto L, Ianaro A, Russo A, Capasso F, Ialenti A. Phytochemical compounds involved in the anti-inflammatory effect of propolis extract. Fitoterapia. 2002;73(suppl.1):S53–S63.

[25]Rossi A, Longo R, Russo A, Borrelli F, Sautebin L. The role of the phenethyl ester of caffeic acid (CAPE) in the inhibition of rat lung cyclooxygenase activity by propolis. Fitoterapia. 2002;73(suppl.1):S30–S37.

[26]Ozturk F, Kurt E, Cerci M, Emiroglu L, Inan U, Turker M, Ilker S. The effect of propolis extract in experimental chemical corneal injury. Ophthalmic Res. 2000;32:13–18.

[27]Gregory SR, Piccolo N, Piccolo MT, Piccolo MS, Heggers JP. Comparison of propolis skin cream to silver sulfadiazine: A naturopathic alternative to antibiotics in treatment of minor burns. J Altern Complement Med. 2002;8:77–83.

[28]Ammon HP. Boswellic acids (components of frankincense) as the active principle in treatment of chronic inflammatory diseases [in German]. Wien Med Wochenschr. 2002;152(15–16):373–378.

[29]Gupta I, Parihar A, Malhotra P, Gupta S, Ludtke R, Safayhi H, Ammon HP. Effects of gum resin of Boswellia serrata in patients with chronic colitis. Planta Med. 2001;67:391–395.

[30]Gupta I, Gupta V, Parihar A, Gupta S, Ludtke R, Safayhi H, Ammon HP. Effects of Boswellia serrata gum resin in patients with bronchial asthma: Results of a double-blind, placebo-controlled, 6-week clinical study. Eur J Med Res. 1998;3:511–514.

[31]Wu SJ, Ng LT. Tetrandrine inhibits proinflammatory cytokines, iNOS and COX-2 expression in human monocytic cells. Biol Pharm Bull. 2007 Jan;30(1):59–62.

[32]Chang DM, Kuo SY, Lai JH, Chang ML. Effects of anti-rheumatic herbal medicines on cellular adhesion molecules. Ann Rheum Dis. 1999 Jun;58(6):366–371.

[33]Long Q, Qiu J. [Effects of ethanol extracts from Triptergium wilfordii hook and Stephania tetrandra S. Moore on lymphocytes and cyclooxygenase]. Zhong Yao Cai. 2004 Nov;27(11):851–853.

[34]Wei J, Liu B, Wang L, Qian X, Ding Y, Yu L. Synergistic interaction between tetrandrine and chemotherapeutic agents and influence of tetrandrine on chemotherapeutic agent-associated genes in human gastric cancer cell lines. Cancer Chemother Pharmacol. 2007 Oct;60(5):703–711. Epub 2007 Jan 26.

[35]Riehemann K, Behnke B, Schulze-Osthoff K. Plant extracts from stinging nettle (Urtica dioica), an antirheumatic remedy, inhibit the proinflammatory transcription factor NF-kappaB. FEBS Lett. 1999 Jan 8;442(1):89–94.

[36]Klingelhoefer S, Obertreis B, Quast S, Behnke B. Antirheumatic effect of IDS 23, a stinging nettle leaf extract, on in vitro expression of T helper cytokines. J Rheumatol. 1999 Dec;26(12):2517–2522.

[37]Singh S. Comparative evaluation of antiinflammatory potential of fixed oil of different species of Ocimum and its possible mechanism of action. Indian J Exp Biol. 1998 Oct;36(10):1028–1031.

[38]Kelm MA, Nair MG, Strasburg GM, DeWitt DL. Antioxidant and cyclooxygenase inhibitory phenolic compounds from Ocimum sanctum Linn. Phytomedicine. 2000 Mar;7(1):7–13.

[39]Frondoza CG, Sohrabi A, Polotsky A, Phan PV, Hungerford DS, Lindmark L. An in vitro screening assay for inhibitors of proinflammatory mediators in herbal extracts using human synoviocyte cultures. In Vitro Cell Dev Biol Anim. 2004 Mar–Apr;40(3–4):95–101.

[40]Grzanna R, Lindmark L, Frondoza CG. Ginger—an herbal medicinal product with broad anti-inflammatory actions. J Med Food. 2005 Summer;8(2):125–132.

[41]Srivastava KC, Mustafa T. Ginger (Zingiber officinale) in rheumatism and musculoskeletal disorders. Med Hypotheses. 1992 Dec;39(4):342–348.

[42]Choi JH, Chai YM, Joo GJ, Rhee IK, Lee IS, Kim KR, Choi MS, Rhee SJ. Effects of green tea catechin on polymorphonuclear leukocyte 5¯-lipoxygenase activity, leukotriene B4 synthesis, and renal damage in diabetic rats. Ann Nutr Metab. 2004;48(3):151–155. Epub 2004 May 6.

[43]Ahmed S, Rahman A, Hasnain A, Lalonde M, Goldberg VM, Haqqi TM. Green tea polyphenol epigallocatechin-3-gallate inhibits the IL-1 beta-induced activity and expression of cyclooxygenase-2 and nitric oxide synthase-2 in human chondrocytes. Free Radic Biol Med. 2002 Oct 15;33(8):1097–1105.

[44]Wheeler DS, Catravas JD, Odoms K, Denenberg A, Malhotra V, Wong HR. Epigallocatechin-3-gallate, a green tea-derived polyphenol, inhibits IL-1 beta-dependent proinflammatory signal transduction in cultured respiratory epithelial cells. J Nutr. 2004 May;134(5):1039–1044.

[45]Urano T, Ihara H, Umemura K, Suzuki Y, Oike M, Akita S, Tsukamoto Y, Suzuki I, Takada A. The profibrinolytic enzyme subtilisin NAT purified from Bacillus subtilis Cleaves and inactivates plasminogen activator inhibitor type 1. J Biol Chem. 2001 Jul 6;276(27):24690–24696. Epub 2001 Apr 26.

[46]Fujita M, Hong K, Ito Y, Fujii R, Kariya K, Nishimuro S. Thrombolytic effect of nattokinase on a chemically induced thrombosis model in rat. Biol Pharm Bull. 1995 Oct;18(10):1387–1391.

[47]Suzuki Y, Kondo K, Ichise H, Tsukamoto Y, Urano T, Umemura K. Dietary supplementation with fermented soybeans suppresses intimal thickening. Nutrition. 2003 Mar;19(3):261–264.

[48]Suzuki Y, Kondo K, Matsumoto Y, Zhao BQ, Otsuguro K, Maeda T, Tsukamoto Y, Urano T, Umemura K. Dietary supplementation of fermented soybean, natto, suppresses intimal thickening and modulates the lysis of mural thrombi after endothelial injury in rat femoral artery. Life Sci. 2003 Jul 25;73(10):1289–1298.

[49]Mazzone A, Catalani M, Costanzo M, Drusian A, Mandoli A, Russo S, Guarini E, Vesperini G. Evaluation of Serratia peptidase in acute or chronic inflammation of otorhinolaryngology pathology: A multicentre, double-blind, randomized trial versus placebo. J Int Med Res. 1990 Sep–Oct;18(5):379–388.

21

IODINE, A CRITICALLY OVERLOOKED NUTRIENT

Iodine is a trace element required by the body for an increasing number of identified physiologic functions. This element belongs to the halogen family of elements, a group of highly reactive nonmetals that includes fluorine, chlorine, bromine, and astatine. Iodine is found naturally in large amounts in seafood, such as kelp and saltwater fish. Most iodine intake in the United States is from iodized table salt. Iodation of salt in the United States began in the 1920s in response to the large number of goiters in certain populations in areas where soil and water levels of iodine were low. The upper Midwest and Great Lakes region, where the incidence of goiter was as high as 30%–40% in 1922, was named the "goiter belt."[1] Currently, the recommended daily allowance (RDA) of iodine for adults is 150 mg per day, for pregnant women it is 220 mg per day, and for lactating women it is 290 mg per day; although some studies indicate that Americans' iodine intake is adequate, many other studies suggest a prevalence of subclinical iodine deficiency. In this regard, it is worth considering that although many Americans consume large amounts of sodium in processed foods, many such foods do not use the iodized form of salt, and even if they do, research suggests that only 10% of the iodide in iodized salt is bioavailable.[2] Moreover, with cautionary recommendations that Americans limit their sodium intake, an adequate intake of iodine is of concern because iodine deficiency is associated with numerous abnormalities including hypothyroidism, goiter, cretinism, cognitive disorders, neurological disorders, and breast disease. Iodine deficiency is especially hazardous in pregnant women, developing fetuses, and newborn infants because of its ability to cause irreversible damage to fetuses and newborns. The World Health Organization (WHO) has established that the mean urine iodine concentration should exceed 10 mg=dL, and should be less than 5 mg=dL in no more than 20% of a population. The National Health and Nutrition Examination Surveys (NHANES), which periodically measure urine iodine concentrations to evaluate iodine status in the United States, indicate that iodine intake is adequate. Moreover, because the adult RDA for iodine is 150 mg per day, and goiter is controlled with only 0.05 mg of iodide per day, many scientists believe that iodine intake is sufficient. However, between NHANES I (1971–1974) and NHANES III (1988–1994), Americans' median urine iodine concentration decreased by 50%, while a low urine excretory level of iodine of less than 5 mg=dL increased by 4.5-fold in this same period. Monitoring of high-risk groups showed that 6.7% of pregnant women and 14.9% of women of childbearing age had a urine excretory level of less than 5 mg=dL of iodine.[3] The most recent NHANES (NHANES IV: 2001–2002) indicated that the mean urine excretory level of iodine has stabilized since NHANES III.[4]

THE RDA FOR IODINE

The suggested daily RDA of 150 mg per day for iodine may be influenced by the fear that an excess of iodine can cause diseases including hyperthyroidism, hypothyroidism, goiter, rashes, and iodine allergy. However, most of these reactions are caused by pharmacologic doses of iodine. Some research has linked iodine excess to autoimmune thyroid disease, which can cause both hypo- and hyperthyroidism,[5,6] but such autoimmune disease has been increasing

during the same period in which iodine intake has been decreasing in the United States.[7] A high intake of iodine, largely in the form of seaweed, is also typical in the Japanese population, which has generally good overall health. Research has found that the typical Japanese diet has a daily intake of elemental iodine ranging as high as 13.8 mg.[8] Historically, physicians have prescribed iodine in a dose of 0.1–0.3 mL of Lugol's solution, a 5% solution containing 50 mg of iodine and 100 mg of potassium iodide per milliliter, thus providing 12.5–37.5 mg of the elemental iodine needed to treat iodine-deficiency disorders and promote overall well-being.[8,9] In order to minimize the risk of reactivity to iodine, assays of thyroid function should be done before supplementation with iodine is undertaken in any patient.

Perchlorate inhibits thyroid function by inhibiting iodine uptake by the thyroid at doses of 200 mg per day or more.

METABOLISM OF IODINE

Iodide is removed from circulating blood primarily by the thyroid gland and kidneys. The body can also concentrate iodide in the salivary glands, breast tissue, gastric mucosa, and choroid plexus, among other sites. Sodium=iodide transporters—protein molecules also known as ''symporters''—take up iodide from the blood into the thyroid gland across a concentration gradient that may be as high as 50-fold, and concentrate the iodide in the cells of the gland to a level adequate for hormone synthesis. This iodide is incorporated into precursors that are transformed into thyroxine, or T4, a hormone secreted primarily by the thyroid, which is converted in peripheral tissues to the hormone triiodothyronine (T3), which regulates growth and cellular metabolism. Because the enzyme responsible for the conversion of T4 to T3 is selenium-dependent, selenium deficiency decreases this conversion. The average adult thyroid gland in an iodine-sufficient area contains 15 mg of iodine.[10,11]

IODINE DEFICIENCY

An enlarged thyroid, or goiter, is the most overt sign of iodine deficiency. Hypothyroidism from iodine deficiency presents with a decrease in T3 and T4 and an increase in thyroid-stimulating hormone (TSH), thyroglobulin, and reverse T3, an inactive form of thyroid hormone generated by the removal of an iodine group from thyroxine. Symptoms of hypothyroidism include fatigue, dry skin, hair loss, weight gain, cognitive impairment, and depression. Several factors can cause iodine deficiency. As already noted, low levels of iodine in the soil or water in particular areas may cause this deficiency, as may salt-restrictive diets. Intake of large amounts of cruciferous vegetables, cassava, millet, and soya flour is another source of iodine deficiency through the goitrogenic substances such as C-glycosylflavones (C-GFs), glucosinolates, and isoflavones, and this will also affect thyroid function. Additionally, vitamin A and iron deficiency, as well as the selenium deficiency noted earlier, can exacerbate iodine deficiency.[10] Intake of particular elements that compete with iodine for uptake and utilization, such as chlorine, fluorine, and bromine, may also be a factor.

DIAGNOSIS OF IODINE DEFICIENCY

Studies indicate that 90% of ingested iodine is eventually excreted in the urine. According to the WHO, median urine iodine levels should exceed 10 mg=dL in ''iodine sufficient'' populations. Iodine deficiency is commonly identified by measuring urinary iodine excretion. Urinary iodine excretion may also be expressed in relation to creatinine excretion, as mg of iodine per g of creatinine. Levels of thyroxine, TSH, thyrotropin, and thyroglobulin have also been measured as indicators of the adequacy of in vivo iodine concentrations, and some investigators believe that measuring thyroglobulin is a more accurate indicator of such concentrations than is measuring urine iodine levels.[12] Other researchers have reported that measurements of TSH and T4 are inaccurate indicators of iodine adequacy in ''iodine-sufficient'' populations.[13] The Iodine Loading test may also be used measuring 24-hour urinary excretion after a 50 mg iodine load.

BROMINE

Halogens other than iodine are important factors in health because they can displace iodine in physiologic reactions. Bromine has replaced iodine for use as a dough softener in bread making, and is also an environmental contaminant found in both food and water. Studies of thyroid function in rats indicate that with increased intake, bromine replaces iodine in this organ.[14] Animal studies also suggest that in the presence of an iodine-deficient state, bromine may induce hypothyroid symptoms of decreased thyroxine synthesis and increased thyroid gland size, as well as decreasing iodine concentrations in the skin.[14] Studies with pregnant and lactating rats have demonstrated that increased bromine intake decreases the iodine content of mammary tissue, decreases T4 in both mothers and offspring, and decreases the body weight of offspring. Bromine also increases the renal excretion of iodine in these animals.[14] Treating rats with bromine has been shown to induce goiter and decrease the thyroid iodine concentration, while supplementation with iodine and selenium has been found to reduce by 50% the amount of bromine taken up by the thyroid as compared to that in rats without such supplementation.[15]

CHLORINE-CONTAINING ANIONS

Perchlorate, an environmental contaminant, is a known competitive inhibitor of the iodine= sodium symporter and decreases thyroid function by inhibiting iodine uptake by the thyroid at doses of 200 mg per day or more.[16] Perchlorate is found in fireworks, explosives, and solid jet and rocket fuel, and is a contaminant found in some fertilizers. Perchlorate is often consumed in plants such as lettuce and leafy greens, drinking water, and milk, generally accumulated from contaminated groundwater. Studies have found that the majority of dairy milk samples and all samples of breast milk tested contained perchlorate. A recent study demonstrated a mean perchlorate level in breast milk of 10.5 mg=L, suggesting that the average breastfed infant consumes more than twice the recommended maximum daily level of perchlorate established by the National Academy of Sciences.[17] Studies of perchlorate levels in drinking water and their relation to diseases in the United States have provided conflicting results. Several studies have measured thyroid hormone values as indicators of the health effects of perchlorate in drinking water, and have found no effect.[18] One study did find a statistically significant increase in newborns' TSH levels in an area where all samples of drinking water were contaminated with

perchlorate, as compared to the TSH levels of newborns in an area without such contamination.[19] Some researchers suggest that the combination of perchlorate with other competitors of the iodine=sodium symporter, such as nitrates and thiocyanate, as well as the combination of perchlorate with iodine itself, increases the risk of thyroid-related disease.[20] A further study examining the incidence of attention-deficit=hyperactivity disorder (ADHD), autism, and the academic performance of fourth graders in areas with and without perchlorate contamination did not find a statistically significant difference in these conditions in the two groups. However, this study did not take into account the residence locations of mothers at the time of gestation, or their individual perchlorate exposure.[21] Also, one study showed that higher levels of perchlorate excretion were associated with increased levels of TSH and decreased levels of T4 in iodine-deficient women.[22]

Benign, fibrocystic breast disease is associated with iodine deficiency.

FLUORINE

Fluorine, a halogen like bromine and chlorine, is commonly added to drinking water and used as a component of dental products for decreasing the risk of caries. Research on possible effects of fluorine on the thyroid gland has given controversial results. However, some animal studies have shown that increased intake of fluoride can decrease serum T3 and T4 levels in iodine-deficient mice.[23]

IODINE DEFICIENCY AND THYROID DISEASE

Maternal hypothyroidism during pregnancy can result in preeclampsia, miscarriage, early rupture of membranes, abnormal fetal growth, perinatal morbidity, and neonatal death. Early fetal brain development beginning at the 15th week of gestation relies on thyroxine from the mother, and maternal hypothyroidism can produce fetal brain damage, cretinism, and a decreased intelligence quotient. Cretinism, a severe neuropathology caused by iodine deficiency, is marked by gross mental retardation along with varying degrees of shortness of stature, deaf-mutism, and spasticity. Because of decreased iodine retention, preterm infants, in whom renal function is not fully developed, require twice the daily intake of iodine for normal infants. To decrease these risks, the WHO in 2001 suggested an increased iodine intake for infants and an increased iodine content in infant formula.[24]

IODINE DEFICIENCY AND BREAST DISEASE

Besides being important in thyroid function, iodine is required for the normal growth and development of breast tissue. The high level of iodine intake by Japanese women, noted earlier, has been associated with a low incidence of both benign and cancerous breast disease in this population. Evidence links iodine deficiency with an elevated risk of breast, endometrial, and ovarian cancer.[25] Antiproliferative iodolactones in the thyroid may be responsible for this

effect.[26] Although autoimmune antibodies directed against thyroid peroxidase have been associated with a better prognosis in breast cancer,[27] thyroid supplementation may increase the risk of breast cancer[28]—a subject that remains in debate. In vitro studies have found that molecular iodine inhibits induction and proliferation and induces apoptosis in some human breast cancer cell lines, as well as exhibiting antioxidant activity.[29] Benign, fibrocystic breast disease is also associated with iodine deficiency. Blocking of iodine with perchlorate in the mammary tissue of rats has been found to cause histologic changes indicative of fibrocystic breast disease, as well as precancerous lesions.[30] Conversely, iodine supplementation has been shown to ease mastalgia. Supplementation with 3 or 6 mg per day of molecular iodine significantly decreased pain reported by patients, as well as physicians' assessments of pain, tenderness, and nodularity in benign breast disease, with a dose of 6 mg per day providing significant reduction of pain in more than 50% of patients.[31]

IODINE DEFICIENCY AND COGNITIVE AND NEUROLOGIC DISORDERS

T3 and T4 are particularly important for myelination of the developing brain. Hypothyroidism during pregnancy and lactation causes numerous neurologic and cognitive deficits. A study of schoolchildren with mild iodine deficiency found that urine iodine levels above 100 mg=L were associated with significantly higher IQ scores, while levels below 100 mg=L increased the risk of an IQ below 70.[32] The same study also found that consuming noniodized salt and drinking milk less than once daily increased the risk of an IQ below the 25th percentile.[33] Another study found that children from severely iodine-deficient areas had IQ scores that were 12.45 points below average.[33] A small study comparing the prevalence of ADHD in children from a mildly iodine-deficient area and a moderately iodine-deficient area found that 68.7% of those from the latter area had a diagnosis of ADHD, as compared with an absence of this diagnosis in the children from the mildly iodine-deficient area, and that IQ scores were lower in the moderately deficient area. Of the children with ADHD, 63.6% were born to mothers who had become hypothyroxinemic in early gestation.[34] Studies have also suggested that iodine deficiency affects hearing. Children in a mildly iodine-deficient area who had elevated serum thyroglobulin levels had higher auditory thresholds for sound of higher frequencies than did children with lower thyroglobulin levels.[35] Another comparative study examining children from a severely iodine-deficient and a mildly iodine-deficient region found that the former group had lower thyroxine levels, higher TSH levels, lower scores on achievement motivation tests, and were slower learners than the latter group.[36] Research on endemic cretinism from congenital iodine deficiency has shown specific severe neurologic deficits including deaf-mutism and a varying degree of bilateral hearing loss, as well as dysarthria, mental deficiency, spasticity of the proximal lower extremities, rigidity, and bradykinesia. In some cases, strabismus and kyphoscoliosis were also present.[37]

IODINE DEFICIENCY AND GASTRIC CANCER

Iodine deficiency has been linked to an increased risk of gastric carcinoma. One study demonstrated an increased prevalence of gastric cancer and an increased risk of atrophic gastritis in areas with a greater than average prevalence of iodine-deficiency-related goiter. The researchers also reported that competitive inhibitors of intracellular iodine transport, such as

nitrates, thiocyanate, and salt increased the risk of gastric cancer.[38] Another study found a significant correlation between decreased mean urinary iodine levels and prevalence of stomach cancer, as well as a greater frequency of severe iodine deficiency in stomach cancer than in controls.[39] There is also evidence for lower levels of iodine in cancerous gastric tissue than in surrounding normal tissue.[40]

TREATMENT OF IODINE DEFICIENCY

The American Thyroid Association (ATA) recommends that iodine supplementation of 150 mg per day be given to all pregnant and lactating women, and suggests that all prenatal vitamin supplements contain 150 mg of iodine.[41] Based on this recommendation, it may be possible to extrapolate this increased need to the general population. Considering that the consumption of iodine from food sources in Japan exceeds by more than 10-fold the minimally recommended ATA figure for daily iodine intake, there arises the issue of adjusting iodine-intake recommendations to optimal levels, rather than to a level that is marginally sufficient to prevent overt thyroid disease. As with far too many nutrients, the 1940s approach of dosing at marginal levels to prevent ''breakthrough'' disease fails to consider that a specific nutrient, such as iodine, does not have a single limited role, such as preventing goiter.

CONCLUSIONS

Iodine has been used for many other purposes than those named here. It is, for example, still widely used as an antibacterial and antifungal agent and topical antiseptic. One notable use for iodine is radiation exposure. Potassium iodide tablets are often distributed to individuals living near nuclear power plants in case of a radiation-releasing nuclear accident. This is because immediate supplementation with potassium iodide will block the absorption of radioactive iodide into the thyroid gland.

Iodine deficiency is a worldwide concern with serious consequences to health. Although endemic goiter is decreasing, overt iodine deficiency continues to exist in some areas. With the increased presence of other halogens in food and water supplies, relative iodine deficiency is a growing concern. Perhaps with increasing knowledge of the physiologic functions that require iodine, it will be possible to sharpen the definition of an adequate iodine intake. As with vitamin D, folic acid, the omega-3 fatty acids, and other nutrients recognized as deficient in the Western diet, subclinical iodine deficiency may then become a thing of the past. We recommend that before supplementation is begun with iodine at levels above those of its dietary intake, testing should be done to rule out thyroid cancer, autoimmune disease, or other thyroid pathology; this should include testing for iodine saturation, thyroid peroxidase, antithyroglobulin antibodies, TSH, and free T3 and free T4, with thyroid ultrasound examination and other tests as indicated by the patient's clinical presentation.

REFERENCES

[1]Markel H. ''When it rains it pours'': Endemic goiter, iodized salt, and David Murray Cowie, M.D. Am J Public Health. 1987;77:219–229.

[2]Abraham GE. The concept of orthoiodosupplementation and its clinical implications. Original Internist. 2004;11:29–38.

[3]Hollowell JG, Staehling NW, Hannon WH, et al. Iodine nutrition in the United States: Trends and public health implications. Iodine excretion data from National Health and Nutrition Examination Surveys I and III (1971–1974 and 1988–1994). J Clin Endocrinol Metab. 1998;83:3401–3408.

[4]Blackburn GL. National Health and Nutrition Examination Survey: Where nutrition meets medicine for the benefit of health. Am J Clin Nutr. 2003;78:197–198.

[5]Prummel MF, Strieder T, Wiersinga WM. The environment and autoimmune thyroid diseases. Eur J Endocrinol. 2004;150:605–618.

[6]Zois C, Stavrou I, Svarna E, et al. Natural course of autoimmune thyroiditis after elimination of iodine deficiency in northwestern Greece. Thyroid. 2006;16:289–293.

[7]Abraham GE, Flechas JD, Hakala JC. Orthoiodosupplementation: Iodine sufficiency of the whole human body. Original Internist. 2002;9:30– 41.

[8]Abraham GE, Brownstein D. A rebuttal of Dr. Gaby's editorial on iodine. Townsend Letter for Doctors & Patients, October 2005. Online document at: www.townsendletter.com/Oct2005/gabyrebuttal1005.htm. Accessed April 1, 2007.

[9]Jamieson A, Semple CG. Successful treatment of Graves' disease in pregnancy with Lugol's iodine. Scott Med J. 2000;45:20–21.

[10]National Academies Press. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. 2000. Online document at: www.nap.edu/openbook.php?record_id=10026&page=268. Accessed on April 1, 2007.

[11]Gaitan E, Cooksey RC, Legan J. Antithyroid effects in vivo and in vitro of vitexin: A C-glucosylflavone in millet. J Clin Endocrinol Metab. 1995;80:1144–1147.

[12]Simsek E, Safak A, Yavuz O, et al. Sensitivity of iodine deficiency indicators and iodine status in Turkey. J Pediatr Endocrinol Metab. 2003;16:197–202.

[13]Soldin OP, Tractenberg RE, Pezzullo JC. Do thyroxine and thyroid-stimulating hormone levels reflect urinary iodine concentrations? Ther Drug Monit. 2005;27:178–185.

[14]Pavelka S. Metabolism of bromide and its interference with the metabolism of iodine. Physiol Res. 2004;53(suppl.1):S81–S90.

[15]Kotyzova D, Eybl V, Mihaljevic M, Glattre E. Effect of long-term administration of arsenic (III) and bromine with and without selenium and iodine supplementation on the element level in the thyroid of rat. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2005;149:329–333.

[16]Crump C, Michaud P, Tellez R. Does perchlorate in drinking water affect thyroid function in newborns or school-age children? J Occup Environ Med. 2000;42:603–612.

[17]Kirk AB, Martinelango PK, Tian K, et al. Perchlorate and iodide in dairy and breast milk. Environ Sci Technol. 2005;39:2011–2017.

[18]Li Z, Li FX, Byrd D, et al. Neonatal thyroxine level and perchlorate in drinking water. J Occup Environ Med. 2000;42:200–205.

[19]Brechner RJ, Parkhurst GD, Humble WO, et al. Ammonium perchlorate contamination of Colorado River drinking water is associated with abnormal thyroid function in newborns in Arizona. J Occup Environ Med. 2000;42:777–782.

[20]De Groef B, Decallonne BR, Van der Geyten S, et al. Perchlorate versus other environmental sodium= iodide symporter inhibitors: Potential thyroid-related health effects. Eur J Endocrinol. 2006;155:17–25.

[21]Chang S, Crothers C, Lai S, Lamm S. Pediatric neurobehavioral diseases in Nevada counties with respect to perchlorate in drinking water: An ecological inquiry. Birth Defects Res [A] Clin Mol Teratol. 2003;67:886–892.

[22]Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, Caldwell KL. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environ Health Perspect. 2006 Dec;114(12):1865–1871.

[23]Zhao W, Zhu H, Yu Z, et al. Long-term effects of various iodine and fluorine doses on the thyroid and fluorosis in mice. Endocr Regul. 1998;32:63–70.

[24]World Health Organization and Food and Agriculture Organization Vitamin and Mineral Requirements in Human Nutrition, 2nd Edition. 2004. Online document at: http:=whqlibdoc.who.int=publications=2004=9241546123_chap16.pdf. Accessed April 1, 2007.

[25]Stadel BV. Dietary iodine and risk of breast, endometrial, and ovarian cancer. Lancet. 1976;1:890–891.

[26]Aceves C, Anguiano B, Delgado G. Is iodine a gatekeeper of the integrity of the mammary gland? J Mammary Gland Biol Neoplasia. 2005;10:189–196.

[27]Smyth PP. The thyroid, iodine and breast cancer. Breast Cancer Res. 2003;5:235–238.

[28]Kapdi CC, Wolfe JN. Breast cancer: Relationship to thyroid supplements for hypothyroidism. JAMA. 1976;236:1124–1127.

[29]Shrivastava A, Tiwari M, Sinha RA. Molecular iodine induces caspase-independent apoptosis in human breast carcinoma cells involving the mitochondria-mediated pathway. J Biol Chem. 2006;281:19762–19771. Epub 2006 May 5.

[30]Eskin BA, Shuman R, Krouse T, Merion JA. Rat mammary gland atypia produced by iodine blockade with perchlorate. Cancer Res. 1975;35:2332–2339.
[31]Kessler JH. The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. Breast J. 2004;10:328–336.
[32]Santiago-Fernandez P, Torres-Barahona R, Muela-Martinez JA, et al. Intelligence quotient and iodine intake: A cross-sectional study in children. J Clin Endocrinol Metab. 2004;89:3851–3857.
[33]Qian M, Wang D, Watkins WE, et al. The effects of iodine on intelligence in children: A meta-analysis of studies conducted in China. Asia Pac J Clin Nutr. 2005;14:32–42.
[34]Vermiglio F, Lo Presti VP, Moleti M, et al. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild–moderate iodine deficiency: A possible novel iodine deficiency disorder in developed countries. J Clin Endocrinol Metab. 2004;89:6054–6060.
[35]van den Briel T, West CE, Hautvast JG, Ategbo EA. Mild iodine deficiency is associated with elevated hearing thresholds in children in Benin. Eur J Clin Nutr. 2001;55:763–768.
[36]Tiwari BD, Godbole MM, Chattopadhyay N, et al. Learning disabilities and poor motivation to achieve due to prolonged iodine deficiency. Am J Clin Nutr. 1996;63:782–786.
[37]DeLong GR, Stanbury JB, Fierro-Benitez R. Neurological signs in congenital iodine-deficiency disorder (endemic cretinism). Dev Med Child Neurol. 1985;27:317–324.
[38]Venturi S, Venturi A, Cimini D, et al. A new hypothesis: Iodine and gastric cancer. Eur J Cancer Prev. 1993;2:17–23.
[39]Behrouzian R, Aghdami N. Urinary iodine=creatinine ratio in patients with stomach cancer in Urmia, Islamic Republic of Iran. East Mediterr Health J. 2004;10:921–924.
[40]Gulaboglu M, Yildiz L, Celebi F, et al. Comparison of iodine contents in gastric cancer and surrounding normal tissues. Clin Chem Lab Med. 2005;43:581–584.
[41]Becker DV, Braverman LE, Delange F, et al. Iodine supplementation for pregnancy and lactation—United States and Canada: Recommendations of the American Thyroid Association. Thyroid. 2006;16: 949–951.

22

NATURAL THERAPIES TO PRESERVE AND ENHANCE COGNITION AND MEMORY

For many patients, one of the most disturbing prospects of aging is the possibility of a decreasing ability to recall desired memories and comprehend new information and stimuli. This is understandably a very real concern considering the reports that in 2007, there are now more than 5 million people in the United States living with Alzheimer's disease, and it is estimated that the prevalence could reach 7.7 million people with this disease by 2030. Alzheimer's disease is the seventh leading cause of death in the United States and the fifth leading cause of death for individuals over the age of 65. Additionally, the direct and indirect costs of Alzheimer's disease and other dementias amount to more than $148 billion annually.[1] It is safe to estimate that less-severe mental deterioration is substantially more prevalent. This chapter explores some of the simplest interventions, such as modest dietary changes and botanical and supplemental interventions. Essential to maintaining cognitive ability is adhering to a long-term health maintenance plan that can be sustained over the course of a lifetime; thus, a simple and high-compliance preventive approach is of paramount importance.

WISE DIETARY CHOICES

The most crucial consideration when devising a comprehensive health intervention is understanding how to prevent or slow the degenerative process best. Without question, dietary factors constitute the single most important preventive focus. In one prospective study, 586 participants without clinical symptoms of dementia, age 55 or older, had their diets assessed at the beginning of the study and were screened for symptoms of dementia an average of two years later.[2] After adjusting for other factors, such as age, gender, and education, subjects with the highest total fat intake had a significantly elevated relative risk (RR) of dementia (RR 2.4[1.1–5.2]). Other dietary factors associated with an increased risk of dementia were a high intake of saturated fat (RR 1.9 [0.9–4.0]) and cholesterol (RR 1.7 [0.9–3.2]). An encouraging finding was that a high intake of fish was associated with a significantly lower risk of dementia in general (RR 0.4 [0.2–0.91]) and was particularly associated with a lower risk of the dementia of Alzheimer's disease (RR 0.3 [0.1–0.9]). Several other epidemiologic studies produced similar findings.[3,4] Current research supports a free-radical-based theory of cognitive decline that is supported by data suggesting that foods that are rich in antioxidants, such as strawberries and spinach, and supplemental vitamin E, retards the age-related onset of cognitive deficits.[5] It is also noteworthy that, in individuals 65 and older (a population facing an ever-increasing risk of dementia), higher beta-carotene and vitamin C levels have been shown to correlate with enhanced memory performance.[6] Thus, following a diet rich in whole foods and emphasizing fresh fruits and vegetables provides the low fat and antioxidant abundance protection essential for sustained cognitive function and overall enhanced longevity.

A small randomized, crossover, nonblinded study in patients with Alzheimer's disease examined the effect of increasing the amount of carbohydrates with meals, without changing the protein intake. The results showed poorer memory, and increased aberrant motor behavior with the increased carbohydrate intake.[7] Research has also examined the Mediterranean diet and the risk of Alzheimer's disease. The results indicate that higher adherence to the Mediterranean diet was associated with lower risk for Alzheimer's disease, and the association does not seem to be mediated by vascular comorbidity.[8] In addition, a literature review showed that high energy intake of monounsaturated fatty acids appeared to be associated with a high level of protection against age-related cognitive decline, fish consumption and cereals are found to reduce the prevalence of Alzheimer's disease, and the relative risk of dementia was lower in subjects who drank three or four glasses of red wine each day compared with total abstainers.[9]

In both animal and clinical research, a combination of ginseng with ginkgo seems to hold promise.

It should also be noted that some clinicians believe that following a low-calorie diet that provides a wide array of fresh fruits and vegetables can lessen oxidative damage to the central nervous system, thus slowing cognitive decline. This area of research shows some promise; yet, as with all dietary modifications, finding the appropriate balance between therapeutic goals and sustained wellness can be challenging. Calorie restriction has shown to prevent amyloid beta-peptide generation and neuritic plaque deposition in the brain of a mouse model of Alzheimer's disease neuropathology suggesting it may be beneficial in preventative measures aimed at delaying the onset of Alzheimer's disease amyloid neuropathology.[10]

Dietary and Botanical Strategies for Supporting Healthy Cognition

Dietary considerations

- Total fat intake limited, especially saturated fat
- Cholesterol intake should be controlled
- At least 2–3 servings of fish per week
- 4–5 daily servings of foods that are rich in antioxidants, especially fresh fruits and vegetables

Botanical supports

- Quality extract of Ginkgo biloba,[a] 240 mg per day, if taken alone or 120 mg per day if taken with 200 mg per day of Panax ginseng
- Huperzine A, 200 mg, 2 times per day

[a]Use of ginkgo should be stopped prior to surgery to prevent bleeding. Patients should tell physicians about taking ginkgo for this reason.

SUPPORTIVE BOTANICAL MEDICINES

Ginkgo

If additional interventions to maintain cognition become warranted, one of the first considerations, and by far the most popular one, is ginkgo (Ginkgo biloba). It is by way of various mechanisms of action, perhaps most notably inhibition of lipid peroxidation, that ginkgo may help to preserve, and to some extent restore, healthy cognition. Extracts of ginkgo have been shown to act as free-radical scavengers, preventing induced lipid peroxidation of neural tissue under several experimental conditions.[11,12] A review of the literature also suggests that additional actions, such as a relaxing effect on vascular walls, inhibition of platelet-activating factor, enhancement of microcirculation, and stimulation of neurotransmitters,[13] could all contribute to ginkgo being a multifaceted therapeutic agent for patients with dementia (see the box below entitled ''How Ginkgo biloba Supports Cognition'').

In the context of already existing dementia, botanical medicines may prove to be some of the most effective treatment options available.

It would be remiss, however, not to acknowledge that, while many trials show benefit with the use of ginkgo,[14,15] there are notable exceptions. A 24-week trial failed to show any benefit of ginkgo for more than 200 elderly subjects with dementia.[16] Such results stand in sharp contrast to those of other trials, such as a year-long study of more than 300 subjects with dementia who received only 120 mg of an extract of this herb and who manifested stabilized or even improved cognitive performance for six months to a year during the study.[17] In such situations, when data from peer-reviewed sources seem to disagree, it is important to remember that many factors may combine to skew the data of one, or even several studies, in a particular direction. A recent review of the ginkgo literature points out that discrepancies between results of one study and another may be the result of factors such as the study population used, the outcome measures utilized, the duration of treatment, and the dosing regimen of the subjects.[18] Additionally, many of the studies utilize a particularly potent form of ginkgo, EGb 761, which is a standardized extract of dried leaves containing 24% ginkgo-flavonol glycosides, 6% terpene lactones such as ginkgolides A, B, C, J and bilobalide. Thus, variations in study outcomes may be related to the potency and form of ginkgo used in the trials. Generally, the literature seems to support the benefit of ginkgo extract for subjects with dementia. Also, equally important is that, clinically, ginkgo has repeatedly demonstrated itself to be an effective and safe intervention.

How Ginkgo biloba Supports Cognition

- Inhibition of free-radical damage to lipid neural tissue
- Inhibition of platelet-activating factor
- Relaxation of vascular walls
- Increase in local blood flow
- Increase in neurotransmitter activity

In addition to senior subjects with dementia, however, there is also evidence that ginkgo extract may enhance memory for those who are younger. In a smaller study of 20 subjects, volunteers were given 120 mg, 240 mg, or 360 mg of Ginkgo biloba extract or a placebo. A series of computerized tests was then done to assess speed and accuracy of attention and speed and quality of memory. The most striking change was a dose-dependent improvement in the speed of attention that was apparent at both 240 mg and 360 mg after 2.5 hours and was still present after 6 hours. While this was a small study, it is encouraging that the botanical was effective enough to produce a dose-dependent response.[19] Additionally, a study with 262 cognitively intact patients age 60 and older participated in a six-week, randomized, double-blind, fixed-dose, placebo-controlled, parallel-group, clinical trial with 180 mg per day of Ginkgo biloba. The treatment group showed significantly more improvement on the Selective Reminding Test tasks involving delayed (30 minutes) free recall and recognition of non-contextual, auditory-verbal material, compared with the placebo group. The treatment group also demonstrated significantly greater improvement on the Wechsler Memory Scale-III and Faces II subtest assessing delayed (30 minutes) recognition of visual material (i.e., human faces), compared with the placebo group. In addition, the subjective ratings of overall ability to remember improved significantly in the Ginkgo supplemented group.[20]

Ginseng

Another botanical that may be helpful for cognitive support, in combination with ginkgo, is ginseng (Panax ginseng). The biologic effects of the various constituents of ginseng are complex: While one of its phytochemicals shows affinity for the nicotinic acid receptor,[21] a receptor for which reduced stimulation is associated with cognitive decline, another of its phytochemicals blocks this receptor.[22] However, in both animal and clinical research, a combination of ginseng with ginkgo seems to hold promise. In rats, for example, a ginkgo=ginseng combination was shown to enhance the learning ability of both older and younger rats.[23] A recent double-blind, placebo-controlled trial of more than 250 human subjects over a 14-week period has been reported. In this study, subjects' cognition=memory were assessed every 4 weeks using a number of standard scales and questionnaires. Overall, there was significant improvement (mean 7.5%) in subjects who received the botanical combination (120 mg per day of ginkgo and 200 mg per day of ginseng), including gains in working and long-term memory.[24] A double-blind, placebo-controlled, balanced-crossover study with 27 healthy young adults examined the effects of ginseng with cognitive-demanding tests. The results showed that Panax ginseng supplementation enhanced performance of a mental arithmetic task and ameliorated the increase in subjective feelings of mental fatigue experienced by the participants during the later stages of the sustained, mentally demanding tasks.[25] In a similar placebo-controlled, double-blind, balanced, crossover design study, 20 healthy young adults received 200, 400, or 600 mg of Panax ginseng, with a seven-day wash-out period between treatments. The results showed a significant improvement in ''Quality of Memory'' and the associated ''Secondary Memory'' factor at 1, 2.5, 4, and 6 hours after the day's treatment following 400 mg of ginseng.[26]

Club Moss

One of the chemicals found in a rare club moss (Huperzia serrata), huperzine A, has been studied in China for its effects on memory, cognition, and behavior in patients with Alzheimer's disease. Huperzine A inhibits acetylcholinesterase, protects cells against beta-amyloid

protein, hydrogen peroxide, glutamate, ischemia, and staurosporine-induced cytotoxicity and apoptosis. These protective effects are due to the ability of huperzine A to attenuate oxidative stress, regulate the expression of apoptotic proteins, protect mitochondria, up-regulate nerve growth factor and its receptors, and interfere with amyloid precursor protein metabolism.[27] Three double-blind trials enrolling a total of more than 450 people indicated that huperzine A can significantly improve symptoms of Alzheimer's disease and other forms of dementia.[28–30]

Periwinkle

Vinpocetine is another cognitive enhancer. It is derived from vincamine, a constituent of common periwinkle (Vinca minor). One study investigated 12-week oral vinpocetine therapy and blood flow parameters in patients with ischemic stroke and mild cognitive impairment both in resting conditions or following chemical stimulus, as well as the severity of mental deterioration. The results showed that vinpocetine treatment increased the blood flow velocity in resting conditions compared to baseline in the vascular group. The percent increase of mean velocity after the breath holding transcranial Doppler test showed a significant increase compared to the baseline in both ischemic stroke and mild cognitive impairment groups after 12 weeks of vinpocetine supplementation. Also, there was both objective and subjective significant improvement of cognitive functions with vinpocetine supplementation.[31] Meta-analysis of three studies involving a total of 583 people with dementia treated with vinpocetine or a placebo showed benefit with treatment of vinpocetine 30 mg per day and 60 mg per day compared with a placebo.[32]

KEY NUTRIENTS AND SUPPLEMENTS

Table 22–1 on page 254 summarizes recommended dosages for the nutrients discussed next. It is assumed that the practitioner will draw upon personal experience and familiarity with the individual nutrients in planning treatment. Regular consumption of one to two of the nutrients could help to prevent loss of mental function, whereas three to four nutrients might be more appropriate to slow loss that has already begun, and three to five nutrients might be needed to address substantial loss.

Acetyl-L-Carnitine

One nutritional supplement that has been studied extensively for the treatment of dementia is acetyl-L-carnitine, which is believed to be a precursor for the synthesis of acetylcholine. In one double-blind study, typical of other similar trials, half of 60 subjects with mild dementia were treated with 2 g per day of acetyl-L-carnitine and half received a placebo for three months. When subjects were assessed, using scales of behavior, memory, attention, and verbal fluency, there was significant improvement in the group receiving the acetyl-L-carnitine.[33] Several other studies also suggest positive findings, indicating that acetyl-L-carnitine may be helpful in slowing the progression of Alzheimer's disease and in improving cognitive function in patients with this disorder.[34,35]

Enthusiasm for acetyl-L-carnitine may be tempered somewhat, however, by several year-long trials showing less-promising results. In the first of these trials, with more than 350

patients completing treatment consisting of 3 g per day of acetyl-L-carnitine for one year, a trend was seen toward a slower progression of Alzheimer's disease symptoms. However, the trend was only seen in subjects who were under 65, while older subjects who were given acetyl-L-carnitine might actually have experienced a more rapid progression of their symptoms.[36] In an additional study of several hundred subjects under 65 with onset of Alzheimer's disease, treatment with 3 g per day of acetyl-L-carnitine for one year, again, did not slow decline.[37] While it is difficult to understand completely why some studies show positive results and others do not, it may be that, for early-onset cases of Alzheimer's dementia, a short-term treatment protocol might offer some slowing of the progressing dementia. If there is even some improvement clinically, such a course seems justified within the context of the progressing and debilitating dementia of Alzheimer's disease.

Phosphatidylserine and Choline

Phosphatidylserine (PS) is a glycerophospholipid that is an important component of cell membranes. It has been shown to increase acetylcholine, norepinephrine, serotonin, and dopamine levels in patients with Alzheimer's disease. While some work suggests that 300 mg of PS in divided doses might help to improve cognition in dementia of the Alzheimer's type,[38] other work seems to be less encouraging.[39] In this context, perhaps one of the most important studies is one in which subjects who took supplemental PS were assessed by several techniques, including neuropsychologic testing, monitoring their cerebral metabolism of glucose, and measuring electroencephalograms over the course of six months. While improvements were noted during the study, it is interesting that the improvement was most noticeable at 8 and 16 weeks and that the improvement faded toward the end of the six-month study. Thus, it may be important to bear in mind that this therapy might offer only short-term instead of long-term benefit for patients with Alzheimer's dementia. What is noteworthy is that the variance seen among studies of PS could have been caused, in part, by the origin of the PS. The original studies used animal-tissue derivatives, which have a very different fatty-acid composition than PS from soy, which is used more typically by many clinicians and researchers today. An important concern about using animal-derived PS in the current research and clinical environment is the risk of exposing patient populations to prion-infected material.

Choline is of interest and has been studied in the treatment of Alzheimer's disease because it is a precursor to acetylcholine. In a double-blind, randomized, placebo-controlled trial, patients affected by mild to moderate dementia of the Alzheimer type were treated with the cholinergic precursor choline alfoscerate at a dose of 400 mg three times daily for 180 days. According to the Mini-Mental State Examination, Global Deterioration Scale, Alzheimer's Disease Assessment Scale-Behavioral Subscale, Alzheimer's Disease Assessment Scale, and Clinical Global Impression, the choline alfoscerate supplemented group consistently improved after 90 and 180 days versus baseline, whereas in the placebo group they remained unchanged or worsened.[40]

Dimethylaminoethanol

Dimethylaminoethanol (DMAE) is a naturally occurring substance that has been studied as a possible anti-aging therapy that improves cognitive function. DMAE is the precursor to choline and may increase acetylcholine levels.[41] DMAE inhibits production of the age-related pigment lipofuscin, which accumulates in all aging tissues. This is significant because cells with

Table 22–1. Supplements for Cognitive Support

Supplement	Dosing
Acetyl-L-carnitine	1 g 3 times per day[a]
Phosphatidylserine	200 mg, 2 times per day
Mixed vitamin E	800–1,200 IU per day, under close supervision
Vitamin C with bioflavonoids	1,000–2,000 mg per day
Vitamin B complex	100 mg 2 times per day
Methylcobalamin	2,000 mg per day sublingually
Folic acid[b]	800 mg per day orally

[a]It is advisable to limit use to patients who are under 65 years old.
[b]Because folic acid can mask the symptoms of vitamin B_{12} deficiency, it should always be taken with vitamin B_{12}.
IU international unit.

increased lipofuscin cause lysosomes to perform poorly, which leads to increased accumulation of poorly functioning mitochondria and increased ROS production.[42] Evidence also suggests that DMAE decreases the extent of cross-linking of proteins possibly by acting as a free-radical scavenger.[43]

One potentially emerging biomarker for risk of Alzheimer's disease could be blood levels of homocysteine.

Vitamin B_{12} and Folic Acid

One potentially emerging biomarker for risk of Alzheimer's disease could be blood levels of homocysteine. In a study of 164 patients with clinical diagnoses of dementia of the Alzheimer's type and 108 controls, the patients with Alzheimer's disease had significantly higher levels of total homocysteine and significantly lower levels of serum vitamin B_{12} and folate compared to controls.[44] In addition, a follow-up for three years of the subjects with Alzheimer's disease showed a correlation between the progression of the disease measured radiographically and the level of homocysteine seen at the beginning of the study. Additional studies have shown that higher folate intake may decrease the risk of Alzheimer's disease independent of other risk factors and levels of vitamins B_6 and B_{12}.[45] Such research may underscore the importance of maintaining a healthy vasculature throughout the whole body. Indeed, as we learn more about the involvement of vascular health as it relates to dementia, we may begin to see that cardiovascular disease and dementia are varying manifestations of the same underlying, and treatable, deficiencies and imbalances. The same supplemental vitamin B_{12} and folic acid that may curb the chronic inflammation of cardiovascular disease associated with increased homocysteine, may help to support and protect the cerebral vasculature of patients with dementia who also tend to suffer from homocysteinemia.

OTHER CONSIDERATIONS

Also essential to prevent the progression of deterioration of neuronal tissues and vasculature is the consumption of sufficient antioxidants, and supportive nutrients, and the avoidance of free-radical sources. Well-proven antioxidant nutrients, such as vitamin C and vitamin E, should be given strong consideration. In addition, vitamin E has an anti-platelet-aggregation effect assisting in optimal cerebral blood flow and the prevention of occlusive strokes and impedance of optimal blood flow. General support for nervous-system function including optimal cognition also depends on sufficient levels of each of the B vitamins to support neurotransmitter production and function. Finally, as conventional approaches to prevention of dementia have continued to focus on the use of anti-inflammatory agents such as COX-2 inhibitors, the practitioner may find that eicosapentaenoic acid from fish oil is helpful as adjunctive therapy.

CONCLUSIONS

As with degenerative disorders, the causes of decreasing cognitive prowess and dementia are certainly multifactorial. When focusing on the dementia of Alzheimer's disease specifically, epidemiologic evidence highlights as probable risk factors a diet high in total fat, saturated fat, and cholesterol, and suggests that an increased consumption of fish is associated with a decreased risk. In the context of already existing dementia, botanical medicines, such as Ginkgo biloba and Panax ginseng, especially when combined, may prove to be some of the most effective treatment options available. In particular, highly concentrated Ginkgo biloba causes many synergistic actions, such as inhibiting lipid peroxidation, improving microcirculation, and stimulating neurotransmission, which speaks to this plant's ability to tonify neural tissue. While as yet inconsistent, there is sufficient positive literature on several nutrients, namely acetyl-L-carnitine and PS to justify their use, at least over a short time period as a trial. As further research allows us a clearer and broad understanding of dementia, we may find that a combined approach of wise dietary choices and botanical and nutritional interventions increases our chances greatly of maintaining and even increasing cognition and memory throughout the lives of our patients.

REFERENCES

[1]Alzheimer's Disease Facts and Figures 2007. Available at: www.alz.org=national=documents=Report_2007FactsAndFigures.pdf. Accessed November 25, 2007.

[2]Kalmijn S, et al. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol. 1997;42(5):776–782.

[3]Smith MA, Petot GJ, Perry G. Diet and oxidative stress: A novel synthesis of epidemiological data on Alzheimer's disease. Alzheimer Dis Rev. 1997;2:58–59.

[4]Grant WB. Dietary links to Alzheimer's disease. Alzheimer Dis. 1997;Rev 2:42–55.

[5]Joseph JA, et al. Long-term dietary strawberry, spinach, or vitamin E supplementation retards the onset of age-related neuronal signal transduction and cognitive behavioral deficits. J Neurosci. 1998;18(19):8047–8055.

[6]Perrig WJ, Perrig P, Stahelin HB. The relation between antioxidants and memory performance in the old and very old. J Am Geriatr Soc. 1997;45(6):718–724.

[7]Young KW, Greenwood CE, van Reekum R, Binns MA. A randomized, crossover trial of high-carbohydrate foods in nursing home residents with Alzheimer's disease: associations among intervention response, body mass index, and behavioral and cognitive function. J Gerontol A Biol Sci Med Sci. 2005 Aug;60(8):1039–1045.

[8]Scarmeas N, Stern Y, Mayeux R, Luchsinger JA. Mediterranean diet, Alzheimer disease, and vascular mediation. Arch Neurol. 2006 Dec;63(12):1709–1717. Epub 2006 Oct 9.

[9]Panza F, Solfrizzi V, Colacicco AM, D'Introno A, Capurso C, Torres F, Del Parigi A, Capurso S, Capurso A. Mediterranean diet and cognitive decline. Public Health Nutr. 2004 Oct;7(7):959–963.

[10]Wang J, Ho L, Qin W, Rocher AB, Seror I, Humala N, Maniar K, Dolios G, Wang R, Hof PR, Pasinetti GM. Caloric restriction attenuates beta-amyloid neuropathology in a mouse model of Alzheimer's disease. FASEB J. 2005 Apr;19(6):659–661. Epub 2005 Jan 13.

[11]Koc R, Akdemir H, Kurtsoy A, et al. Lipid peroxidation in experimental spinal cord injury: Comparison of treatment with Ginkgo biloba, TRH and methylprednisone. Res Exp Med (Berlin). 1995;195(2):117–123.

[12]Dorman D, Cote L, Buck W. Effects of an extract of Ginkgo biloba on bromethalin-induced cerebral lipid peroxidation and edema in rats. Am J Vet Res. 1992;53(1):138–142.

[13]Yoshikawa T, Naito Y, Kondo M. Ginkgo biloba leaf extract: review of biological actions and clinical applications. Antioxid Redox Signal. 1999;1(4):469– 480.

[14]Gebner B, Voelp A, Klasser M. Study of the long-term action of a Ginkgo biloba extract on vigilance and mental performance as determined by means of quantitative pharmaco-EEG and psychometric measurements. Arzneim-Forsch. 1985;35:1459–1465.

[15]Vorberg, G. Ginkgo biloba extract (GBE): A long-term study of chronic cerebral insufficiency in geriatric patients. Clin Trials J. 1985;22:149–157.

[16]VanDougen JA, et al. The efficacy of ginkgo for elderly people with dementia and age-associated memory impairment: New results of a randomized clinical trial. J Am Geriatr Soc. 2000;48(10):1183–1194.

[17]LeBars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia: North American EGb study Group. JAMA. 1997;278(16):1327–1332.

[18]Le Bars PL, Kastelan J. Efficacy and safety of a Ginkgo biloba extract. Pub Health Nutr. 2000;3(4A): 495– 499.

[19]Kennedy DO, Scholey AB, Wesnes KA. The dose-dependent cognitive effects of acute administration of Ginkgo biloba to healthy young volunteers. Psychopharmacology (Berlin). 2000;151(4):416– 423.

[20]Mix JA, Crews WD Jr. A double-blind, placebo-controlled, randomized trial of Ginkgo biloba extract EGb 761 in a sample of cognitively intact older adults: Neuropsychological findings. Hum Psychopharmacol. 2002 Aug;17(6):267–277.

[21]Lewis R, Walse G, Court G, et al. Nonginsenoside nicotinic activity in ginseng species. Phytother Res. 1999;13(1):59–64.

[22]Tachikawa E, Kudo K, Harada K, et al. Effect s of ginseng saponins on responses induced by various receptor stimuli. Eur J Pharmacol. 1998;369(1):23–32.

[23]Petkov VV, Kehayov R, et al. Memory effects of standardized extracts of Panax ginseng (G115), Ginkgo biloba (GK501) and their combination Gincosan (PHL-00701). Planta Medica. 1993;59:106–114.

[24]Wesnes KA, Ward T, McGinty A, Petrini O. The memory enhancing effects of a Ginkgo biloba= Panax ginseng combination in healthy middle-aged volunteers. Psychopharmacology (Berlin). 2000;152(4): 353–361.

[25]Reay JL, Kennedy DO, Scholey AB. Effects of Panax ginseng, consumed with and without glucose, on blood glucose levels and cognitive performance during sustained ''mentally demanding'' tasks. J Psychopharmacol. 2006 Nov;20(6):771–781. Epub 2006 Jan 9.

[26]Kennedya DO, Scholeya AB, Wesnes KA. Dose dependent changes in cognitive performance and mood following acute administration of Ginseng to healthy young volunteers. Nutr Neurosci. 2001;4(4):295–310.

[27]Wang R, Yan H, Tang XC. Progress in studies of huperzine A, a natural cholinesterase inhibitor from Chinese herbal medicine. Acta Pharmacol Sin. 2006 Jan;27(1):1–26.

[28]Xu SS, Gao ZX, Weng Z. Efficacy of tablet huperzine-A on memory, cognition, and behavior in Alzheimer's disease. Zhongguo Yao Li XueBao. 1995;16:391–395.

[29]Zhang RW, Tang XC, Han YY. Drug evaluation of huperzine A in the treatment of senile memory disorders [in Chinese; English abstract]. Zhongguo Yao Li XueBao. 1991;12:250–252.

[30]Zhang Z, Wang X, Chen Q. Clinical efficacy and safety of huperzine alpha in treatment of mild to moderate Alzheimer disease: A placebo-controlled, double-blind, randomized trial. Zhonghua Yi XueZaZhi. 2002;82:941–944.

[31]Valikovics A. [Investigation of the effect of vinpocetine on cerebral blood flow and cognitive functions]. Ideggyogy Sz. 2007 Jul 30;60(7–8):301–310.

[32]Szatmari SZ, Whitehouse PJ. Vinpocetine for cognitive impairment and dementia. Cochrane Database Syst Rev. 2003; CD003119.

[33]Passeri M, Cucinotta D, et al. Acetyl-L-carnitine in the treatment of mildly demented elderly patients. Int J Clin Pharmacol Res. 1990;10(1–2):75–79.

[34]Rai G, Wright G, et al. Double-blind, placebo-controlled study with acetyl-L-carnitine in patients with Alzheimer's dementia. Curr Med Res Opin. 1990;11:638–647.

[35]Bonavita E. Study of the efficacy and tolerability of acetyl-L-carnitine therapy in the senile brain. Int J Clin Pharmacol Ther Toxicol. 1986;24:511–516.
[36]Thal LJ, Carta A, et al. A 1-year multicenter placebo-controlled study of acetyl L-carnitine in patients with Alzheimer's disease. Neurology. 1996;47(3):705–711.
[37]Thal LJ, Calvani M, Amato A, Carta A. A 1-year controlled trial of acetyl-L-carnitine in early onset AD. Neurology. 2000;55(6):805–810.
[38]Crook T, et al. Effects of phosphatidylserine in Alzheimer's disease. Psychopharmacol Bull. 1992;28:61–66.
[39]Engel RR, Satzger W, Gunther W, et al. Double-blind cross-over study of phosphatidylserine vs. placebo in patients with early dementia of the Alzheimer type. Eur Neuropsychopharmacol. 1992;2:149–155.
[40]De Jesus Moreno, Moreno M. Cognitive improvement in mild to moderate Alzheimer's dementia after treatment with the acetylcholine precursor choline alfoscerate: A multicenter, double-blind, randomized, placebo-controlled trial. Clin Ther. 2003 Jan;25(1):178–193.
[41]Grossman R. The role of dimethylaminoethanol in cosmetic dermatology. Am J Clin Dermatol. 2005; 6:39–47.
[42]Terman A, Brunk UT. Oxidative stress, accumulation of biological "garbage," and aging. Antioxid Redox Signal. 2006;8(1–2):197–204.
[43]Nagy I, Nagy K. On the role of cross-linking of cellular proteins in aging. Mech Ageing Dev. 1980;14 (1–2):245–251.
[44]Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folate, vitamin B_{12}, and serum total homocysteine levels in confirmed Alzheimer's disease. Arch Neurol. 1998;55(11):1449–1455.
[45]Luchsinger JA, Tang MX, Miller J, Green R, Mayeux R. Relation of higher folate intake to lower risk of Alzheimer disease in the elderly. Arch Neurol. 2007 Jan;64(1):86–92.

23

ANXIETY, DEPRESSION, ADHD, AND MORE

A Matter of Cellular Biochemistry

The adage ''the mind is a terrible thing to waste'' is especially true when it comes to nutrition and its effects on mental disease. The literature has numerous studies that indicate multiple nutritional deficiencies as contributors to mental illnesses and their symptoms. From this research, we can extrapolate that fueling an individual based on his or her biochemical needs heightens neurologic performance. Symptoms and efficient neurologic functioning are the body's and the brain's responses to either illness or health. Today, we know the power of thoughts, not only as creative, thinking beings; we also know the power that positive thoughts have on human lives. Taking this further, a brain that may require more of a certain nutrient, or has a deficiency of several nutrients, cannot be expected to perform properly and thus will experience mental symptoms. What follows are a select group of ''mental health'' conditions that reflect just as much a state of body as they do a state of mind. The artificial division of mind from body is much the same as the division of one's nose from one's face, or the proverbial trees from the forest.

ANXIETY

As a permanent fixture in many people's lives, anxiety affects not only the mind, but the body and daily functioning. Anxiety can be defined in two ways: the first as an apprehensive, uneasy state of mind, often as the result of anticipated events (i.e., life stress); and the second, more clinical definition characterizes anxiety as an abnormal, overwhelming feeling of apprehension or fear that is punctuated by physiologic reactions, such as rapid pulse, tension, and sweating. Anxiety affects both the mind and the body to varying degrees, and people experience these feelings in their lives regardless of the definition.

The current prevalence of anxiety in the population (particularly Americans) is undoubtedly caused by people working longer hours while attempting to balance their relationships with family and home responsibilities. It is not surprising that today more people experience stress and anxiety than ever before, and many more are seeking treatment to relieve their suffering. It is estimated that 19 million adults in the United States suffer from anxiety disorders, with a cost estimated to be nearly $42 billion per year. Nearly $23 billion has been spent for repeated medical visits by patients seeking relief from symptoms that appear to be physical illnesses caused by anxiety. People with anxiety are three to five times more likely to see a doctor and are six times more likely to be hospitalized for these disorders than those without such problems.[1] Because these conditions can be chronic and often disabling, the economic and individual burdens of anxiety disorders are quite high. People with anxiety disorders tend to use primary health care providers more than psychiatric medical personnel, creating a strain on the health care system. These patients seek medical care more often, in part because of increased concerns about their health and the manifestations of a racing heart, insomnia, shortness of breath, and other physical presentations. Only 30% of individuals afflicted with

anxiety disorders seek treatment for their conditions, and 30 million people will experience some type of anxiety disorder at some point in their lives.[2]

Niacin

Niacinamide (also known as nicotinamide) is a form of the B vitamin niacin (vitamin B3). Niacinamide has effects similar to benzodiazepines on the brain.[3] Nicotinamide stimulates the gamma aminobutyric acid (GABA)–benzodiazepine receptor complex, which is an inhibitory neuron grouping, and by modulating these specific neurons, exerts a calming effect.[4] Experiments designed to test the efficacy of nicotinamide and brain function demonstrate that GABA nerve receptors were less stimulated when nicotinamide was lacking in individuals, and that reintroduction of nicotinamide led to a calming effect on the GABA receptors.[5] Based on this research, it is reasonable to assume that supplementation with nicotinamide may contribute to fewer or less-severe anxiety symptoms.

Pyridoxine

Pyridoxine (vitamin B6) is an important coenzyme in the biosynthesis of several important neurotransmitters, including GABA, dopamine, and serotonin, all of which may be affected in anxiety. Pyridoxine deficiency causes an increased sympathetic discharge and hypertension in animals that have been suggested to reflect a decrease in production of GABA, dopamine, and serotonin. In addition, supplementing pyridoxine in these animals lowered their blood pressure.[6] In another study, the use of magnesium and pyridoxine on anxiety-related premenstrual syndrome (PMS) symptoms was investigated. Researchers showed that women who were supplemented 200 mg of magnesium with 50 mg of pyridoxine daily experienced significant reductions in anxiety-related PMS symptoms, including irritability, nervous tension, and generalized anxiety.[7]

Magnesium

Supplementation with magnesium has a reputation for producing a calming effect on patients with anxiety symptoms and=or elevated stress levels. In one study, nervousness and insomnia levels decreased in patients who were given 200 mg of magnesium combined with 400 mg of calcium.[8] Another researcher found an association between magnesium deficiency and anxiety symptoms.[9] In a study investigating the use of magnesium to alleviate pain in postsurgical patients, the patients were infused with magnesium both during and following surgery and were evaluated for anxiety levels. Patients who received the magnesium infusion required significantly less pain medication compared to the subjects in the control group who did not receive magnesium. In addition, the magnesium-treated group reported less anxiety symptoms.[10] Magnesium deficiency is common in the typical American diet. One large survey determined that adequate magnesium was lacking in nearly 72% of diets, and that 50% consume less than 75% of the recommended daily allowance (RDA) of magnesium; 30% of these people ate less than 50% of the RDA of magnesium.[11] Also, individuals who take oral contraceptives or diuretics and who overuse laxatives may be at increased risk of magnesium deficiency as well.

Kava (Piper methysticum)

Numerous studies have shown the efficacy of kava standardized to 70% kavalactones for anxiolytic activity. In a 25-week multicenter, randomized, placebo-controlled, double-blind

trial, kava supplementation showed significant superiority over a placebo, both objectively and subjectively, beginning in week 8 of treatment.[12] In another randomized, placebo-controlled, double-blind study, two groups containing 29 patients each with anxiety syndrome not caused by psychotic disorders were treated for a period of four weeks with kava extract. The Hamilton-Anxiety-Scale overall score of anxiety symptomatology showed a significant reduction in the kava group after one week of treatment.[13] Research suggests that one mechanism in which kava induces sedation is via the constituents kava pyrones, which modulate GABA(A) receptor binding.[14] Standardized kava is, however, difficult to find as many companies have stopped selling it.

L-theanine

Theanine is an amino acid found in high concentrations in green tea. Theanine can pass through the brain-blood barrier and may act as an agonist or an antagonist of some receptors. Research has shown that L-theanine supplementation does provide some relaxing effects, possibly by increasing levels of GABA and serotonin.[15] A small study showed that administration of 200 mg of L-theanine increased alpha brain wave activity and induced a sense of relaxation.[16] L-theanine is also known to block the binding of L-glutamic acid to glutamate receptors in the brain. A double-blind, placebo-controlled study showed that L-theanine intake resulted in a reduction in heart rate and salivary immunoglobulin A responses to an acute stress task, compared to the placebo group, likely attributable to an attenuation of sympathetic nervous activation suggesting antistress activity of theanine.[17] Using animal models, L-theanine has been shown to cause dopamine release from dopaminergic neurons, and may inhibit excitatory neurotransmission and cause inhibitory neurotransmission via glycine receptors, suggesting a possible mechanism for its anxiolytic activity.[18]

Valerian (Valeriana officinalis)

A study examined the effects of either valerian or kava supplementation for seven days and physiological and subjective response to stress tasks. The results showed a significant decrease in systolic blood pressure responsivity in both the kava and valerian groups relative to the first stress task. Between the first and second stress tasks, the heart rate reaction to mental stress was found to decline in the valerian group but not in the kava group. Individuals taking either kava or valerian reported less pressure during the second stress task after seven days of supplementation.[19] Valeriana wallichii was used in another study in which 33 subjects were supplemented with 500 mg capsules, twice daily for 60 days. Valerian not only significantly attenuated stress and anxiety, but also significantly improved depression and also enhanced the ''willingness to adjustment'' in this study.[20] In one study, a valerian=lemon balm combination was supplemented in 918 children under 12 years old suffering from restlessness and dyssomnia. The results showed that 80.9% of the patients who suffered from dyssomnia experienced an improvement for this symptom and 70.4% of the patients with restlessness also improved.[21] Research has demonstrated that the pharmacological effects of valerian extract and the constituent valerenic acid are mediated through modulation of GABA(A) receptor function.[22]

Other antianxiety botanicals and supplements include passionflower (Passiflora incarnata), skullcap (Scutellaria lateriflora), cowhage (Mucuna pruriens), and GABA.

BIPOLAR DISORDER

Bipolar disorder, also known as manic depression, is a condition characterized by wide alterations in thought, mood, energy levels, and behavior. Depression and mania can occur cyclically or episodically, or episodes of mixed mania and depression also can appear. The episodes can become increasingly frequent, disrupting all aspects of a person's life. It is estimated that 2.3 million adults in the United States,[23] or nearly 1.2 percent of the population 18 years and older in any given year, have bipolar disorder.[24] Bipolar disorder typically begins in late adolescence, with the average age at onset of the first episode of mania in the early 20s.[25] Bipolar disorder runs in families and has a genetic component. In fact, research indicated that two-thirds of people with bipolar disorder have one close relative with bipolar disorder or depression.[26] Studies using twins have also shown that if one twin has the mood disorder, the chance of an identical (monozygotic) twin also having the disorder is three times higher than that of a fraternal (dizigotic) twin. In addition, the concordance rate among identical twins is 80% while fraternal twins have a concordance rate of only 16%.[27] However, the cause of bipolar disorder is not only genetically linked; environmental factors must also play a role. Multiple biologic and psychologic factors interact to create the condition.

Folic Acid

Folic acid (vitamin B_9) is crucial for proper brain functioning, and particularly important for mania and depression. The roles of folic acid in psychiatric diseases have been repeatedly studied, and research indicates that it may play an important role in regard to bipolar disorder. Levels of folate are closely related to the pharmaceutical treatments for mania and depression, with a negative effect on folate levels. In one study, 45 patients diagnosed with mania had their folate levels measured. The results showed that these patients had red-blood-cell folate levels that were slightly less than 20% of subjects in the control group.[28] In a review of folic acid and its role in neurobiology, the following was stated:[29]

> Deficiency of folic acid is common among individuals with various psychiatric disorders.
> Multiple studies show that folic acid is effective for treating psychiatric symptoms in patients deficient in folate.
> Many psychiatric symptoms are associated with folic acid deficiency.
> Absorption of folate is inhibited by anticonvulsant medications (the standard treatment for bipolar disorder).
> Low levels of folate will lower brain levels of 5-hydroxytryptamine (serotonin) and S-adenosyl-methionine (SAMe), both of which are important for proper brain function. SAMe has antidepressant activity and increases levels of serotonin in the brain, which suggests that folic acid deficiency is related to decreased levels of brain serotonin.

Cobalamin

Cobalamin (vitamin B_{12}) is another B vitamin important for psychiatric health. A deficiency of vitamin B_{12} can lead to psychiatric symptoms; and this has been documented in the medical literature for several decades.[30] In one particular study, the occurrence of manic psychosis in

patients was evaluated. There was no apparent vitamin B_{12} deficiency, although there were changes in the patients' electroencephalograms along with mental changes.[31] Citing the causal link between vitamin B_{12} deficiency and brain dysfunction, the authors of this study suggest that the manifestation of psychiatric symptoms may occur prior to other standard signs such as macrocytic anemia and spinal-cord disease, and that all patients with psychiatric disease should be evaluated for vitamin B_{12} deficiency.

Lithium

People with mood disorders (especially depression) are at a much higher risk of suicide than the general population.[32] Lithium has been shown to lessen the incidence of suicide in patients with bipolar disorder and depression who are taking it, compared to those who take antidepressants or antipsychotics alone.[33,34] Lithium has been used with success in a variety of conditions other than mood disorders, including alcoholism, anemia, and migraine and cluster headaches.[35] Lithium orotate is a mineral available as a nutritional preparation that has significant effects on conditions such as depression and bipolar disorder. Lithium orotate is available as an alternative to prescription-strength lithium, which has a high risk of several dangerous side effects. Lithium orotate may provide the same positive effects on mood as prescription lithium.

Omega-3 Fatty Acids

The omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have shown benefit in numerous mood disorders. Omega-3 fatty acids, when added to an existing psychopharmacological maintenance treatment for bipolar disorder, can have beneficial effects on depressive symptoms. In a 12-week, double-blind study, individuals with bipolar depression were supplemented with 1 g per day or 2 g per day of EPA or a placebo. Significant improvement was seen with EPA treatment compared with a placebo, according to the Hamilton Depression Rating Scale.[36] In a small open-label study, 1.5–2 g per day of the omega-3 fatty acid EPA was given to patients with bipolar depression. The results showed that 8 of the 10 patients who completed at least one month of follow-up achieved a 50% or greater reduction in Hamilton Depression Rating Scale scores within one month of supplementation.[37]

Botanical Medicines

Lavender (Lavendula officinalis) is a botanical used for mild relaxing properties and is used traditionally for addressing symptoms such as insomnia, depression, restlessness, and nervousness. Preparations of Lavender are frequently derived from the plant oil for inhalation, and internal ingestion is contraindicated. The constituents of lavender oil lead to relaxation and decreased alertness when inhaled.[38] Inhalation of lavender oil may decrease symptoms of anxiety in manic patients.

Lemon balm (Melissa officinalis) is another herb often utilized for mild calming effects and the ability to decrease alertness,[39] which is useful for treating nervous anxiety. The terpenes are a constituent of lemon balm and are thought to act on some of the inhibitory neurons such as GABA in the brain, thereby eliciting a calming effect.[40] One study using both lemon balm and valerian (Valeriana officinalis) demonstrated improvements in the amount and the quality of sleep in subjects who took the combination.[41]

DEPRESSION

Nearly 9.5% of the adult population suffers with depression in a given year, which equates to approximately 19 million American adults with the condition.[42] Women are affected nearly twice as frequently (12%) as men (6.6%) by depressive disorders each year, which is equivalent to 12.4 million women and 6.4 million men in the United States.[23] Depressive disorder, including major depressive disorder, dysthymic disorder, and bipolar disorder, are the leading causes of disability in the United States and other developed nations, with major depressive disorder ranking number one. Often, patients who suffer from depressive disorders also have additional medical conditions[43] such as anxiety. Major depressive disorder can develop at any age, although it occurs most commonly during the mid 20s. Dysthymic disorder, however, often develops in childhood, adolescence, or early adulthood.[25] Depressive disorder is a mental illness that has both mental and physical symptomology and can disrupt every aspect of an individual's life.

5-HTP

5-Hydroxytryptophan (5-HTP) is the precursor to the neurotransmitter serotonin. 5-HTP is related to the amino acid L-tryptophan, which is converted in the body into 5-HTP. 5-HTP is able to cross into the brain and augment supplies of serotonin, and thus acts as an effective therapy for depression. Insufficient activity of serotonin (and other neurotransmitters) is a key element in the currently accepted view regarding the pathogenesis of depression. In one review article of the various treatments for depression, the authors stated that precursor therapies hold a therapeutic value in treating depression and that more research is needed to confirm the efficacy of such treatment.[44] Another article reported that the efficacy of 5-HTP was ''high'' for treating disorders such as depression, binge eating, and insomnia.[45] Used as a nutritional food supplement, 5-HTP may be a beneficial adjunctive treatment for patients with depression. The greatest task in medicine is identifying and removing the cause of disease, and this nutrient can act to augment a patient's neurochemistry while other nutritional treatments can be used that may restore brain neurotransmitter functioning. Tapering supplemental 5-HTP down as a patient's symptoms decrease will allow the patient to continue functioning normally.

Vitamin C

Vitamin C, also known as ascorbic acid, is a nutrient that is frequently studied for various conditions. In a review article regarding the clinical effects of ascorbic-acid deficiency, the authors noted that depression is one of the first symptoms of scurvy in humans who are subjected to deficient vitamin C in their diet.[46] Scurvy is relatively rare in today's society. However, diets containing low amounts of vitamin C are not, especially with the increase of processed food in the diet. Studies on vitamin C and scurvy suggest an interesting relationship between vitamin C levels and psychiatric patients. One study of psychiatric patients (some of whom had bipolar depression) showed that many of these subjects were in a state of low vitamin C saturation, referred to as ''subacute'' scurvy.[47] Another study involving a similar population of psychiatric patients also revealed decreased vitamin C loads, or borderline scurvy, without the patients actually manifesting the symptoms of this condition.[48]

Omega-3 Fatty Acids

The omega-3 fatty acids have been shown in numerous studies to benefit depressive symptoms. Depressive patients show significant depletions of total omega-3 polyunsaturated fatty acids

(PUFAs) and particularly DHA in the fatty acid composition of phospholipid in cell membranes from red blood cells.[49] Epidemiological studies have shown that countries with high rates of fish oil consumption (known to be high in levels of EPA=DHA) have low rates of depressive disorder.[50] A meta-analysis of 10 studies supplementing omega-3 PUFAs showed significant antidepressant effects of omega-3 PUFA supplementation.[51] In a double-blind, placebo-controlled study with depressed patients, 2 g per day of fish oil for four weeks was supplemented in addition to ongoing antidepressant therapy. The results showed highly significant benefits with the addition of the omega-3 fatty acid compared with placebo, by week three of treatment.[52] In one study, patients who repeatedly exhibited self-harm behavior were randomized to receive 1.2 g EPA plus 0.9 g DHA or a placebo for 12 weeks in addition to standard psychiatric care. The omega-3 supplemented group had significantly greater improvements in scores for depression, suicidality, and daily stresses.[53] Additionally, one study found that a low DHA percentage and low omega-3 proportions of lipid profiles in depressed patients predicted increased risk of suicidal behavior over a two-year period.[54]

St. John's Wort

St. John's wort (Hypericum perforatum) is an effective alternative to standard pharmacotherapy for depression, and is one of the most studied botanical medicines. St. John's wort affects several biochemical pathways that play a central role in the pathology of depression such as the monoamine oxidase, serotonin, GABA, and dopamine neurotransmitter systems.[55] The extracts and constituents of this plant have been intensely studied for the last decade and are currently considered a viable alternative medicine for depression. The mechanisms of action(s) of the constituents of St. John's wort include the ability to down-regulate beta adrenergic receptors, bind to GABA receptors, and up-regulate serotonin 5-HT(2) receptors. These effects lead to positive changes in neurotransmitter concentrations in particular areas of the brain that are associated with depression.[56] In a multicenter, randomized, double-blind study, 900 or 1,800 mg per day of St. John's wort was given for six weeks plus a 16-week continuation phase and compared to the effectiveness of the potent SSRI paroxetine. The Hamilton Depression Rating Scale score decreased by 92.0% with St. John's wort supplementation and decreased by 85.5% with paroxetine. Remission occurred in 81.6% of the patients with St. John's wort and in 71.4% for paroxetine.[57]

Acetyl-L-carnitine

In a randomized, placebo-controlled study, subjects ranging from 60–80 years old with dysthymic disorder were given acetyl-L-carnitine at 3 g per day over 60 days. The results showed that supplementation with acetyl-L-carnitine induced a significant reduction in the severity of depressive symptoms, and also a significant improvement in the items measuring the quality of life compared to the placebo group.[58] An additional study with depressed geriatric patients showed acetyl-L-carnitine treatment was highly effective and statistically significant, providing clear evidence that it was particularly effective in patients showing more serious clinical symptoms of depression.[59]

S-adenosyl-L-methionine (SAMe)

SAMe is a naturally occurring molecule that acts as a methyl donor and is involved in more than 100 biochemical reactions. Deficiencies in vitamin B12 and folate can cause decreased

Table 23–1. Dosing Recommendations

Nutrient	Doses
Pyridoxine (vitamin B_6)	50–100 mg per day, in divided doses
Cobalamin (vitamin B_{12})	1,000 mg per day, in divided doses
Magnesium	400 mg per day, in divided doses
Ascorbate (vitamin C)	1,000–2,000 mg per day, in divided doses
Folate (vitamin B_9)	1,000 mg per day
Nicotinamide (vitamin B_3)	1,000 mg per day, 2 times per day
5-Hydroxytryptophan	150–300 mg per day
Phosphatidylserine	300 mg per day
Zinc	5 mg per day
Essential fatty acids	3–4 g per day (eicosapentaenoic acid= docosahexaenoic acid in ratio of 180:120 mg, respectively)
Lavender (Lavendula officinalis)	Essential oil, inhaled scent 3 times per day
Lemon balm (Melissa officinalis)	80–100 mg, 3 times per day
St. John's wort (Hypericum perforatum)	300 mg, 3 times per day (standardized to 0.3% hypericin or 5% hyperforin content)
S-adenosyl-L-methionine (SAMe)	400-1,600 mg per day

SAMe concentrations in the central nervous system.[60] SAMe has been shown to be an effective antidepressant in numerous studies. A meta-analysis showed a greater response rate with SAMe supplementation compared with a placebo, with a global effect ranging from 17%–38%, and antidepressant activity comparable to standard tricyclic antidepressants.[61] In one study, oral SAMe supplementation was given as an adjunct therapy among partial and nonresponders to standard pharmaceutical treatment with persisting major depressive disorder. SAMe was given at a dose of 800–1,600 mg per day for six weeks. Based on the Hamilton Depression Rating Scale, the results showed a response rate of 50% and a remission rate of 43% following the SAMe augmentation.[62] Another study showed SAMe given intramuscularly at a dose of 400 mg per day was comparable in efficacy to 150 mg per day oral imipramine in patients with the diagnosis of major depressive episode, and the SAMe was significantly better tolerated.[63]

L-Tyrosine and L-Phenylalanine

Phenylalanine is an essential amino acid metabolized into tyrosine. Tyrosine is the precursor used for the synthesis of norepinephrine, epinephrine, and dopamine. In a double-blind study, DL-phenylalanine at a dosage of 150–200 mg per day or the pharmaceutical imipramine at 150–200 mg per day was administered to a group of depressed patients for 30 days. No statistical difference could be found between these two drug treatment groups, suggesting antidepressant activity of phenylalanine. In an open study, DL-phenylalanine in doses from 75–200 mg per day was administered to 20 depressed patients for 20 days. The results showed that 60% of patients had complete or "good" response to treatment.[64]

Depletion of brain stores of norepinephrine is associated with stress-induced impairment of performance. Research shows tyrosine supplementation improves stress-associated declines in both neural norepinephrine levels and performance.[65] In addition, individuals under psychosocial and physical stress who were supplemented with tyrosine performed better on memory and tracking tasks.[66] Tyrosine supplementation generally ranges from 100–150 mg=kg.

ATTENTION DEFICIT DISORDER AND ATTENTION DEFICIT= HYPERACTIVITY DISORDER

Attention deficit disorder and attention deficit=hyperactivity disorder (ADD=ADHD) is one of the most prevalent mental disorders among children. Three to five percent of all children, or nearly 2 million American children, have ADD=ADHD, according to the National Institute of Mental Health, and boys are affected two to three times as frequently as girls.[67] This indicates that, statistically, one child in each classroom in the United States has the disorder. No single causative factor has been identified for the various behavior patterns observed in these patients. ADD=ADHD is diagnosed by observing particular characteristic behavior patterns over time, as there are no other clear physical signs. A national survey revealed that parents of 7% of children ages 6–11 were told by a health care professional that their children had ADD=ADHD, and a statement issued by the Centers for Disease Control and Prevention (CDC) noted that nearly 1.6 million elementary school-age children have been diagnosed.[68] The following information was also included in the CDC report:

> Boys are approximately three times as likely to have ADD=ADHD as girls.
> Children with health insurance were diagnosed with ADD=ADHD more frequently than children without health insurance.
> Children with ADD=ADHD use more health care services, such as mental health services, than those without the condition.
> White children are twice as likely as black and Hispanic children to have a diagnosis of ADHD.

Phosphatidylserine

Phosphatidylserine is a biologic phospholipid molecule. Phospholipids are one of the main components of cellular membranes in the human body and function to stabilize the other constituents found in cellular membranes. Phosphatidylserine is the main phospholipid of human brain cells and regulates cellular functions, including controlling the internal environment of the cell, signal transduction, cell-cell communication, release of secretory vesicles, and regulation of cell growth and division.[69] Phosphatidylserine is beneficial for several different brain functions in addition to contributing to nerve-cell synaptic membranes, an important anatomic aspect of nerve-signal production and transmission. Benefits of phosphatidylserine supplementation include increased production, release, and effectiveness of the neurotransmitter dopamine, as well as increased neurologic energy through facilitated synaptic communication.[70] In one clinical trial, phosphatidylserine supplementation was investigated to treat patients with ADD=ADHD. The results showed a greater than 90% improvement in these cases. Using doses of 200–300 mg per day for up to a four-month duration provided the greatest resolution of symptoms in this study.[71] Supplementation of phosphatidylserine is believed to normalize brain-lipid content, thus supporting the return of normalized function of the euronal

cells.[72] In addition to ADHD, a small study with 10 elderly women with depressive disorders was performed. The women were treated with a placebo for 15 days followed by phosphatidylserine 300 mg per day for 30 days. Phosphatidylserine induced consistent improvement of depressive symptoms, memory, and behavior.[73]

Omega-3 Fatty Acids

Supplementation with the omega-3 fatty acids DHA and EPA have been shown to positively affect individuals with ADHD, as well as depression. Evidence indicates that deficiencies or metabolic imbalances of these fatty acids might be associated with childhood developmental disorders such as ADHD. In one study, the proportion of omega-3 fatty acids was found to be significantly lower in plasma phospholipids and erythrocytes in the ADHD group compared to the control group. Additionally, saturated fatty acid proportions were higher and intake of saturated fat was 30% higher in the ADHD group.[74] A small pilot study examined the effect of 16.2 g EPA=DHA concentrates per day in children with ADHD for eight weeks. Supplementation resulted in significant increases in plasma EPA and DHA, as well as a significant reduction in the arachidonic acid to EPA ratio. Significant improvements in behavior such as inattention, hyperactivity, oppositional=defiant behavior, and conduct disorder were reported by the psychiatrist who was blinded to supplement compliance or dosage modifications.[75] In a randomized, placebo-controlled, double-blind intervention trial over 15 weeks, polyunsaturated fatty acids (PUFAs) were supplemented to children aged 7 to 12 years with ADHD. The results showed that significant positive treatment effects were found based on parent ratings of core ADHD symptoms, including inattention and hyperactivity=impulsivity with PUFA supplementation compared to the control group.[76]

Zinc

Several studies have indicated that zinc levels are low in individuals with ADD=ADHD.[77] Also, research has demonstrated that lower serum zinc levels were found in children with ADD=ADHD compared to children without the disorder.[78] There is also a relationship between the levels of free fatty acids in the blood and zinc levels in children with ADD=ADHD. Children with ADD=ADHD were found to have low blood levels of zinc and free fatty acids compared to controls without the disorder, suggesting that the low levels of free fatty acids may be a result of the decreased zinc levels.[79] These results indicate that a deficiency of zinc may be involved with the development or dysfunction found with ADD=ADHD. Another study revealed a relationship between zinc levels in the body and the responsiveness to standard stimulant pharmacotherapy. Low zinc levels correlated to a poor response to the medication.[80] Zinc is a cofactor in neurotransmitter synthesis and affects dopamine metabolism indirectly. Dopamine is a neurotransmitter that is thought to be involved in ADD=ADHD, as low levels of dopamine are associated with the condition and dopamine supplementation has alleviated some associated symptoms.[81] In a 12-week, double-blind, clinical trial with zinc sulfate and children with ADHD, the zinc sulfate–supplemented group showed reduced hyperactive, impulsive, and impaired socialization symptoms.[82]

SCHIZOPHRENIA

Schizophrenia is a chronic, severe, and disabling neurological condition. It is characterized by symptoms such as hearing internal voices, and believing that other people may be reading

one's mind, controlling one's thoughts, or plotting against one. This can be a terrifying condition to the person experiencing the symptoms. Individuals with schizophrenia are often fearful and withdrawn, with speech and behavior that appears to be disorganized. The first signs of schizophrenia often present as troubling changes in behavior. Schizophrenia is one of the most common mental illnesses, affecting an estimated 1 out of every 100 people; this equates to approximately 1% of the population,[83] and more than 2 million Americans in a given year. Schizophrenia affects men and women equally, yet seems to appear earlier in men than women. Men usually develop signs in their early 20s, whereas women more often develop signs in their late 20s to early 30s. The societal cost of schizophrenia has been estimated at $32.5 billion per year in the United States alone.[83] Fatty acid supplementation may be beneficial for modulating this devastating illness.

Fatty Acids

Disordered membrane phospholipid metabolism may play a role in schizophrenia. One theory suggests that there is abnormal membrane phospholipid metabolism, which is associated with an increased loss of polyunsaturated fatty acids (PUFAs) from the cellular membrane due to increased activity of the enzyme phospholipase A2.[84]

Table 23–2. Condition–Nutrient Cross-Reference Chart

	Anxiety	Bipolar	Depression	ADD=ADHD	Schizophrenia
Ascorbate (vitamin C)			1,000–2,000 mg		
Pyridoxine (vitamin B_6)	200 mg				
Cobalamin (vitamin B_{12})		1,000 mg			
Magnesium	400 mg				
Niacin (vitamin B_3)	300 mg				
Folate (vitamin B_9)		1–10 mg			
5-Hydroxytryptophan			150–300 mg		
Hypericum (from St. John's wort; Hypericum perforatum)			300 mg		
Lavender (Lavendula officinalis)		Inhale essential oil			
Lemon balm (Melissa officinalis)		80–100 mg			
Zinc				15–50 mg	
Phosphatidylserine				300 mg	
Essential fatty acids				2,000 mg	2,000–3,000 mg
S-adenosyl-L-methionine			400–1,600 mg		

Sequential coordination of millions of neurons are dependent on unified functioning on the cellular membrane, and thus membrane changes that occur from this dysfunction may lead to adverse effects on the brain. Another theory suggests that there is abnormal brain turnover of phospholipids, as detected by magnetic resonance imaging, as well as reduced cellular membrane levels of omega-3 and omega-6 polyunsaturated fatty acids. Supporting this theory, four of five clinical trials using eicosapentaenoic acid (EPA) to treat schizophrenia demonstrated positive results.[85] Decreased levels of phospholipid PUFAs and increased phospholipid breakdown and have been repeatedly demonstrated.[86] Researchers are currently investigating the various physiologic functions of membrane phospholipids and PUFAs, and their possible roles in the pathology of schizophrenia. Research suggests altered cellular signaling and how it relates to neurobiologic manifestations of schizophrenia. In one clinical trial, patients with schizophrenia were given a mixture of PUFAs (ratio of 180 mg EPA:120 mg DHA) and antioxidant vitamins (ratio of 400 IU vitamin E:500 mg vitamin C) twice daily for four months. The results showed a significant decrease in psychopathology according to scores of several psychiatric rating scales.[87] According to a comprehensive review of the scientific literature of clinical trials using PUFAs to treat schizophrenia symptoms, the authors of the review concluded that using PUFAs to treat schizophrenia produced positive results in these patients, with few side effects.[88]

CONCLUSIONS

Nutritional deficiencies can play roles in mental illness, and addressing such disorders or their symptoms can be helpful for patients who seek relief. Further research will reveal more about the mind–body link in these disorders.

REFERENCES

[1]Greenberg PE, Sisitsky T, Kessler RC, Finkelstein SN, Berndt ER, Davidson JR, Ballenger JC, Fyer AJ. The economic burden of anxiety disorders in the 1990s. J Clin Psychiatry. 1999;60:427–435.

[2]Lepine JP. The epidemiology of anxiety disorders: Prevalence and societal costs. J Clin Psychiatry. 2002;63(suppl.14):4–8.

[3]Mohler H, Polc P, Cumin R, Pieri L, Kettler R. Nicotinamide is a brain constituent with benzodiazepinelike actions. Nature. 1979;5;278:563–565.

[4]Akhundov RA, Rozhanets VV, Voronina TA, Val'dman AV. Mechanism of the tranquilizing action of electron structural analogs of nicotinamide. Biull Eksp Biol Med. 1986;101:329–331.

[5]Fomenko AI, Parkhomets PK, Stepanenko SP, Donchenko GV. Participation of benzodiazepine receptors in the mechanism of action of nicotinamide in nerve cells. Ukr Biokhim Zh. 1994;66:75–80.

[6]McCarty MF. High-dose pyridoxine as an ''anti-stress'' strategy. Med Hypotheses. 2000;54:803–807.

[7]De Souza MC, Walker AF, Robinson PA, Bolland K. A synergistic effect of a daily supplement for 1 month of 200 mg magnesium plus 50 mg vitamin B6 for the relief of anxiety-related premenstrual symptoms: A randomized, double-blind, crossover study. J Women's Health Gend Based Med. 2000;9:131–139.

[8]Daro AF, Zivkovic DM. Clinical nutrition: Surgical and medical therapy of the future. Int Surg. 1976;61:262–265.

[9]Seelig MS et al. Latent tetany and anxiety, marginal Mg deficit and normocalcemia. Dis Nerv Syst. 1975;36:461–465.

[10]Kara H, Sahin N, Ulusan V, Aydogdu T. Magnesium infusion reduces perioperative pain. Eur J Anaesthesiol. 2002;19:52–56.

[11]Landy L. Gallup survey finds majority of American diets lack sufficient magnesium—at potential cost to health. Searle News. Sept. 21, 1994.

[12]Volz HP, Kieser M. Kava-kava extract WS 1490 versus placebo in anxiety disorders–a randomized placebo-controlled 25-week outpatient trial. Pharmacopsychiatry. 1997 Jan;30(1):1–5.

[13]Kinzler E, Krömer J, Lehmann E. [Effect of a special kava extract in patients with anxiety-, tension-, and excitation states of non-psychotic genesis. Double blind study with placebos over 4 weeks]. Arzneimittelforschung. 1991 Jun;41(6):584–588.

[14]Jussofie A, Schmiz A, Hiemke C. Kavapyrone enriched extract from Piper methysticum as modulator of the GABA binding site in different regions of rat brain. Psychopharmacology (Berl). 1994 Dec;116(4): 469–474.

[15]Lu K, Gray MA, Oliver C, Liley DT, Harrison BJ, Bartholomeusz CF, Phan KL, Nathan PJ. The acute effects of L-theanine in comparison with alprazolam on anticipatory anxiety in humans. Hum Psychopharmacol. 2004 Oct;19(7):457–465.

[16]Anon. L-theanine. Monograph. Altern Med Rev. 2005 Jun;10(2):136–138.

[17]Kimura K, Ozeki M, Juneja LR, Ohira H. L-Theanine reduces psychological and physiological stress responses. Biol Psychol. 2007 Jan;74(1):39– 45. Epub 2006 Aug 22.

[18]Yamada T, Terashima T, Okubo T, Juneja LR, Yokogoshi H. Effects of theanine, r-glutamylethylamide, on neurotransmitter release and its relationship with glutamic acid neurotransmission. Nutr Neurosci. 2005 Aug;8(4):219–226.

[19]Cropley M, Cave Z, Ellis J, Middleton RW. Effect of kava and valerian on human physiological and psychological responses to mental stress assessed under laboratory conditions. Phytother Res. 2002 Feb; 16(1):23–27.

[20]Bhattacharyya D, Jana U, Debnath PK, Sur TK. Initial exploratory observational pharmacology of Valeriana wallichii on stress management: A clinical report. Nepal Med Coll J. 2007 Mar;9(1):36–39.

[21]Müller SF, Klement S. A combination of valerian and lemon balm is effective in the treatment of restlessness and dyssomnia in children. Phytomedicine. 2006 Jun;13(6):383–387. Epub 2006 Feb 17.

[22]Yuan CS, Mehendale S, Xiao Y, Aung HH, Xie JT, Ang-Lee MK. The gamma-aminobutyric acidergic effects of valerian and valerenic acid on rat brainstem neuronal activity. Anesth Analg. 2004 Feb;98(2):353–358, table of contents.

[23]Narrow WE. One-year prevalence of depressive disorders among adults 18 and over in the U.S.: NIMH ECA prospective data. Population estimates based on U.S. Census estimated residential population age 18 and over on July 1, 1998. Unpublished table.

[24]Regier DA, Narrow WE, Rae DS, et al. The de facto mental and addictive disorders service system: Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry. 1993;50:85–94.

[25]American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. (DSM-IV). Washington, DC: American Psychiatric Press, 1994.

[26]NIMH Genetics Workgroup. Genetics and Mental Disorders. NIH Publication No. 98-4268. Rockville, MD: National Institute of Mental Health, 1998.

[27]Durand VM, Barlow DH. Abnormal Psychology: An Introduction. Scarborough, Ontario, Canada: Wadsworth, 2000.

[28]Hasanah CI, Khan UA, Musalmah M, Razali SM. Reduced red-cell folate in mania. Affect Disord. 1997;46:95–99.

[29]Young SN, Ghadirian AM. Folic acid and psychopathology. Prog Neuropsychopharmacol Biol Psychiatry. 1989;13:841–863.

[30]Hector M, Burton JR. What are the psychiatric manifestations of vitamin B12 deficiency? J Am Geriatr Soc. 1988 Dec;36(12):1105–1112.

[31]Evans DL, Edelsohn GA, Golden RN. Organic psychosis without anemia or spinal cord symptoms in patients with vitamin B12 deficiency. Am J Psychiatry. 1983;140:218–221.

[32]Moscicki EK. Epidemiology of completed and attempted suicide: Toward a framework for prevention. Clinical Neuroscience Research. 2001;1:310–323.

[33]McElroy SL, Kotwal R, Kaneria R, Keck PE Jr. Antidepressants and suicidal behavior in bipolar disorder. Bipolar Disord. 2006 Oct;8(5 Pt 2):596–617.

[34]Howland RH. Lithium: underappreciated and underused? J Psychosoc Nurs Ment Health Serv. 2007 Aug;45(8):13–17.

[35]Sartori HE. Lithium orotate in the treatment of alcoholism and related conditions. Alcohol. 1986 Mar;3(2):97–100.

[36]Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. Br J Psychiatry. 2006 Jan;188:46–50.

[37]Osher Y, Bersudsky Y, Belmaker RH. Omega-3 eicosapentaenoic acid in bipolar depression: report of a small open-label study. J Clin Psychiatry. 2005 Jun;66(6):726–729.

[38]Schulz V, Hansel R, Tyler VE; Telger TC, transl. Rational Phytotherapy: A Physician's Guide to Herbal Medicine, 3rd Edition. Berlin: Springer, 1998.

[39]Kennedy DO, Scholey AB, Tildesley NT, et al. Modulation of mood and cognitive performance following acute administration of Melissa officinalis (lemon balm). Pharmacol Biochem Behav. 2002;72:953–964.
[40]Burns A, Byrne J, Ballard C, Holmes C. Sensory stimulation in dementia. Br Med J. 2002;325:1312–1313.
[41]Cerny A, Shmid K. Tolerability and efficacy of valerian lemon balm in healthy volunteers (a double blind, placebo-controlled, multicentre study). Fitoterapia. 1999;70:221–228.
[42]Regier DA, Narrow WE, Rae DS, et al. The de facto mental and addictive disorders service system. Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry. 1993;50:85–94.
[43]Murray CJL, Lopez AD, eds. Summary: The global burden of disease. A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge, MA: Harvard School of Public Health, Harvard University Press, 1996. [on behalf of the World Health Organization and the World Bank]; online document at: www.who.int msa mnh ems dalys intro.htm.
[44]Meyers S. Use of neurotransmitter precursors for treatment of depression. Altern Med Rev. 2000; 5:64–71.
[45]Birdsall TC. 5-Hydroxytryptophan: A clinically-effective serotonin precursor. Altern Med Rev. 1998; 3:271–280.
[46]Hodges RE, Hood J, Canham JE, Sauberlich HE, Baker EM. Clinical manifestations of ascorbic acid deficiency in man. Am J Clin Nutr. 1971;24:432–443.
[47]Milner G. Ascorbic acid in chronic psychiatric patients: A controlled trial. Br J Psychiatry. 1963;109: 294–299.
[48]Leitner, ZA, Church IC. Nutritional studies in a mental hospital. Lancet. 1956;i:565–567.
[49]Peet M, Murphy B, Shay J, Horrobin D. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. Biol Psychiatry. 1998 Mar 1;43(5):315–319.
[50]Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamäki H, Lehtonen J, Vartiainen E. Fish consumption and depressive symptoms in the general population in Finland. Psychiatr Serv. 2001 Apr;52(4):529–531.
[51]Lin PY, Su KP. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. J Clin Psychiatry. 2007 Jul;68(7):1056–1061.
[52]Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. Am J Psychiatry. 2002 Mar;159(3):477–479.
[53]Hallahan B, Hibbeln JR, Davis JM, Garland MR. Omega-3 fatty acid supplementation in patients with recurrent self-harm. Single-centre double-blind randomised controlled trial. Br J Psychiatry. 2007 Feb;190: 118–122.
[54]Sublette ME, Hibbeln JR, Galfalvy H, Oquendo MA, Mann JJ. Omega-3 polyunsaturated essential fatty acid status as a predictor of future suicide risk. Am J Psychiatry. 2006 Jun;163(6):1100–1102.
[55]Miller, AL. St. John's wort (Hypericum perforatum): Clinical effects on depression and other conditions [review]. Altern Med Rev. 1998;3:18–26.
[56]Butterweck V. Mechanism of action of St. John's wort in depression: What is known? CNS Drugs. 2003;17:539–562.
[57]Anghelescu IG, Kohnen R, Szegedi A, Klement S, Kieser M. Comparison of Hypericum extract WS 5570 and paroxetine in ongoing treatment after recovery from an episode of moderate to severe depression: results from a randomized multicenter study. Pharmacopsychiatry. 2006 Nov;39(6):213–219.
[58]Bella R, Biondi R, Raffaele R, Pennisi G. Effect of acetyl-L-carnitine on geriatric patients suffering from dysthymic disorders. Int J Clin Pharmacol Res. 1990;10(6):355–360.
[59]Tempesta E, Casella L, Pirrongelli C, Janiri L, Calvani M, Ancona L. L-acetylcarnitine in depressed elderly subjects. A cross-over study vs placebo. Drugs Exp Clin Res. 1987;13(7):417–423.
[60]Friedel HA, Goa KL, Benfield P. S-adenosyl-L-methionine. A review of its pharmacological properties and therapeutic potential in liver dysfunction and affective disorders in relation to its physiological role in cell metabolism. Drugs. 1989;38:389–416.
[61]Bressa GM. S-adenosyl-l-methionine (SAMe) as antidepressant: meta-analysis of clinical studies. Acta Neurol Scand Suppl. 1994;154:7–14.
[62]Alpert JE, Papakostas G, Mischoulon D, Worthington JJ 3rd, Petersen T, Mahal Y, Burns A, Bottiglieri T, Nierenberg AA, Fava M. S-adenosyl-L-methionine (SAMe) as an adjunct for resistant major depressive disorder: an open trial following partial or nonresponse to selective serotonin reuptake inhibitors or venlafaxine. J Clin Psychopharmacol. 2004 Dec;24(6):661–664.
[63]Pancheri P, Scapicchio P, Chiaie RD. A double-blind, randomized parallel-group, efficacy and safety study of intramuscular S-adenosyl-L-methionine 1,4-butanedisulphonate (SAMe) versus imipramine in patients with major depressive disorder. Int J Neuropsychopharmacol. 2002 Dec;5(4):287–294.

[64]Beckmann H, Strauss MA, Ludolph E. Dl-phenylalanine in depressed patients: an open study. J Neural Transm. 1977;41(2-3):123–134.
[65]Salter CA. Dietary tyrosine as an aid to stress resistance among troops. Mil Med. 1989 Mar;154(3): 144–146.
[66]Deijen JB, Wientjes CJ, Vullinghs HF, Cloin PA, Langefeld JJ. Tyrosine improves cognitive performance and reduces blood pressure in cadets after one week of a combat training course. Brain Res Bull. 1999 Jan 15;48(2):203–209.
[67]NIH Publication No. 96-3572 [booklet]. Bethesda, MD: National Institutes of Health, 1994; reprinted 1996.
[68]Centers for Disease Control and Prevention. Prevalence of Attention Deficit Disorder and Learning Disability: Attention Deficit Disorder and Learning Disability: United States, 1997–98. Series 10, No. 206. (PHS) 2002–1534.
[69]Blokland A, Honig W, Brouns F, Jolles J. Cognition-enhancing properties of subchronic phosphatidylserine (PS) treatment in middle-aged rats: Comparison of bovine cortex PS with egg PS and soybean PS. Nutrition. 1999;15:778–783.
[70]Kidd PM. A review of five nutrients and botanicals in the integrative management of cognitive dysfunction. Altern Med Rev. 1999;4:144–161.
[71]Kidd PM. Attention deficit hyperactivity disorder (ADHD) in children: Rationale for its integrative management. Altern Med Rev. 2000;5:402–428.
[72]Crook TH, et al. Effects of phosphatidylserine in age-associated memory impairment. Neurology. 1991;41:644–649.
[73]Maggioni M, Picotti GB, Bondiolotti GP, Panerai A, Cenacchi T, Nobile P, Brambilla F. Effects of phosphatidylserine therapy in geriatric patients with depressive disorders. Acta Psychiatr Scand. 1990 Mar; 81(3):265–270.
[74]Antalis CJ, Stevens LJ, Campbell M, Pazdro R, Ericson K, Burgess JR. Omega-3 fatty acid status in attention-deficit hyperactivity disorder. Prostaglandins Leukot Essent Fatty Acids. 2006 Oct–Nov;75(4–5): 299–308. Epub 2006 Sep 8.
[75]Sorgi PJ, Hallowell EM, Hutchins HL, Sears B. Effects of an open-label pilot study with high-dose EPA DHA concentrates on plasma phospholipids and behavior in children with attention deficit hyperactivity disorder. Nutr J. 2007 Jul 13;6:16.
[76]Sinn N, Bryan J. Effect of supplementation with polyunsaturated fatty acids and micronutrients on learning and behavior problems associated with child ADHD. J Dev Behav Pediatr. 2007 Apr;28(2):82–91.
[77]Galland L. Nutritional supplementation for ADHD. In: Bellanti JA, Crook WG, Layton RE, eds. Attention Deficit Hyperactivity Disorder: Causes and Possible Solutions (Proceedings of a Conference). Jackson, TN: International Health Foundation, 1999.
[78]Toren P, Eldar S, Sela BA, et al. Zinc deficiency in attention-deficit hyperactivity disorder. Biol Psychiatry. 1996;40:1308–1310.
[79]Bekaroglu M, Aslan Y, Gedik Y, Deger O, Mocan H, Erduran E, Karahan C. Relationships between serum free fatty acids and zinc, and attention deficit hyperactivity disorder: A research note. J Child Psychol Psychiatry. 1996;37:225–227.
[80]Arnold LE, Pinkham SM, Votolato N. Does zinc moderate essential fatty acid and amphetamine treatment of attention-deficit hyperactivity disorder? J Child Adolesc Psychopharmacol. 2000;10:111–117.
[81]Cocores JA, Davies RK, Mueller PS, Gold MS. Cocaine abuse and adult attention deficit disorder. J Clin Psychiatry. 1987;48:376–377.
[82]Bilici M, Yildirim F, Kandil S, Bekaroğlu M, Yildirmis S, Değer O, Ulgen M, Yildiran A, Aksu H. Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivitym disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2004 Jan;28(1):181–190.
[83]Online document at: web.sfn.org.
[84]Horrobin DF. Schizophrenia as a membrane lipid disorder which is expressed throughout the body. Prostaglandins Leukot Essent Fatty Acids. 1996;55(1–2):3–7.
[85]Peet M. Eicosapentaenoic acid in the treatment of schizophrenia and depression: Rationale and preliminary double-blind clinical trial results. Prostaglandins Leukot Essent Fatty Acids. 2003;69:477–485.
[86]Skosnik PD, Yao JK. From membrane phospholipid defects to altered neurotransmission: Is arachidonic acid a nexus in the pathophysiology of schizophrenia? Prostaglandins Leukot Essent Fatty Acids. 2003;69:367–384.
[87]Arvindakshan M, Ghate M, Ranjekar PK, Evans DR, Mahadik SP. Supplementation with a combination of omega-3 fatty acids and antioxidants (vitamins E and C) improves the outcome of schizophrenia. Schizophr Res. 2003;62:195–204.
[88]Joy CB, Mumby-Croft R, Joy LA. Polyunsaturated fatty acid (fish or evening primrose oil) for schizophrenia. Cochrane Database Syst Rev. 2000;(2):CD001257.

24

NATURAL TREATMENTS FOR METABOLIC SYNDROME

Using Nutraceuticals to Thwart a Deadly Trend

Metabolic syndrome, also known as syndrome X or cardiovascular metabolic syndrome, is comprised of hyperlipidemia (elevated triglycerides and low levels of high-density lipoprotein [HDL] cholesterol), central (abdominal) obesity, hypertension, and concomitant insulin resistance=glucose intolerance. Although no specific cause-and-effect relationship has been established, the outcomes of these associative factors are significantly increased risks for developing diabetes and heart disease. Eric S. Freedland, M.D., a senior editor of Metabolic Syndrome and Related Disorders[1] based in Boston, Massachusetts, notes that ''the escalating worldwide epidemic of metabolic syndrome affects each of us—either directly or indirectly. It demands multidisciplinary efforts and cooperation to [e]nsure better understanding of its causes and to develop effective approaches to preventing and treating its associated conditions.'' Using a sample of 3,477 Mexican-American, 3,305 African-American, and 5,581 Anglo-American men and nonpregnant=non-lactating women 20 years and older, the Third National Health and Nutrition Examination Survey's assessment of metabolic syndrome–associated factors and prevalence[2] revealed the following information about the syndrome in the United States:

Metabolic syndrome was present in 22.8% of men and 22.6% of women.
Age-specific prevalence was highest in male and female Mexican-Americans and lowest in male and female African-Americans. Ethnic differences did not change after adjusting for age, body–mass index (BMI), and socioeconomic status.
Metabolic syndrome was present in 4.6% of normal-weight men.
Metabolic syndrome was present in 22.4% of overweight men.
Metabolic syndrome was present in 59.6% of obese men.
A similar distribution was noted for women.
Increasing age, postmenopause, elevated BMI, cigarette smoking, avoidance of alcohol, physical inactivity, low socioeconomic status, and Mexican-American ethnicity are associated with an increased occurrence of metabolic syndrome.

The researchers' conclusions were that approximately 20% of adults in the United States have metabolic syndrome, and it is associated with several modifiable lifestyle factors.[2] Metabolic syndrome, as defined by the Adult Treatment Panel III criteria includes:

a waist circumference greater than 102 cm in men and 88 cm in women
blood pressure of 130=85 mmHg or greater
fasting serum glucose level of greater than 110 mg=dL
serum triglycerides of 150 mg=dL or greater
HDL cholesterol less than 40 mg=dL in men and 50 mg=dL in women.[3]

Individually, these risk factors have been known for some time to contribute to chronic disease. It is the clustering of these factors into a syndrome and their prevalence that bring metabolic syndrome X into the forefront of epidemic conditions in the United States. But ''poor nutrition heads the list of lifestyle factors that make up the underlying causes of metabolic syndrome. Lifestyle intervention, including a focus on improving macro and micronutrient consumption, may provide a solution,'' Dr. Freedland observes.

THE CONNECTION BETWEEN DIET AND NUTRIENTS

Currently, 66% of adults are overweight or obese; 16% of children and adolescents are overweight and 34% are at-risk of becoming overweight. By 2015, 75% of adults will be overweight or obese, and 41% will be obese.[4] Being overweight increases the risk of hypertension, dyslipidemia (high total cholesterol or high levels of triglycerides), type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, asthma, respiratory problems, and some cancers such as endometrial, breast, and colon.[5] The prevalence of serious obesity among the adult population has doubled in the last decade despite mass marketing of diet and weight-loss plans and products, fitness clubs, and home exercise machines and videos.[6] American children have also increased their girth. Weight problems are not unique to Americans either; the World Health Organization has estimated that 1 billion people on the planet are obese.[7] It is well known that the Western diet of refined carbohydrates, saturated fat, and sugary foods is the primary suspect in this epidemic and other conditions such as cancer. Consumption of refined carbohydrates elevates insulin, cholesterol, and triglyceride levels, and reversal of this trend with a low–glycemic index (GI), low-fat, high-protein diet is attainable.[8] Hyperinsulinemia and insulin resistance are identified as key players in the development of metabolic syndrome. Elevated insulin contributes to obesity and high blood pressure, which are also reversible, using similar dietary therapies.[9] Other therapies directed toward decreasing insulin resistance are thought to mitigate problems associated with this syndrome; these approaches include lowered saturated fat intake, low-GI food consumption,

Strategies for Preventing Metabolic Syndrome

Increased fiber intake is associated with decreased insulin resistance.
Reduce saturated fat intake to reduce insulin resistance.
Increased consumption of vegetables with carotenoids is associated with decreased fasting insulin.
Exercise prevents and reverses insulin resistance.
Stress reduction reduces insulin resistance.
Magnesium produces favorable changes in insulin sensitivity.
Chromium produces favorable changes in insulin sensitivity.
a-lipoic acid exerts antioxidative effects and improves insulin resistance.
Inula racemosa produces favorable changes in insulin sensitivity and blood glucose levels.
Gymnema sylvestre produces favorable changes in insulin sensitivity and blood glucose levels.

obesity prevention, and exercise.[10] Mild to moderate alcohol intake, particularly red wine, has been shown to be protective.[11]

Therapeutic strategies aimed at reducing the morbidity of the four factors that comprise metabolic syndrome are currently widely available. Today, weight loss, physical activity, and treatment of the individual risk factors are the main approaches. In the meantime, research efforts focus on determining a particular genetic susceptibility to the syndrome and the interrelationships among bodily organs that may precipitate insulin resistance, with the aim of developing improved therapies.

However, one does not need to look far for the basic causes of metabolic syndrome. All four conditions (obesity, hypertension, hypertriglyceridemia, and hyperinsulinemia) can be linked to one related cause: poor dietary choices, namely, imbalanced consumption of simple carbohydrates. Thus, the main treatment for metabolic syndrome is dietary therapy. One study in women with a family history of cardiovascular disease, following a low-GI diet for four weeks, resulted in increased insulin sensitivity after a glucose challenge and increased glucose uptake in isolated fat cells. Even in lean young adults, a low-GI diet reduced muscle triglycerides, a marker of insulin resistance.[12] In addition, consuming high levels of high-glycemic carbohydrates causes enhanced appetite and a tendency to overeat.[13,14] However, a complete reversal of consuming refined carbohydrates and saturated fats and switching to a complex carbohydrate, protein-rich diet with healthy fatty-acid ratios is not likely to occur overnight. Patient compliance may be less than optimal, especially after 40 to 50 years of undesirable dietary habits. Switching to a low-glycemic natural sweetener, such as xylitol, may be helpful for some patients, as it has negligible effects on blood sugar levels.[15] Attention must be paid to the metabolic costs of a highly refined carbohydrate diet; in particular, one must look at nutrients (minerals and vitamins) that are used to metabolize processed foods. During metabolism, the body uses simple carbohydrates (sugars and starches) to create energy. However, these foods contain very little or, in some instances, no vitamins or minerals, mainly as a result of food processing. The combined effect of eating these foods produces nutritional deficits because the nutritional cofactors (various vitamins and minerals) that are inherently missing from these foods are recruited from body stores to help the body metabolize nutritionally bereft foods. Over time, depletion and inadequate consumption of nutritional cofactors may make the body unable to function properly, which culminates in disease processes. The burden that these foods put on the body contributes to long-term suboptimal micronutrient levels that may result in lower levels of micronutrients, such as chromium and magnesium, in persons who have

Adjunctives for Treating Metabolic Syndrome

40–50 minutes of aerobic exercise, 4–5 times per week (after physician consent)
5–6 servings per day of vegetables
200–1,500 mg of magnesium, in divided doses, per day (may act as a cathartic laxative)
600 mg of chromium, in divided doses, per day
25–50 mg of vanadyl sulfate, twice per day
600 mg of a-lipoic acid, 3 times per day (high dose is used for severe conditions)
500 mg of Inula racemosa (root powder), 3 times per day
400 mg per day of Gymnema sylvestre (GS4, a water-soluble, standardized extract of the leaves of this herb)

metabolic syndrome. Perhaps, over time, chronic underreplacement of micronutrients may lead to yet another syndrome of which we are currently unaware. Today, we are only in the early stages of truly understanding and appreciating the roles that micronutrients play in human health and must deal with metabolic syndrome.

ADDRESSING INSULIN RESISTANCE

Consumption of lower-GI foods and physical fitness will contribute to decreased insulin secretion and resistance, respectively. For patients who receive treatment for this syndrome, insulin regulation is indicated. Borrowing from our knowledge of treating diabetes with natural medicines, many of the same treatment principles may be applied as part of this treatment regimen, including consumption of specific nutrients via diet or supplementation. The remainder of this chapter concentrates on supplementation and exercise.

MAGNESIUM

A low ratio of intracellular magnesium to intracellular calcium has been identified in all four of the conditions that comprise metabolic syndrome.[16] Thus, low magnesium levels are implicated as an important precipitating factor in metabolic syndrome. Ionic intracellular imbalances are associated with cardiovascular diseases and occur in this syndrome as well.[17] Magnesium also plays a main role in controlling insulin-mediated cellular glucose uptake and in counteracting calcium-directed arterial constriction.[18] According to epidemiologic studies, magnesium supplementation for patients with type 2 diabetes and people with hypertension is protective against these disorders, whether they occur alone or are coexistent in an individual.[19] In one study, patients with diabetes were observed to be significantly hypomagnesemic compared to control subjects, and magnesium supplementation exerted positive effects on blood-lipid profiles.[20] The disorders of metabolic syndrome occur less frequently in regions where magnesium sources (in diets and water) are replete.[21] This type of evidence underscores the important role of magnesium for potentially preventing the conditions that comprise metabolic syndrome.[22]

CHROMIUM

A relationship between chromium status and insulin resistance is known to exist in humans,[23] and various studies in animals have demonstrated a link between chromium deficiency and insulin resistance.[24] The benefits of chromium supplementation on serum glucose, lipids, and insulin resistance have occurred in both diabetes types, with a dose-dependent effect.[25] One study that examined the effects of high-dose chromium supplementation (with a calculated reference dose of 70 mg per day) noted the occurrence of DNA fragmentation.[26] Despite a few anecdotal reports of chromium toxicity, and the tendency of chromium to accumulate within the kidney tissues, no other side-effects have been reported in the literature. Chromium as a treatment cofactor in insulin resistance is supported further by research that implies that a lack of, or low amounts of, ingested chromium may be associated with glucose and insulin-regulation disorder. Thus, using a chromium supplement may help to prevent these occurrences.[27] However, despite the established role of chromium in regulation of glucose and

Potential Lifestyle Factors Contributing to Metabolic Syndrome

- High-fat diet
- High-carbohydrate diet
- High glycemic–index foods
- Low-protein diet
- Low consumption of vegetables or fibers
- High consumption of refined sugars and starches
- Micronutrient deficiencies (calcium, magnesium, chromium, vanadium)
- Lack of exercise or sedentary lifestyle
- High stress level

insulin resistance, much controversy exists as to which form of chromium is most effective, and ongoing research in this area continues. Chromium picolinate produces significantly more oxidative stress and DNA damage compared to niacin-bound chromium, which has been demonstrated to be more bioavailable and efficacious and for which no toxicity has been reported.[25]

VANADIUM

Vanadyl sulfate ($VOSO_4$), a form of the trace mineral vanadium, is associated with improved insulin-receptor sensitivity.[28] Vanadyl sulfate has been shown to reduce hyperglycemia and insulin resistance in patients with type 2 diabetes who took 150 mg per day for six weeks.[29] In these subjects, fasting plasma glucose levels, hemoglobin A1c, total cholesterol, and low-density lipoprotein (LDL) cholesterol were all decreased.[30] Vanadium acts as an oral-insulin mimic, decreasing hyperglycemia and improving beta-cell insulin storage and secretory function,[30] thus indicating that vanadium supplementation can be used to treat prediabetic and recently diagnosed insulin-dependency conditions, making it also a useful choice for treating metabolic syndrome. Organic vanadium compounds such as bis(maltolato)oxovanadium(IV) are two to three times as potent as inorganic vanadium and may have less side effects. Although much of the research surrounding vanadium has been conducted on streptozotocin-induced diabetic models and its normalizing effect on elevated blood glucose, vanadium has been shown, in subsequent studies, to lower cholesterol and triglycerides.[31] Poucheret et al. indicated that, although vanadium is deposited in bone, this does not appear to affect bone strength or modeling negatively and that, while a definitive mechanism of action for vanadium is yet to be completely elucidated, vanadium may act as a phosphatase inhibitor, activating protein kinases beyond the insulin receptor.

ALPHA-LIPOIC ACID

Originally classified as a vitamin upon its discovery more than 50 years ago, alpha-lipoic acid is an endogenous coenzyme that acts in conjunction with pyrophosphatase in carbohydrate metabolism and synthesis of adenosine triphosphate (ATP). Supplemental alpha-lipoic acid exerts potent antioxidant activity and is well known for its usefulness as an intra- and extracellular free-radical scavenger and as a water- and fat-soluble antioxidant. In addition, alpha-lipoic acid can regenerate endogenous antioxidants, such as vitamin E, vitamin C, and glutathione.[32] Patients with type 2 diabetes who took alpha-lipoic acid daily experienced

improved insulin resistance and glucose tolerance after several weeks of treatment in one study.[33] Both single and short-term administrations of alpha-lipoic acid have produced increased insulin sensitivity; one study demonstrated an increased glucose clearance of nearly 50%.[34] In another trial, daily infusions of 500 mg of alpha-lipoic acid over 10 days in patients with type 2 diabetes resulted in approximately a 30% increased glucose metabolized clearance.[35] Studies such as these, as well as the known potent antioxidative=replenishing effects of alpha-lipoic acid, support using this supplement for treating metabolic syndrome. It is a wise choice for helping to normalize metabolism by enhancing insulin effectiveness and performing general antioxidation to address the pro-oxidative effects of the conditions comprising metabolic syndrome.

PUSHKARMOOLA

A traditional Ayurvedic botanical medicine, Pushkarmoola (Inula racemosa), has demonstrated blood glucose-lowering effects and enhanced liver glycogen storage without elevating plasma insulin in animal studies. This effect was not due to increased adrenal gland activity or beta-cell degranulation.[36] In addition, the researchers involved in one animal study suggested that the hypoglycemic response that Inula produces may occur peripherally via enhancement of insulin sensitivity, not via up-regulation or release of insulin itself. Inula extract decreased serum glucose concentration in corticosteroid-induced hyperglycemia animal models, also suggesting that additional studies of this botanical medicine may shed light on its use for treating insulin sensitivity.[37] Additional research in human models is needed to quantify the effects of this herb further as an adjunctive treatment for metabolic syndrome.

GYMNEMA

Another botanical medicine from the Ayurvedic system, gymnema (Gymnema sylvestre) leaf extract is used as an adjunctive to insulin and oral hypoglycemic therapies for treating patients with either type 1 or type 2 diabetes. Gymnema causes additional reductions in blood glucose levels as well as decreasing glycosylated hemoglobin.[38] In addition, this herb is effective for lowering total cholesterol and triglycerides in patients with type 2 diabetes, and researchers have speculated that therapy with a specific gymnema extract may stimulate production of endogenous insulin by regenerating and=or revitalizing residual beta cells in these patients.[39] Other studies have shown that gymnema decreases blood-sugar levels, serum triglycerides, and total cholesterol including very low-density lipoprotein and LDL cholesterol.[40] One early study suggested that gymnemic acids, which are derivatives of the leaf, may inhibit intestinal absorption of glucose and may stimulate pancreatic beta-cell growth.[41] Although this herb is a useful adjunct for lowering blood sugar, more research is needed, especially to examine claims regarding beta-cell regeneration with their obvious implications concerning the usefulness of this plant. In the meantime, gymnema is another tool for promoting metabolic normalcy via control of blood sugar and insulin levels. It is interesting that gymnemic acid can inhibit the ability to taste sweet or bitter items without affecting pungent, sour, or astringent tastes.

There are many other botanicals shown to benefit blood-sugar balancing including bitter melon (Momordica charantia), fenugreek (Trigonella foenum-graecum), cassia cinnamon (Cinnamomum aromaticum), and banaba (Lagerstroemia speciosa). (See Chapter 11 on diabetes.)

CARDIOVASCULAR THERAPIES

There are numerous natural therapies that have shown efficacy in balancing abnormal lipids and blood pressure. Botanicals often used for modulating lipids include guggulipid (Commiphora mukul), garlic (Allium sativum), artichoke (Cynara scolymus), turmeric (Curcuma longa), and red yeast rice. (See Chapter 8 on cardiovascular health.) Many botanicals and nutrients have demonstrated blood-pressure lowering action such as hawthorn (Crataegus spp.), coenzyme Q10 (CoQ10), olive leaf (Olea europaea), coleus (Coleus forskohlii), garlic (Allium sativum), pomegranate juice (Punica granatum), L-arginine, fish oils, and the minerals calcium, magnesium, and potassium. (See Chapter 19 on hypertension.)

EXERCISE

Physical activity is quite possibly the single most important preventative choice among patients whose diseases and conditions arise from a sedentary lifestyle. Sedentary lifestyle is one of the main risk factors for multiple chronic disease conditions today and sedentary death syndrome was identified and named to describe the growing life-threatening health problems caused by this lifestyle. Exercise remains the most effective therapy for preventing and reversing insulin resistance.[42] The literature contains numerous references citing how effectively exercise ameliorates cardiovascular risk factors (low HDL cholesterol, obesity, hypertension, and hypertriglyceridemia) and mitigates insulin resistance and glucose intolerance.[43] Regular exercise causes a loss of abdominal body fat in a preferential fashion (increased abdominal girth is used as a quantifying factor in diagnosing metabolic syndrome), and can increase resting fatty-acid metabolism.[44] Exercise has produced improvement of insulin sensitivity in both skeletal muscle and fatty tissue, leading to decreased fasting blood-sugar and insulin levels.[45] Exercise performed for four months improved the factors associated with metabolic syndrome, including insulin resistance in obese children, and these effects were reversed with discontinuation of exercise over time.[46] Physical fitness produces numerous positive effects on the human body, with negligible adverse results on metabolic function (with the exception of overtraining injuries and syndromes). The availability, ease, and benefits of physical fitness in all human conditions make it the most superior therapy for prevention and treatment of metabolic diseases. All four factors of metabolic syndrome are improved directly by exercise, with continuous benefits produced for the duration of the regimen.

CONCLUSIONS

In modern populations, metabolic syndrome is a deadly combination of obesity, hypertension, elevated triglycerides, and hyperinsulinemia. The syndrome is primarily a nutritional disease caused by eating the wrong types of foods and is one of the largest disease epidemics to ever strike North America. The search for genetic propensities and for improved pharmaceutical medications for treating metabolic syndrome may very well help us to determine the root cause of this condition. The statistics tell the story vividly—metabolic syndrome affects 20% of the U.S. population alone. Thus, it is imperative to teach both physicians and patients to recognize and treat this condition early in life, before symptoms become manifest. Food is our fuel as well as our medicine. Poor dietary habits continue to disrupt the order of nature, playing a

major contributory role in decreasing the quality of human health. Metabolic syndrome really is no mystery. Better dietary habits, exercise, and ingestion of the very nutrients that are discarded by food processing will help patients to normalize their metabolism. Botanical medicines also help to repair metabolic processes that have gone awry.

REFERENCES

[1]Published by Mary Ann Liebert, Inc.; for more information visit www.liebertpub.com.

[2]Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: Prevalence and associated risk factor findings in the U.S. population from the Third National Health and Nutrition Examination Survey, 1988–1994. Arch Intern Med. 2003;163:427–436.

[3]Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among U.S. adults: Findings from the third National Health and Nutrition Examination Survey. JAMA. 2002;287:356–359.

[4]Wang Y, Beydoun MA. The obesity epidemic in the United States—gender, age, socioeconomic, racial=ethnic, and geographic characteristics: A systematic review and meta-regression analysis. Epidemiol Rev. 2007;29:6–28. Epub 2007 May 17.

[5]Centers for Disease Control and Prevention. Overweight and Obesity. Available at: www.cdc.gov=nccdphp=dnpa=obesity=index.htm. Accessed November 19, 2007.

[6]Keller KB, Lemberg L. Obesity and the metabolic syndrome. Am J Crit Care. 2003;12:167–170.

[7]World Health Day 7 April 2002–''Move for Health.'' International Obesity Task Force [press release]. April 4, 2002.

[8]Dumesnil JG, Turgeon J, Tremblay A, Poirier P, Gilbert M, Gagnon L, St-Pierre S, Garneau C, Lemieux I, Pascot A, Bergeron J, Despres JP. Effect of a low-glycaemic index–low-fat–high protein diet on the atherogenicmetabolic risk profile of abdominally obese men. Br J Nutr. 2001; 86:557–568.

[9]Lopes HF, Martin KL, Nashar K, Morrow JD, Goodfriend TL, Egan BM. DASH diet lowers blood pressure and lipid-induced oxidative stress in obesity. Hypertension. 2003;41:422–430; Epub 2003 Feb 3.

[10]Minehira K, Tappy L. Dietary and lifestyle interventions in the management of the metabolic syndrome: Present status and future perspective. Eur J Clin Nutr. 2002;56(12):7-page insert following p. 1262.

[11]Jelski W, Szmitkowski M. [Effect of ethanol on metabolic syndrome]. Pol Arch Med Wewn. 2007 Jul;117(7):306–311.

[12]Brand-Miller JC. Glycemic index in relation to coronary disease. Asia Pac J Clin Nutr. 2004; 13(suppl.):S3.

[13]Speechly DP, Buffenstein R. Appetite dysfunction in obese males: evidence for role of hyperinsulinaemia in passive overconsumption with a high fat diet. Eur J Clin Nutr. 2000 Mar;54(3):225–233.

[14]Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. Pediatrics. 1999 Mar;103(3):E26.

[15]Pierini C. Xylitol: A Sweet Alternative. Unique Sweetener Supports Oral Health. Vitamin Research News. Available at www.vrp.com=art=673.asp.

[16]Resnick LM. Ionic basis of hypertension, insulin resistance, vascular disease, and related disorders. The mechanism of ''syndrome X.'' Am J Hypertens. 1993;6(suppl.):123S–134S.

[17]Resnick LM. Cellular ions in hypertension, insulin resistance, obesity, and diabetes: A unifying theme. J Am Soc Nephrol. 1992;3(4 suppl.):S78–S85.

[18]Altura BM, Zhang A, Altura BT. Magnesium, hypertensive vascular diseases atherogenesis, subcellular compartmentation of Ca and Mg and vascular contractility. Miner Electrolyte Metab. 1993;19:323–336.

[19]Paolisso G, Barbagallo M. Diabetes mellitus, and insulin resistance: The role of intracellular magnesium. Am J Hypertens. 1997;10:346–355.

[20]Lal J, Vasudev K, Kela AK, Jain SK. Effect of oral magnesium supplementation on the lipid profile and blood glucose of patients with type 2 diabetes mellitus. J Assoc Physicians India. 2003;51:37–42.

[21]Seelig MS. Epidemiologic data on magnesium deficiency–associated cardiovascular disease and osteoporosis: Consideration of risks of current recommendations for high calcium Intake. In: Rayssiguier Y, ed. Advances in Magnesium Research: Nutrition and Health. Proceedings of the 9th International Symposium on Magnesium, Vichy, France, 2000. Vichy, France: John Libbey & Co., 2001: 177–190.

[22]Guerrero-Romero F, Rodriguez-Moran M. Low serum magnesium levels and metabolic syndrome: Research Group on Diabetes and Chronic Illnesses, Medical Research Unit in Clinical Epidemiology, Mexican Social Security Institute, Durango, Mexico. Acta Diabetol. 2002;39:209–213.

[23]Fulop T Jr, Nagy JT, Worum I. Glucose intolerance and insulin resistance with aging—studies on insulin receptors and post-receptor events. Arch Gerontol Geriatr. 1987;6:107–115.

[24]Striffler JS, Polansky MM, Anderson RA. Overproduction of insulin in the chromium-deficient rat. Metabolism. 1999;48:1063–1068.
[25]Lamson DS, Plaza SM. The safety and efficacy of high-dose chromium. Altern Med Rev. 2002;7(3): 218–235.
[26]Bagchi D, Stohs SJ, Downs BW, Bagchi M, Preuss HG. Cytotoxicity and oxidative mechanisms of different forms of chromium. Toxicology. 2002;180:5–22.
[27]Anderson RA, Polansky MM, Bryden NA, Canary JJ. Supplemental chromium effects on glucose, insulin, glucagon, and urinary chromium losses in subjects consuming controlled low-chromium diets. Am J Clin Nutr. 1991;54:909–916.
[28]Boden G, Chen X, Ruiz J, et al. Effects of vanadyl sulfate on carbohydrate and lipid metabolism in patients with non-insulin–dependent diabetes mellitus. Metabolism. 1996;45:1130–1135.
[29]Cusi K, Cukier S, DeFronzo RA, Torres M, Puchulu FM, Redondo JC. Vanadyl sulfate improves hepatic and muscle insulin sensitivity in type 2 diabetes. J Clin Endocrinol Metab. 2001;86:1410–1417.
[30]Cam MC, Rodrigues B, McNeill JH. Distinct glucose lowering and beta cell protective effects of vanadium and food restriction in streptozotocin-diabetes. Eur J Endocrinol. 1999;141:546–554.
[31]Poucheret P, Verma S, Grynpas MD, McNeill JH. Vanadium and diabetes. Mol Cell Biochem. 1998;188(1–2):73–80.
[32]Biewenga GP, Haenen GR, Bast A. The pharmacology of the antioxidant lipoic acid. Gen Pharmacol. 1997;29:315–331.
[33]Konrad T, Vicini P, Kusterer K, et al. Alpha-lipoic acid treatment decreases serum lactate and pyruvate concentrations and improves glucose effectiveness in lean and obese patients with type 2 diabetes. Diabetes Care. 1999;22:280–287.
[34]Jacob S, Henriksen EJ, Schiemann AL. Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid. Arzneimittelforschung. 1995;45:872–874.
[35]Jacob S, Henriksen EJ, Tritschler HJ. Improvement of insulin-stimulated glucose-disposal in type 2 diabetes after repeated parenteral administration of thioctic acid. Exp Clin Endocrinol Diabetes. 1996;104: 284–288.
[36]Kobayashi T, Song QH, Hong T, Kitamura H, Cyong JC. Preventative effects of the flowers of Inula britannica on autoimmune diabetes in C57BL=KsJ mice induced by multiple low doses of streptozotocin. Phytother Res. 2002;16:377–382.
[37]Gholap S, Kar A. Effects of Inula racemosa root and Gymnema sylvestre leaf extracts in the regulation of corticosteroid induced diabetes mellitus: Involvement of thyroid hormones. Pharmazie. 2003;58:413–145.
[38]Baskaran K, Kizar-Ahamath B, Shanmugasundaram MR, Shanmugasundaram ERB. Antidiabetic effect of leaf extract from Gymnema sylvestre in non-insulin–dependent diabetes mellitus patients. J Ethnopharmacol. 1990;30:295–300.
[39]Shanmugasundaram ER, Rajeswari G, Baskaran K. Use of Gymnema sylvestre leaf extract in the control of blood glucose in insulin-dependent diabetes mellitus. J Ethnopharmacol. 1990;30:281–294.
[40]Online document at: www.naturaldatabase.com=monograph.
[41]Sinsheimer JE, Subba-Rao G, McIlhenny HM. Constituents from G. sylvestre leaves: Isolation and preliminary characterization of the gymnemic acids. J Pharmacol Sci. 1970;59:622–628.
[42]Kelley DE, Goodpaster B, Wing RR, Simoneau JA. Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. Am J Physiol. 1999;277:E1130–E1141.
[43]Thompson PD, Lim V. Physical activity in the prevention of atherosclerotic coronary heart disease. Curr Treat Options Cardiovasc Med. 2003;5:279–285.
[44]Lehmann R, Vokac A, Niedermann K, Agosti K, Spinas GA. Loss of abdominal fat and improvement of the cardiovascular risk profile by regular moderate exercise training in patients with NIDDM. Diabetologia. 1995;38:1313–1319.
[45]Horber FF, Kohler SA, Lippuner K, Jaeger P. Effect of regular physical training on age-associated alteration of body composition in men. Eur J Clin Invest. 1996;26:279–285.
[46]Ferguson MA, Gutin B, Le NA. Effects of exercise training and its cessation on components of the insulin resistance syndrome in obese children. Int J Obes Relat Metab Disord. 1999;23:889–895.

25

NATURAL APPROACHES TO MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS). The disease is characterized by loss of myelin, the fatty tissue that surrounds and protects nerve fibers allowing them to conduct electrical impulses. In MS, scar tissue, or sclerosis, forms at the sites of demyelination, with destruction of neuronal axons and progressive neurologic disability. The National Multiple Sclerosis Society estimates that 400,000 individuals in the United States have MS.[1]

ETIOLOGY AND EPIDEMIOLOGY

The etiology of MS is unknown, but evidence suggests that genetic, environmental, and immunologic factors and infectious agents may be involved. Currently, MS is presumed to be an autoimmune disease that develops in genetically susceptible individuals upon activation by some unknown environmental trigger. Several risk factors have been associated with MS. Tobacco smoking significantly increases the odds of developing MS.[2] So do other lifestyle factors, such as drinking coffee and alcohol.[3] Women are two to three times more likely to develop MS than men, and Caucasians, particularly those of Northern European descent, are more likely to develop MS than other ethnic groups. Individuals living at northern latitudes are also at increased risk, suggesting a possible link with vitamin D and sun exposure. In addition, migration from one geographic area to another changes an individual's risk for MS.

Individuals who move before the age of 15 take on the risk associated with their new geographical location. If an individual migrates after the age of 15, the change in risk is seen in the next generation.[3] It is apparent that genetics plays a role in the etiology of MS, given the increased risk of the disease in siblings of individuals with MS, as well as a greater concordance rate in monozygotic compared to dizygotic twins.[4] In addition, research indicates that first-degree relatives of individuals with MS have a sevenfold greater than average risk of developing the disease.[5] Considerable research is being done to determine the gene or genes that cause(s) susceptibility to MS, and currently, the most consistent finding involves the major histocompatibility complex (MHC), also called the human leukocyte antigen (HLA) system. A specific finding is that a variant in the HLA-DRB1 allele is linked to an increased risk of MS. Most recently, scientists have also found that variants of the gene for the alpha chain of the interleukin (IL)–7 receptor and the gene for the alpha chain of the interleukin IL-2 receptor are associated with an increased risk of MS.[6]

Numerous infectious agents have also been associated with MS and are currently being investigated. Evidence indicates that infectious mononucleosis caused by the Epstein-Barr virus increases the risk of MS, and that this increased risk persists for at least 30 years after infection.[7] Research also shows that infectious mononucleosis in adolescence or young adulthood increases the risk of MS by 2.3-fold.[8]

Among other findings, Varicella zoster viral DNA has been detected more frequently than average in individuals with MS, and is found in 43.5% of individuals with relapsing–remitting

MS. The results of this same study demonstrated active replication of JC virus and human herpes virus-6 (HHV-6) in the CNS of some individuals with MS.[9]

Some research also suggests that there is a link between the recombinant hepatitis B vaccine and increased risk of developing MS.[10] Studies of pregnancy in women with MS also suggest a role of hormones in the disease. Of the women studied, 75% showed a distinct shift from a Th2 cytokine bias during pregnancy to a Th1 cytokine bias postpartum.[11]

PATHOLOGY

Individuals with MS experience a variety of symptoms, and can have a relapsing–remitting course of disease; or a primary progressive course; or a relapsing–remitting followed by a progressive course; or what is known as a secondary-progressive course; or a progressive-relapsing course. Relapses of MS are defined as the appearance of new or worsening neurologic symptoms lasting longer than 24 hours. These symptoms usually evolve over a period of 24–48 hours, plateau for several weeks, and may resolve over periods ranging from weeks to several months. Common symptoms of MS include fatigue, visual changes, numbness, weakness, muscle spasticity, and depression. Additional symptoms may include difficulty with walking, problems with balance and coordination, dizziness or vertigo, emotional changes, cognitive impairment, bladder or bowel problems, pain, and tremor. The most common presenting symptoms of MS are diplopia, numbness and tingling in the extremities, and unilateral loss of vision from optic neuritis.

The pathology of MS includes dysfunction in both the immune and nervous systems. Inflammatory cytokines, macrophages, microglia, antibodies, and free radicals may all cause damage to myelin and axons. Degenerative changes are characteristic of progressive forms of MS, while inflammatory changes within the CNS are characteristic of the relapsing–remitting form of the disease. Large numbers of inflammatory cells are seen in new lesions, while fewer are seen in chronic lesions.

Immune Dysfunction

The immune response plays a key role in the pathogenesis of MS. T-lymphocytes are implicated in the disease process. The activation of CD4 T-cells and their differentiation into T-helper-1(Th1) cells are critical events in the initial steps of MS, and these cells are probably also important mediators in the long-term progression of the disease. Cytokines secreted by Th1 cells, such as IL-12, interferon (IFN)–gamma, tumor necrosis factor-alpha (TNF-a), and IL-2, are believed to be involved in the pathology of MS. Th2 cytokines suppress Th1 activity and include IL-4, IL-10, and transforming growth factor-beta (TGF-b). MS patients have increased circulating T-cell and antibody reactivity to the myelin proteins and gangliosides that are essential to the structural integrity of the myelin sheath. The pathogenesis of MS involves a breakdown in T-cell tolerance to myelin proteins, such as myelin basic protein (MBP).

Free Radicals

Free radicals are believed to play a role in the pathogenesis of MS. Persons with MS have elevated concentrations of markers of nitric oxide (NO) production, including nitrate and nitrite, in their cerebrospinal fluid (CSF), blood, and urine. Research suggests that NO has a role in the axonal degeneration and impairment of axonal conduction, disruption of the blood-brain

barrier, and oligodendrocyte injury and demyelination in MS.[12] NO is also found in increased concentrations in inflammatory MS lesions, possibly as the result of increased expression of inducible nitric oxide synthase (iNOS) by astrocytes and macrophages. Astrocytes, macrophages, and oligodendrocytes in these lesions have also shown elevated levels of nitrotyrosine, indicating the presence of peroxynitrite, a highly reactive metabolite of NO, that may be the primary source of injury of oligodendrocytes in MS patients.[13] A study of CSF levels of nitrate and nitrite in MS patients over a period of three years found increased CSF levels of nitrate and nitrite in mildly disabled individuals, which correlated with the volume of lesions found on magnetic resonance imaging (MRI). Greater than normal levels of nitrate and nitrite in the CSF at the time of baseline examination of MS patients also correlated with clinical progression of the disease and with MRI results.[14]

Neurologic Dysfunction

Abnormalities in the concentrations and relative concentrations of various neurotransmitters are thought to play a part in the pathogenesis of MS. Research has found that persons with MS have increased levels of CSF and the excitatory neurotransmitters glutamate, aspartate, and noradrenaline. Increased blood levels of glutamine, asparagine, and glycine were also found in these patients.[15] Further suggesting neuronal and axonal dysfunction in MS is the finding of altered levels of myoinositol, creatine, choline, glutamate, glutamine, and N-acetyl-aspartate in surrounding white and gray matter.[16]

DIAGNOSIS

No specific test or set of criteria now exists for making a definitive diagnosis of MS. The current, generally accepted diagnostic standard, known as the revised McDonald criteria, was first described in 2005 and is based on the patient's history, diagnostic tests, results of neurologic examination, and findings on MRI. A positive diagnosis requires at least two distinct, CNS-related neurologic symptoms occurring in different anatomical locations and on different occasions, which are not caused by another disease process. An MRI scan performed at least 30 days after the onset of symptoms and showing lesions compatible with MS can be used to establish a second episode of the disease in the absence of prior clinical evidence of its presence. Further tests for the diagnosis of MS may include analysis of the CSF to detect an elevated immunoglobulin (Ig)G index, and=or the finding on protein electrophoresis of bands indicating oligoclonal IgG in the CSF but not in the serum. An electroencephalogram may show a greater than normal number of evoked potentials. Additional testing may be needed to exclude other causes, such as chronic infectious disease, of clinical symptoms often seen in MS.

CONVENTIONAL THERAPIES

IFN-beta (IFN-b) (e.g., IFNA-beta-1b, Betaseron; IFN-beta-1a, Avonex; and IFN-beta-1a, Rebif)[17] is used to modify the immune response in MS. IFN-beta affects the immune system by inhibiting T-cell stimulation and increasing the activity of CD8 suppressor lymphocytes. IFN-beta also regulates the production of IFN-gamma. The net effect is to reduce the overall immune response to myelin in MS. Also, IFN-beta restores the integrity of the blood–brain barrier, decreasing T-cell migration into the brain. In inflammatory conditions in the CNS such as

multiple sclerosis or experimental autoimmune encephalomyelitis (EAE), circulating lymphocytes and monocytes=macrophages readily cross the blood–brain barrier and gain access to the CNS leading to edema, inflammation, and demyelination. Also often used to modify the disease process in MS is glatiramer acetate, a mixture of synthetic polypeptides composed of four amino acids, and based on the structure of MBP, which is believed to inhibit the T-cell response to multiple antigens in myelin. Glatiramer acetate induces T-regulatory cells known as GA-specific regulatory CD4 and CD8 lymphocytes, as well as causing a shift from Th1 to Th2 activity, increasing the secretion of anti-inflammatory cytokines and suppressing the autoimmunity led by Th1 cells.[18]

Free radicals are believed to play a role in the pathogenesis of multiple sclerosis.

When IFNs and glatiramer acetate do not effectively control MS, immunosuppressant drugs are often used. The most commonly used such agents are azathioprine, cyclophosphamide, methotrexate, and mitoxantrone. Mitoxantrone (Novantrone) is often used to reduce neurologic disability and=or the frequency of clinical relapses in secondary progressive, progressive-relapsing, and worsening relapsing–remitting MS. This agent acts by suppressing lymphocyte production in bone marrow, decreasing T-cell and B-cell numbers.[19]

High-dose corticosteroids are used to manage acute relapses. Intravenous methylprednisolone is the standard treatment for MS relapses and elicits rapid reduction of gadolinium enhancing (Gd) lesions seen on brain MRIs of patients with MS.[20] Natalizumab (Tysabri) is a recombinant humanized anti-a-4 integrin monoclonal antibody approved for use in relapsing–remitting MS patients. It decreases leukocyte migration from peripheral blood into the CNS.[21]

NATURAL THERAPIES

Vitamin D

Research has found that higher serum levels of 25-hydroxyvitamin D are associated with a decreased risk of developing MS,[22] and animal models of the disease indicate that supplementation with vitamin D reduces the frequency of MS and retards its progression. A study of vitamin D supplementation showed it to be associated with a 40% reduction in MS risk,[23] and another study found a strong association between reduced exposure to sunlight, decreased vitamin D levels, and greater disability in persons with MS.[24] It has also been found that vitamin D levels are lower during relapses of MS than during remission periods, suggesting a possible role of vitamin D on the course of the disease,[25] and the finding that concentrations of 25-hydroxyvitamin D are lower and those of intact parathyroid hormone are higher during relapses than during remissions suggests that altered calcium metabolism may also play a role in the course of MS.[26]

Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) is a potent antioxidant and coenzyme required for numerous biochemical pathways. Studies with animal models of MS indicate that supplementation with

Figure 25–1. Canola plants.

ALA retards progression of the disease and decreases demyelination and T-cell and macrophage infiltration into the CNS.[27] Additional research with animal models indicates that ALA decreases T-cell migration and stabilizes the dysfunctional blood–brain barrier in MS, as well as inhibits damage to the barrier caused by reactive oxygen species (ROS).[28] Human studies indicate that ALA is well tolerated in MS, and decreases the concentrations of such markers of inflammation as matrix metalloproteinase-9 (MMP-9) and soluble intercellular adhesion molecule-1 (sICAMP-1).[29] Additionally, ALA enhances immunomodulatory activity by increasing the concentration of cyclic adenosine monophosphate (cAMP) in human T-cells and natural killer cells.[30]

Essential Fatty Acids

Supplementation with essential fatty acids (EFAs) has proven beneficial in MS. EFAs compete with pro-inflammatory metabolic processes to decrease the synthesis of inflammatory mediators, in addition to suppressing B- and T-lymphocyte proliferation and decreasing antibody production. The two EFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in high concentrations in fatty fish such as cod, salmon, and mackerel. The combination of a low-fat diet and supplementation with omega-3 fatty acids was found to decrease fatigue in patients with MS and to decrease the relapse rate in the disease.[31]

Alpha-linolenic acid, an omega-3 fatty acid commonly found in Linum usitatissimum (flax), canola, and Glycine max (soy) beans, can be taken as a supplement, although this is considered a secondary choice by many clinicians since alpha-linolenic acid does not appear to be as therapeutically efficient as EPA and DHA supplementation. Studies have also found that treatment of microglial cultures with either omega-3 fatty acids or fish oil inhibits the production of the myelin toxin MMP-9,[32] and that supplementation with omega-3 polyunsaturated fatty acids positively affects cytokines in MS patients. The latter study found a decrease in IL-1beta, TNF-alpha, IL-2, and IFN-gamma in association with such supplementation, and a diminished production of the pro-inflammatory eicosanoids prostaglandin E2 and leukotriene B4.[33]

Figure 25–2. Olive oil.

B Vitamins

Several vitamins have been shown to be present in suboptimal concentrations in patients with MS. Vitamin B_{12}, which is important for myelin formation as well as for immunomodulatory activity, may be among these vitamins.[34] Significantly lower serum levels of vitamin B_{12} have been found in persons in whom symptoms of MS appear before the age of 18 than in patients with symptoms of later onset.[35] In addition to serum B_{12} deficiency, evidence also indicates decreased levels of red blood cell folate in patients with MS.[36]

However, at least one study, rather than finding overtly decreased levels of vitamin B_{12} in MS patients, found that the binding capacity for unsaturated vitamin B_{12} was significantly decreased in these patients as compared to controls and individuals with other neurologic disorders. When the scientists went on to provide massive supplemental doses of 60 mg daily of methyl-vitamin B_{12} for six months to a small group of patients with chronic progressive MS, the scientists found that abnormalities in visual and brainstem auditory evoked potentials improved more often during the therapy than in the period before supplementation.[37] Researchers have suggested that vitamin B_{12} deficiency may make an individual more susceptible to immunologic or viral insults.

Antioxidants

ROS appear to play a role in the pathology of MS. Epigallocatechin-3-gallate (EGCG), a constituent of Camellia sinensis (green tea) known for its antioxidant activity, reduced the clinical severity of experimental autoimmune encephalomyelitis (EAE) in mice when given at or after the onset of EAE in the animals, by limiting brain inflammation and reducing neuronal damage. EAE is the animal model used to study MS as this condition can be induced in laboratory animals. EAE is a demyelinating disease in which the myelin is damaged and exhibits similar clinical progression. EGCG also directly inhibited the formation of neurotoxic ROS in neurons.[38] Curcumin, a constituent of Curcuma longa (turmeric) with potent antioxidant activity, is also known for its anti-inflammatory activity. Supplementation with curcumin in animal models of MS decreased the duration and severity of the disease by decreasing secretion of the pro-inflammatory cytokine IL-12 from monocytes and microglial cells resulting in decreased T-cell proliferation and Th1 differentiation.[39]

Another supplement with antioxidant properties is Ginkgo biloba (ginkgo) extract. When given at a dose of 240 mg per day to persons with MS, this was found to decrease fatigue and improve functionality over that of controls.[40] Treatment of animal models of MS with the antioxidant supplement N-acetyl-L-cysteine (NAC) was also found to attenuate clinical

disease, increase the concentrations of anti-inflammatory cytokines such as IL-10, and decrease both nitrite production and the Th1-cell secretion of IFN-gamma.[41] Quercetin, a dietary flavonoid found in many plants and known for its anti-inflammatory and antioxidant activity, was found to attenuate EAE, and decrease IL-12-induced T-cell proliferation and Th1-cell differentiation.[42] A further finding in MS has been that of low levels of the antioxidant nutrients beta-carotene, retinol, alpha-tocopherol, and ascorbic acid in serum or CSF.[43]

Carnitine

The results of a randomized, double-blind, crossover study have suggested that acetyl-L-carnitine given supplementally at 1 g twice daily is better tolerated and more effective than amantadine for the treatment of MS-related fatigue as evaluated with the Fatigue Severity Scale.[44] Additional studies have found lower carnitine levels in patients treated for MS than in untreated MS patients or controls. When levocarnitine was given orally as a supplement at a dose of 3–6 g per day, 63% of MS patients undergoing immunosuppressive or immunomodulatory therapy exhibited reductions in the intensity of their fatigue.[45]

Additional Nutrients

Two further nutrients investigated in MS have been glucosamine and retinoic acid. Supplementation with glucosamine in animal models of MS was found to increase levels of Th2 cytokines and suppress the Th1 response. Inflammation and demyelination in the CNS were decreased and EAE was suppressed.[46] This suggests that supplemental glucosamine may act as both an immunosuppressant and immunomodulating agent in MS.[46]

Retinoic acid has been shown to inhibit clinical signs of MS in animal models by preferentially inducing Th2 cytokines over those secreted by Th1 cells.[47] Research has also found that 9-cis-retinoic acid inhibits the production of NO and pro-inflammatory cytokines by microglia and astrocytes, which are processes implicated in the pathology of MS.[48] In other research, the combination of IFN-beta-1b with all-trans-retinoic acid inhibited IFN gamma-secreting cells, enhanced T-suppressor-cell activity, and decreased T-cell proliferation to a greater degree than did either treatment alone.[49]

In addition, significantly decreased levels of manganese and increased levels of copper have been found in the CSF of MS patients as compared to controls.[50]

Diet

Evidence suggests that specific dietary modifications may be beneficial in MS. The Swank diet advocates a low intake of saturated fat of less than 15 g per day and relatively high intake of polyunsaturated oil. Other recommendations of the diet are an unsaturated fat intake of 20–50 g per day; abstention from red meat including pork for the first year, followed by a maximum 3 oz of red meat per week thereafter; consumption of dairy products having no fat or less than 1% butterfat; no use of processed food containing saturated fat; an unlimited intake of fruits and vegetables; and supplementation with cod liver oil at 1 tsp daily.[51] Butter, margarine, lard, shortening, cocoa butter, coconut oil, hydrogenated oil, palm oil, and imitation dairy products must be avoided.

Swank followed a group of patients for 34 years and demonstrated relative success with his low-fat diet. His study showed that patients who adhered to the recommendation of 20 g of fat

per day or less experienced significantly less deterioration and had much lower death rates than subjects who consumed greater fat than this per day. Persons with minimum disability at the beginning of the trial experienced the greatest benefit.[52]

A study compared a diet with 15% fat and fish oil supplementation with a diet of 30% fat and olive oil supplementation in individuals with relapsing–remitting MS. The patients had moderate clinical improvements with the former as compared with the latter regimen as measured with the Physical Components Summary Scale and the Short Health Status Questionnaire. The relapse rate in both groups was decreased.[31] A further study found that consumption of liquid cow's milk was significantly associated with an increased prevalence of MS worldwide, with a weaker correlation for consumption of butter and cream.[53]

HORMONE BALANCING

Research suggests that hormones influence the duration and severity of autoimmunity affecting the CNS. One study found abnormally low levels of testosterone in human males with MS, and animal models of MS have shown low levels of testosterone and increased levels of luteinizing hormone,[54] as well as an inverse relationship between testosterone levels and levels of inflammatory mediators.[54] Another study showed improvement in cognitive performance, a slowing of brain atrophy, and increased lean body mass upon supplementation with a gel containing 100 mg of testosterone given daily to men with relapsing–remitting MS for a 12-month period.[55] However, the supplementation had no significant effect on the numbers or volumes of sclerotic lesions.[55] Levels of the androgen dehydroepiandrosterone (DHEA) have also been found to be significantly lower in MS patients than in healthy individuals.[56]

Estrogen levels also appear to play a role in the severity of MS symptoms. Among a group of menopausal women with MS, 82% reported premenstrually increased symptom severity, 54% reported a worsening of symptoms with menopause, and 75% of those who had tried hormone replacement therapy reported an improvement in symptoms.[57] Studies indicate that low-dose estradiol may be beneficial for women with MS. Animal models show that low-dose estradiol inhibits T-cell migration into the CNS and has neuroprotective effects that promote axon and myelin survival.[58] Estrogens have also been found to inhibit the production of pro-inflammatory Th1 cytokines such as IL-12, TNF-alpha, and IFN gamma, and to stimulate the production of anti-inflammatory Th2 cytokines such as IL-10, IL-4, and TGF-beta. This may explain why estrogen modulates Th1- and Th2-mediated diseases such as MS.[59] Studies of pregnancy in women with MS also suggest a role of hormones in the disease. Of the women studied, 75% showed a distinct shift from a Th2 cytokine bias during pregnancy to a Th1 cytokine bias postpartum.[60] Clinical trials using daily doses of estriol that are equivalent to the amount produced during pregnancy have shown significant reduction in MS lesions in patients with the relapsing–remitting form of the disease.[11]

CONCLUSIONS

MS is a complicated disease of unknown etiology, whose initiation and progression are affected by numerous factors. A number of natural therapies have been shown to benefit individuals with MS, and they need to be more vigorously studied.

REFERENCES

[1]The MS Informational Sourcebook. Epidemiology. Online document at: www.nationalmssociety.org=site=PageServer?pagename HOM_LIB_sourcebook_epidemiology. Accessed August 7, 2007.

[2]Hawkes CH. Smoking is a risk factor for multiple sclerosis: A meta-analysis. Mult Scler. 2007;13:610–615.

[3]Pekmezovic T, Drulovic J, Milenkovic M, et al. Lifestyle factors and multiple sclerosis: A case-control study in Belgrade. Neuroepidemiology. 2006;27:212–216.

[4]Oksenberg JR, Barcellos LF. The complex genetic aetiology of multiple sclerosis. J Neurovirol. 2000; 6(suppl.2):S10–S14.

[5]Nielsen NM, Westergaard T, Rostgaard K, et al. Familial risk of multiple sclerosis: A nationwide cohort study. Am J Epidemiol. 2005;162:774–778.

[6]The International Multiple Sclerosis Genetics Consortium. Risk alleles for multiple sclerosis identified by a genome wide study. N Engl J Med. 2007;357:851–862.

[7]Nielsen TR, Rostgaard K, Nielsen NM, et al. Multiple sclerosis after infectious mononucleosis. Arch Neurol. 2007;64:72–75.

[8]Thacker EL, Mirzaei F, Ascherio A. Infectious mononucleosis and risk for multiple sclerosis: A meta-analysis. Ann Neurol. 2006;59:499–503.

[9]Mancuso R, Delbue S, Borghi E, et al. Increased prevalence of Varicella zoster virus DNA in cerebrospinal fluid from patients with multiple sclerosis. J Med Virol. 2007;79:192–199.

[10]Hernán MA, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: A prospective study. Neurology. 2004;63:838–842.

[11]Sicotte N, Liva S, Klutch R, et al. Treatment of multiple sclerosis with the pregnancy hormone estriol. Ann Neurol. 2002;52:421–428.

[12]Smith KJ, Lassmann H. The role of nitric oxide in multiple sclerosis. Lancet Neurol. 2002;1:232–241.

[13]Jack C, Antel J, Brück W, Kuhlmann T. Contrasting potential of nitricoxide and peroxynitrite to mediate oligodendrocyte injury in multiple sclerosis. Glia. 2007;55:926–934.

[14]Rejdak K, Eikelenboom MJ, Petzold A, et al. CSF nitric oxide metabolites are associated with activity and progression of multiple sclerosis. Neurology. 2004;63:1439–1445.

[15]Barkhatova VP, Zavalishin IA, Askarova LSh, et al. Changes in neurotransmitters in multiple sclerosis. Neurosci Behav Physiol. 1998;28:341–344.

[16]Tiberio M, Chard DT, Altmann DR, et al. Metabolite changes in early relapsing–remitting multiple sclerosis: A two year follow-up study. J Neurol. 2006;253:224–230.

[17]The MS Information Sourcebook. Interferons. Online document at: www.nationalmssociety.org=site=PageServer?pagename HOM_LIB_sourcebook_interferons. Accessed August 9, 2007.

[18]Schrempf W, Ziemssen T. Glatiramer acetate: Mechanisms of action in multiple sclerosis. Autoimmun Rev. 2007;6:469–475.

[19]The MS Information Sourcebook. Chemotherapy. Online document at: www.nationalmssociety.org=site=PageServer?pagename HOM_LIB_sourcebook_chemotherapy. Accessed August 9, 2007.

[20]Then Bergh F, Kümpfel T, Schumann E, et al. Monthly intravenous methylprednisolone in relapsing–remitting multiple sclerosis—reduction of enhancing lesions, T2 lesion volume and plasma prolactin concentrations. BMC Neurol. 2006;6:19.

[21]Horga A, Horga de la Parte JF. Natalizumab in the treatment of multiple sclerosis [in Spanish]. Rev Neurol. 2007;45:293–303.

[22]Munger KL, Levin LI, Hollis BW, et al. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA. 2006;296:2832–2838.

[23]Brown SJ. The role of vitamin D in multiple sclerosis. Ann Pharmacother. 2006;40:1158–1161.

[24]van der Mei IA, Ponsonby AL, Dwyer T, et al. Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. J Neurol. 2007;254:581–590.

[25]Soilu-Hänninen M, Airas L, Mononen I, et al. 25-Hydroxyvitamin D levels in serum at the onset of multiple sclerosis. Mult Scler. 2005;11:266–271.

[26]Soilu-Hanninen M, Laaksonen M, Laitinen I, et al. A longitudinal study of serum 25-hydroxyvitamin D and intact PTH levels indicate the importance of vitamin D and calcium homeostasis regulation in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2007;Jun 19;[Epub ahead of print].

[27]Morini M, Roccatagliata L, Dell'Eva R, et al. Alpha-lipoic acid is effective in prevention and treatment of experimental autoimmune encephalomyelitis. J Neuroimmunol. 2004;148:146–153.

[28]Schreibelt G, Musters RJ, Reijerkerk A, et al. Lipoic acid affects cellular migration into the central nervous system and stabilizes blood–brain barrier integrity. J Immunol. 2006;177:2630–2637.

[29]Yadav V, Marracci G, Lovera J, et al. Lipoic acid in multiple sclerosis: A pilot study. Mult Scler. 2005;11:159–165.

[30]Schillace RV, Pisenti N, Pattamanuch N, et al. Lipoic acid stimulates cAMP production in T lymphocytes and NK cells. Biochem Biop. 2007;354:259–264.
[31]Weinstock-Guttman B, Baier M, Park Y, et al. Low fat dietary intervention with omega-3 fatty acid supplementation in multiple sclerosis patients. Prostaglandins Leukot Essent Fatty Acids. 2005;73:397–404.
[32]Liuzzi GM, Latronico T, Rossano R, et al. Inhibitory effect of polyunsaturated fatty acids on MMP-9 release from microglial cells—implications for complementary multiple sclerosis treatment. Neurochem Res. 2007;Jul11;[Epub ahead of print].
[33]Gallai V, Sarchielli P, Trequattrini A, et al. Cytokine secretion and eicosanoid production in the peripheral blood mononuclear cells of MS patients undergoing dietary supplementation with n-3 polyunsaturated fatty acids. J Neuroimmunol. 1995;56:143–153.
[34]Miller A, Korem M, Almog R, Galboiz Y. Vitamin B_{12}, demyelination, remyelination and repair in multiple sclerosis. J Neurol Sci. 2005;233:93–97.
[35]Sandyk R, Awerbuch GI. Vitamin B_{12} and its relationship to age of onset of multiple sclerosis. Int J Neurosci. 1993;71:93–99.
[36]Reynolds EH, Bottiglieri T, Laundy M, et al. Vitamin B_{12} metabolism in multiple sclerosis. Arch Neurol. 1992;49:649–652.
[37]Kira J, Tobimatsu S, Goto I. Vitamin B_{12} metabolism and massive-dose methyl vitamin B_{12} therapy in Japanese patients with multiple sclerosis. Intern Med 1994;33:82–86.
[38]Aktas O, Prozorovski T, Smorodchenko A, et al. Green tea epigallocatechin-3-gallate mediates T cellular NF-kappa B inhibition and exerts neuroprotection in autoimmune encephalomyelitis. J Immunol. 2004; 173:5794–5800.
[39]Natarajan C, Bright JJ. Curcumin inhibits experimental allergic encephalomyelitis by blocking IL-12 signaling through Janus kinase-STAT pathway in T lymphocytes. J Immunol. 2002;168:6506–6513.
[40]Johnson SK, Diamond BJ, Rausch S, et al. The effect of Ginkgo biloba on functional measures in multiple sclerosis: A pilot randomized controlled trial. Explore (NY). 2006;2:19–24.
[41]Stanislaus R, Gilg AG, Singh AK, Singh I. N-acetyl-L-cysteine ameliorates the inflammatory disease process in experimental autoimmune encephalomyelitis in Lewis rats. J Autoimmune Dis. 2005;2:4.
[42]Muthian G, Bright JJ. Quercetin, a flavonoid phytoestrogen, ameliorates experimental allergic encephalomyelitis by blocking IL-12 signaling through JAK-STAT pathway in T lymphocyte. J Clin Immunol. 2004;24:542–552.
[43]Besler HT, Comoğlu S. Lipoprotein oxidation, plasma total antioxidant capacity and homocysteine level in patients with multiple sclerosis. Nutr Neurosci. 2003;6:189–196.
[44]Tomassini V, Pozzilli C, Onesti E, et al. Comparison of the effects of acetyl-L-carnitine and amantadine for the treatment of fatigue in multiple sclerosis: Results of a pilot, randomised, double-blind, crossover trial. J Neurol Sci. 2004;218(1–2):103–108.
[45]Lebrun C, Alchaar H, Candito M, et al. Levocarnitine administration in multiple sclerosis patients with immunosuppressive therapy–induced fatigue. Mult Scler. 2006;12:321–324.
[46]Zhang GX, Yu S, Gran B, Rostami A. Glucosamine abrogates the acute phase of experimental autoimmune encephalomyelitis by induction of Th2 response. J Immunol. 2005;175:7202–7208.
[47]Racke MK, Burnett D, Pak SH, et al. Retinoid treatment of experimental allergic encephalomyelitis: IL-4 production correlates with improved disease course. J Immunol. 1995;154:450–458.
[48]Xu J, Drew PD. 9-Cis-retinoic acid suppresses inflammatory responses of microglia and astrocytes. J Neuroimmunol. 2006;171(1–2):135–144.
[49]Qu ZX, Dayal A, Jensen MA, Arnason BG. All-trans retinoic acid potentiates the ability of interferon beta-1b to augment suppressor cell function in multiple sclerosis. Arch Neurol. 1998;55:315–321.
[50]Melø TM, Larsen C, White LR, et al. Manganese, copper, and zinc in cerebrospinal fluid from patients with multiple sclerosis. Biol Trace Elem Res. 2003;93(1–3):1–8.
[51]Swank MS Diet. Online document at: http:=swankmsdiet.org=index.php=diet=about. Accessed August 7, 2007.
[52]Swank RL, Dugan BB. Effect of low saturated fat diet in early and late cases of multiple sclerosis. Lancet. 1990;336:37–39.
[53]Malosse D, Perron H, Sasco A, Seigneurin JM. Correlation between milk and dairy product consumption and multiple sclerosis prevalence: A worldwide study. Neuroepidemiology. 1992;11(4–6):304–312.
[54]Foster SC, Daniels C, Bourdette DN, Bebo BF. Dysregulation of the hypothalamic–pituitary–gonadal axis in experimental autoimmune encephalomyelitis and multiple sclerosis. J Neuroimmunol. 2003;140 (1–2):78–87.
[55]Sicotte NL, Giesser BS, Tandon V, et al. Testosterone treatment in multiple sclerosis: A pilot study. Arch Neurol. 2007;64:683–688.
[56]Ramsaransing GS, Heersema DJ, De Keyser J. Serum uric acid, dehydroepiandrosterone sulphate, and apolipoprotein E genotype in benign vs. progressive multiple sclerosis. Eur J Neurol. 2005;12:514–518.

[57]Smith R, Studd JW. A pilot study of the effect upon multiple sclerosis of the menopause, hormone replacement therapy and the menstrual cycle. J R Soc Med. 1992;85:612–613.
[58]Offner H, Polanczyk M. A potential role for estrogen in experimental autoimmune encephalomyelitis and multiple sclerosis. Ann NY Acad Sci. 2006;1089:343–372.
[59]Salem ML. Estrogen, a double-edged sword: Modulation of TH1- and TH2-mediated inflammations by differential regulation of TH1=TH2 cytokine production. Curr Drug Targets Inflamm Allerg. 2004;3:97–104.
[60]Al-Shammri S, Rawoot P, Azizieh F, et al. Th1=Th2 cytokine patterns and clinical profiles during and after pregnancy in women with multiple sclerosis. J Neurol Sci. 2004;222(1–2):21–27.

26

NATURAL SUPPORTS FOR GAINING AND MAINTAINING MUSCLE MASS

Muscle-building research is useful for athletes and bodybuilders as well as for elderly patients and those with muscle-wasting conditions. Research shows that a healthy diet, resistance exercise, and nutritional supplements are beneficial for improving body composition and the body of research on nutritional supplements for athletes is growing. However, supplementation will not improve muscle size and strength without resistance training, such as weight lifting or weight-bearing aerobics. The sports-nutrition and weight-loss industries in the United States comprise a growing market, and there were reports of $14.3 billion in sales of such products in 2004.[1] In addition, according to the Nutrition Business Journal, this product market increased sales by 14% to reach $15.6 billion in 2005 and is estimated to grow at a rate of approximately 5%–7% per year for the next eight years.[2]

BODY COMPOSITION AND ITS EFFECTS ON MUSCLES

Insulin Resistance

Insulin resistance is a state in which the pancreas secretes increasingly higher levels of insulin to facilitate glucose uptake into skeletal, hepatic, and adipose tissue cells. Obesity, the most common cause of insulin resistance, is associated with a decreased number of receptors and with postreceptor failure to activate the tyrosine kinase. The beta subunit of the insulin receptor is a tyrosine kinase, which is activated when insulin binds to the alpha subunit; the kinase activity autophosphorylates and mediates multiple actions of insulin. Specific glucose receptors in muscle and adipose tissue are poorly responsive to high levels of insulin in the blood. Moderate weight loss has been shown to reduce insulin resistance. Hyperinsulinemia increases intracellular lipid accumulation, which, in turn, may increase insulin resistance. Insulin-resistant skeletal muscle has lower oxidative capacity and has decreased fatty-acid oxidation favoring lipid accumulation.[3] In addition, high lipid levels in skeletal muscle also result in a lower oxidative capacity.[4]

Hormones have also been shown to have a great impact on insulin resistance. Stress and its resulting increase in epinephrine and cortisol affects insulin resistance. These adrenal hormones have been shown to increase glycogen breakdown from the liver and affect glucose utilization unfavorably.[5,6] Estrogen supplementation may also increase insulin resistance, particularly in postmenopausal women.[7] Increased testosterone in females and increased estrogens in males decrease peripheral glucose utilization.[8] Studies have shown that dehydroepiandrosterone (DHEA) supplementation increases peripheral glucose utilization.[9] Insulin-like growth factor-1 (IGF-1) is a polypeptide stimulated by growth hormone, which affects growth and glucose metabolism. Studies have shown that IGF-1 increases peripheral glucose utilization as well as decreases protein catabolism.[10]

Aging

Many physiologic changes seen with aging affect muscle size and strength. Many hormones, such as testosterone, estrogen, DHEA, growth hormone, and IGF-1, decrease with age. Research suggests that age-related muscle loss, or sarcopenia, may be related to declines in growth hormone, IGF-1, estrogen, and testosterone and other androgens.[11] In addition, decreased nutritional intake and lowered vitamin D levels cause muscle atrophy in aging patients. Other causes of muscle loss include decreased innervation, lowered physical activity, and increased levels of the pro-inflammatory cytokines tumor-necrosis-factor-alpha (TNF-a) and interleukin-6.[12] Loss in skeletal muscle is estimated to be 35%–40% between ages 20 and 80.[13]

Diet

Macronutrient dietary recommendations for athletes vary greatly. High-protein diets are often recommended to provide protein and amino acids necessary for protein synthesis. However, most organizations still recommend diets with ample carbohydrates to provide glycogen in the muscles during exercise. Sufficient fat in the diet is also necessary to provide essential fatty acids as well as fat-soluble vitamins. High-protein, low-carbohydrate diets have been shown to decrease appetite and caloric intake as well as increasing losses in total body weight and fat mass.[14] Another study on high-protein, low-carbohydrate diets showed increased muscle-protein synthesis, increased whole-body muscle proteolysis, and a 50% decrease in plasma insulin levels, with no changes in total plasma IGF-1, growth hormone, or fat free-mass.[15] High-protein diets are generally designed with the assumption that 30% of the total energy intake will be from protein. A study on college-age women showed that postprandial thermogenesis was twofold higher from a high-protein diet compared to a high-carbohydrate diet, leading to increased energy expenditure and probable weight loss.[16]

Table 26–1. Muscle-Building Supplements

Supplements	Doses
Whey protein	10–20 g per day
Branched chain amino acids	7–12 g per day
Creatine monohydrate	20 g for 5 days, followed by 2 g per day
b-hydroxy-b-methyl butyrate	3 g per day
Glutamine	6–10 g per day
L-carnitine	2 g per day
Conjugated linoleic acid	2–4 g per day
a-lipoic acid	600 mg per day
Testosterone	Physician should adapt to individual patients
Dehydroepiandrosterone	25–100 mg per day
Growth hormone	Physician should adapt to individual patients
Chrysin	300 mg per day
Chromium picolinate	400 mg per day

NUTRITIONAL AND BOTANICAL SUPPLEMENTS FOR MUSCLE BUILDING

Whey Protein and Branched-Chain Amino Acids

Whey is a by-product of cheese manufacturing. Whey contains lactose, minerals, and proteins such as alpha-lactalbumin, beta-lactoglobulin, and lactoferrin. In addition, whey contains approximately 24% branched chain amino acids (BCAAs), which have been shown to stimulate protein synthesis.[17] Studies indicate that whey protein supplementation increases insulin sensitivity and decreases body weight in insulin-resistant rats.[18] Research also shows an increase in satiety following a whey-protein meal compared to a meal containing casein protein.[19] Side effects are rare with whey supplementation but may include fatigue, nausea, increased stool frequency, headaches, and thirst.[17] Whey protein should be avoided in individuals with dairy allergies and may decrease absorption of some medications.[20]

BCAAs are essential amino acids including leucine, isoleucine, and valine. These amino acids play multiple roles in protein metabolism. Specifically, leucine has been shown to signal protein synthesis in skeletal muscle.[21] BCAAs stimulate protein synthesis in adipose tissue and in the liver as well as inducing the pancreas to release insulin, resulting in increased protein synthesis.[22] These amino acids also decrease muscle breakdown during exercise.[23] BCAA supplementation can increase plasma ammonia levels in dosages in the 40–60 g per day ranges or in the presence of metabolic disorders; hence, caution is advised when considering long-term supplementation. Liver enzymes should be measured in patients on long-term BCAAs.

Creatine Monohydrate

Creatine is a nitrogenous organic acid found in meat, dairy products, and fish. The body also synthesizes creatine in the liver, kidneys, and pancreas. This amine is found primarily in skeletal muscle. There are many studies supporting the use of creatine to increase muscle mass, strength, stamina, and endurance. Creatine in skeletal muscle exists as free creatine and phosphocreatine. Phosphocreatine is involved with the conversion of adenosine diphosphate to adenosine triphosphate (ATP). ATP provides quick energy to cells.

Creatine supplementation is believed to allow quicker renewal of ATP, improving high-intensity short-duration activity.[24] Creatine also improves the nitrogen balance, which indicates that the body has sufficient protein for muscle growth. Skeletal muscle has a saturation limit for creatine. Patients are often given an initial high loading dose for five to seven days, which is then followed by a maintenance dosage schedule. Muscle mass gain resulting from creatine supplementation is believed to be caused by an increase in water retention. Studies show that creatine increases intracellular water, which is hypothesized to signal cells to increase protein synthesis.[25] Studies also indicate that creatine plus endurance training increases lean-body mass. Creatine levels return to baseline levels after four weeks upon discontinuation of supplementation.[26] Creatine is metabolized to creatinine and excreted by the kidneys. Caution is advised when considering creatine use in individuals with kidney disease. Side effects of creatine supplementation include muscle cramping, nausea, diarrhea, gastrointestinal (GI) upsets, and possible dehydration. The typical dosage is 20 g per day as a loading dose for the first five to seven days, followed by 2 g per day as a maintenance dose.

Beta-Hydroxy-Beta-Methyl Butyrate

Beta-hydroxy-beta-methyl butyrate (HMB) is a by-product of metabolism of the amino acid leucine. Studies have indicated that resistance training combined with HMB supplementation increases muscle strength and lean-muscle mass, and decreases muscle damage and breakdown compared to resistance training alone. In addition, lean-muscle gain was shown to be correlated directly with increasing dosages of HMB.[27] Some studies have suggested that this effect is more pronounced in individuals who have not undergone prior endurance training.[28,29] In a randomized, double-blind, placebo-controlled trial, patients with HIV-related muscle wasting were supplemented with a combination of HMB, glutamine, and arginine for eight weeks. At eight weeks, the subjects consuming the treatment mixture gained body weight predominantly as lean body mass compared with the placebo-supplemented subjects who lost lean mass.[30] A typical dosage of HMB is 3 g per day, in divided doses.

Glutamine

Glutamine is an amino acid produced primarily in skeletal muscle. Nitrogen is transported in the body primarily as glutamine or alanine. Physical injuries and traumas have been shown to increase nitrogen excretion and induce muscle catabolism. Glutamine supplementation induces a positive nitrogen balance, restores deficient intracellular glutamine levels, and increases skeletal muscle synthesis.[31] Glutamine also stimulates the immune system and improves intestinal-barrier function.

L-Carnitine

L-carnitine is an amino acid made by the body and found in meat and dairy products in the diet. L-carnitine plays a significant role in cellular energy metabolism. Although there is conflicting evidence, some studies indicate that L-carnitine improves athletic performance. L-carnitine levels have been shown to decrease with intense short-duration exercise.[32] One study found that L-carnitine supplementation prior to aerobic training increased power output and maximal oxygen uptake while decreasing plasma lactate, carbon-dioxide production, and pulmonary ventilation.[33] In addition, research has shown that L-carnitine supplementation improves glucose disposal in both healthy individuals and those with type 2 diabetes.[34]

Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) is commonly found in beef and dairy products. Many studies have indicated that CLA improves body composition. CLA has been shown to decrease the size and possibly the number of adipocytes.[34,35] Animal studies indicate that CLA consumption causes increased apoptosis in adipose tissue.[36,37] CLA supplementation has been shown to decrease body fat mass, decrease hunger, and increase a feeling of fullness.[38,39] CLA exists in multiple isomers. Animal and human studies on the trans-10, cis-12 isomer indicate that it can increase insulin resistance and glycemia, and may decrease high-density lipoprotein (HDL) levels. However, most CLA supplements are combinations of the two isomers, and studies on combination isomer products have not demonstrated increased insulin resistance.[40] Animal studies have indicated that CLA combination isomer products actually improve insulin sensitivity.[41] Side effects of CLA may include GI upsets, diarrhea, loose stools, and nausea.

Figure 26–1. Siberian ginseng (Eleutherococcus senticosus) may stimulate protein building as well as stimulating the pituitary-adrenocortical axis.

Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) is a coenzyme involved in ATP production and carbohydrate metabolism, and is a potent antioxidant. Research suggests that ALA improves insulin efficiency and sensitivity.[42] Many studies on patients with type 2 diabetes have shown that ALA increases insulin-dependent glucose disposal. Specifically, one study showed that the rate of metabolic clearance of glucose increased by 50% with ALA supplementation.[43]

ALA can also affect glucose uptake into skeletal muscle directly. One study demonstrated that glucose uptake increased by 40%–300% in muscle cells after subjects were given ALA supplementation.[44] Animal studies have shown that ALA stimulates adenosine monophosphate (AMP)–activated protein kinase in skeletal muscle, which regulates cellular energy metabolism as well as decreasing triglyceride accumulation.[45] Skeletal-muscle triglyceride accumulation has been shown to contribute to insulin resistance. Similar studies have shown that ALA suppresses AMP-activated protein kinase in the hypothalamus, causing a decrease in food intake, increasing energy expenditure, and resulting in significant weight loss.[46] Human studies have shown that ALA supplementation combined with creatine monohydrate and sucrose increases creatine uptake by skeletal-muscle cells more than creatine plus sucrose or creatine alone.[47] Large doses, such as 600–1,200 mg per day, of ALA may cause GI upsets, rashes, or headaches.

Testosterone

Testosterone is an anabolic steroid synthesized in the testes. Anabolic hormones increase muscle mass, protein synthesis, and retention of nitrogen. It is estimated that 4%–12% of adolescent males abuse steroids to improve athletic performance or appearance.[48] Studies on men with low testosterone showed that testosterone supplementation combined with resistance training produced a significant increase in lean-body mass and strength compared to resistance training or testosterone alone.[49] Additional studies have shown that testosterone supplementation increases strength, lean-muscle mass, and bone density as well as reducing fat mass.[50] One study showed that muscle strength and power increased in a dose-dependent manner with increasing testosterone dosage. This study also demonstrated that testosterone supplementation does not improve muscle fatigability or specific tension.[51]

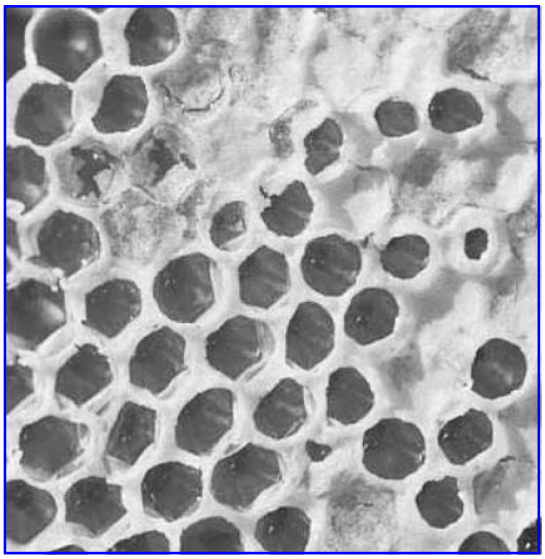

Figure 26–2. Chrysin is a flavonoid found in many plants, such as passionflower (Passiflora incarnata) and geranium (Pelargonium crispum) as well as in honey and propolis. Honeycomb is shown above.

Restoring testosterone levels can improve athletic performance but should be considered only for individuals with low testosterone levels. Side effects of supraphysiologic doses of testosterone can be severe, including liver disease, low sperm counts, changes in mood and behavior, increased hematocrit levels and prostate-specific antigens, decreased high density lipoprotein cholesterol (HDL), increased low-density lipoprotein cholesterol (LDL), and adverse changes in thyroid hormones.[52,53] Unfavorable cardiovascular changes can occur, such as left-ventricular hypertrophy, which remain after discontinuing testosterone supplementation.[54] Androgen precursors to testosterone, such as androstenediol and androstenedione, have also been studied. A study on adult males with normal testosterone levels during high-intensity resistance training found that supplementation with these products initially increased testosterone but that these levels returned to baseline within 16 weeks. In addition, the researchers did not find improvement in muscle strength or body composition, and found that there was an increase in estrogen-related compounds and adverse changes in lipid profiles and results of cardiovascular risk assessments.[55]

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is synthesized in the adrenal glands, liver, testes, and brain. This substance is converted to androstenedione, which is the precursor to other androgens, and improves insulin sensitivity. DHEA levels begin declining at approximately age 25. Studies have indicated that DHEA supplementation improves insulin sensitivity and decreases both subcutaneous and visceral fat.[56] Specifically, animal studies have shown that DHEA decreases both body weight and the cytokine TNF-alpha, which is implicated in causing insulin resistance.[57]

A six-month study on adults showed that DHEA supplementation at 100 mg per day increased IGF-1. However, only the male subjects had decreased fat-body mass and increased muscle strength. Women had increases in total-body mass and had androgen levels that were above normal. No changes were seen in cortisol levels, lipid profiles, glucose levels, fasting insulin levels, bone-mineral density, or basal metabolic rates.[58]

Growth Hormone

Growth hormone (GH) is an anabolic hormone made in the pituitary gland. Secretion of GH is stimulated by exercise, trauma, sleep, acute illness, hypoglycemia, and other hormonal interactions.[51] GH facilitates carbohydrate, fat, and protein metabolism, as well as increasing IGF-1, bone thickness, linear growth, and soft-tissue growth. Studies have shown that GH

supplementation increases strength and lean-muscle mass in individuals who are deficient in GH. However, studies are conflicting regarding the effects of supplementation for individuals with normal growth hormone levels. A study on endurance-trained adult males showed that GH supplementation caused a 50% decrease in leucine oxidation with exercise, which demonstrated the effects of GH on skeletal muscle.[59] In addition, studies on elderly men show that GH injections increase lean-muscle mass and decrease fat mass more than strength training alone.[60]

A study on obese adults combined low-dose GH supplementation with diet restriction. The results indicated that GH produced a positive nitrogen balance, increased lean-muscle mass, increased body weight lost as fat, increased loss of visceral fat, and increased IGF-1.[61] However, several other studies have not supported these findings.[62,63] Supplementation with the amino acids ornithine, lysine, and arginine may increase GH levels, although studies have not supported this finding.[64] GH supplementation is still debated because of its potential for causing serious side effects, such as insulin resistance, carpal-tunnel compression, and water retention.[65]

Chrysin

Chrysin is a flavonoid found in many plants, such as passionflower (Passiflora incarnata) and geranium (Pelargonium crispum) as well as in honey and propolis. Researchers and athletes are interested in this flavonoid because of its potential for increasing testosterone by decreasing the conversion of testosterone to estrogen. Several animal studies have shown that chrysin is a potent inhibitor of the enzyme aromatase.[66] Aromatase converts androstenedione and testosterone to estrogen. However, human studies have not shown an increase in testosterone levels with chrysin supplementation, possibly due to its poor absorption. Studies on aging animals have also shown that chrysin supplementation increased libido, sperm count, and fertilization potential.[67]

Chromium

Chromium is a commonly used product for balancing blood sugar. Chromium picolinate is well-studied and is often used in the supplemented form of chromium, although other forms, such as amino acid chelates, can be used. Researchers have found chromium picolinate supplementation to be effective for treating many individuals with both diabetes and reactive hypoglycemia. Research has also shown that intense aerobic exercise increases chromium excretion.[68] Data from human studies are inconsistent, and many studies do not show that chromium supplementation improves strength, lean-muscle mass, or body-fat loss. However, some studies do indicate that chromium picolinate supplementation may improve body composition as a result of the product's glucose-balancing effects.[69,70]

Additional Supplements

Several other nutritional and botanical supplements have been shown to increase athletic performance. Although scientific evidence is lacking, these supplements may be used to support the body in optimizing metabolism to improve body composition. These supplements include:

Pyruvate—Human studies have found pyruvate supplementation increases glucose extraction in the muscle at rest and during exercise as well as increasing overall endurance.[71]

Siberian ginseng—Siberian ginseng (Eleutherococcus senticosus) is believed to stimulate protein building as well as stimulating the pituitary-adrenocortical axis.[72] However, studies have not found supplementation to improve endurance or athletic performance in endurance-trained individuals.[73]

Cordyceps—Animal studies show that cordyceps (Cordyceps sinensis), an adaptogenic herb, increases endogenous corticosteroid production, and provides improved glucose metabolism and increased insulin sensitivity.[74] Human studies on cordyceps and athletic performance did not show improvement of endurance or oxidative capacity, however.[75]

Puncture vine—Puncture vine (Tribulus terrestris) is believed to act as an androgen. Animal studies indicate that Tribulus supplementation causes androgenic effects, stimulating sexual function in rats.[76] However, human studies did not indicate that the herb improved athletic performance or body composition.[77]

CONCLUSIONS

There are a number of ways to address problems with muscle size and strength as well as assisting athletes who wish to improve their performance and endurance. Treatment approaches should be individualized to each patient's needs with caution used for patients who have coexisting conditions. Additional research and human studies are needed for some supplements.

REFERENCES

[1]NBJ's Sports Nutrition and Weight Loss Report 2004. Nutrition Business Journal, February 2004. Online document at: www.researchandmarkets.com=reportinfo.asp?report_id 53007. Accessed July 14, 2005.

[2]NBJ's Sports Nutrition and Weight Loss Report 2005. Nutrition Business Journal, June 2005. Online document at: www.npicenter.com=anm=anmviewer.asp?a 12678&print yes. Accessed July 14, 2005.

[3]Simoneau JA, Veerkamp JH, Turcotte LP, Kelley DE. Markers of capacity to utilize fatty acids in human skeletal muscle: Relation to insulin resistance and obesity and effects of weight loss. FASEB J. 1999; 13:2051–2060.

[4]Goodpaster BH, He J, Watkins S, Kelley DE. Skeletal muscle lipid content and insulin resistance: Evidence for a paradox in endurance-trained athletes. J Clin Endocrinol Metab. 2001;86:5755–5561.

[5]Weber-Hamann B, Kopf D, Lederbogen F, Gilles M, et al. Activity of the hypothalamus–pituitary–adrenal system and oral glucose tolerance in depressed patients. Neuroendocrinology. 2005;81:200–204.

[6]Watt MJ, Hargreaves M. Effect of epinephrine on glucose disposal during exercise in humans: Role of muscle glycogen. Am J Physiol Endocrinol Metab. 2002;283:E578–E583.

[7]Ryan AS, Nicklas BJ, Berman DM. Hormone replacement therapy, insulin sensitivity, and abdominal obesity in postmenopausal women. Diabetes Care. 2002;25:127–133.

[8]Polderman KH, Gooren LJ, Asscheman H, et al. Induction of insulin resistance by androgens and estrogens. J Clin Endocrinol Metab. 1994;79:265–271.

[9]Perrini S, Natalicchio A, Laviola L, et al. Dehydroepiandrosterone stimulates glucose uptake in human and murine adipocytes by inducing GLUT1 and GLUT4 translocation to the plasma membrane. Diabetes. 2004;53:41–52.

[10]Laager R, Ninnis R, Keller U. Comparison of the effects of recombinant human insulin-like growth factor-I and insulin on glucose and leucine kinetics in humans. J Clin Invest. 1993;92:1903–1939.

[11]Kamel HK, Maas D, Duthie EH Jr. Role of hormones in the pathogenesis and management of sarcopenia. Drugs Aging. 2002;19:865–877.

[12]Grounds MD. Reasons for the degeneration of ageing skeletal muscle: A central role for IGF-1 signalling. Biogerontology. 2002;3(1–2):19–24.

[13]Proctor DN, Balagopal P, Nair KS. Age-related sarcopenia in humans is associated with reduced synthetic rates of specific muscle proteins. J Nutr. 1998;128(2 suppl.):351S–355S.

[14]Weigle DS, Breen PA, Matthys CC, et al. A high-protein diet induces sustained reductions in appetite, ad libitum caloric intake, and body weight despite compensatory changes in diurnal plasma leptin and ghrelin concentrations. Am J Clin Nutr. 2005;82:41–48.
[15]Harber MP, Schenk S, Barkan AL, Horowitz JF. Effects of dietary carbohydrate restriction with high protein intake on protein metabolism and the somatotropic axis. J Clin Endocrinol Metab. 2005;90:5175–5181.
[16]Johnston CS, Day CS, Swan PD. Postprandial thermogenesis is increased 100% on a high-protein, low-fat diet versus a high-carbohydrate, low-fat diet in healthy, young women. J Am Coll Nutr. 2002; 21: 55–61.
[17]Bell SJ. Whey protein concentrates with and without immunoglobulins: A review [review]. J Med Food. 2000;3:1–13.
[18]Belobrajdic DP, McIntosh GH, Owens JA. A high–whey-protein diet reduces body weight gain and alters insulin sensitivity relative to red meat in Wister rats. J Nutr. 2004;134:1454–1458.
[19]Hall WL, Millward DJ, Long SJ, Morgan LM. Casein and whey exert different effects on plasma amino acid profiles, gastrointestinal hormone secretion and appetite. Br J Nutr. 2003;89:239–248.
[20]Martindale W. Martindale: The Extra Pharmacopoeia. Pharmaceutical Press, 1999.
[21]Kimball SR, Jefferson LS. Control of protein synthesis by amino acid availability. Curr Opin Clin Nutr Metab. 2002;5:63–67.
[22]Lynch CJ, Hutson SM, Patson BJ, et al. Tissue-specific effects of chronic dietary leucine and norleucine supplementation on protein synthesis in rats. Am J Physiol Endocrinol Metab. 2002;283:E824–E835.
[23]MacLean DA, Graham TE, Saltin B. Branched-chain amino acids augment ammonia metabolism while attenuating protein breakdown during exercise. Am J Physiol. 1994;267:E1010–E1022.
[24]Williams MH, Branch JD. Creatine supplementation and exercise performance: An update. J Am Coll Nutr. 1998;17:216–234.
[25]Powers ME, Arnold BL, Weltman AL, et al. Creatine supplementation increases total body water without altering fluid distribution. J Athl Train. 2003;38:44–50.
[26]Vandenberghe K, Goris M, Van Hecke P, et al. Long-term creatine intake is beneficial to muscle performance during resistance training. J Appl Physiol. 1997;83:2055–2063.
[27]Nissen S, Sharp R, Ray M, et al. Effect of leucine metabolite betahydroxy-beta-methylbutyrate on muscle metabolism during resistance exercise training. J Appl Physiol. 1996;81:2095–2104.
[28]Kreider RB, Ferreira M, Wilson M, Almada AL. Effects of calcium beta-hydroxy-beta-methylbutyrate (HMB) supplementation during resistance-training on markers of catabolism, body composition and strength. Int J Sports Med. 1999;20:503–509.
[29]Slater GJ, Jenkins D. Beta-hydroxy-beta-methylbutyrate (HMB) supplementation and the promotion of muscle growth and strength. Sports Med. 2000;30:105–116.
[30]Clark RH, Feleke G, Din M, Yasmin T, Singh G, Khan FA, Rathmacher JA. Nutritional treatment for acquired immunodeficiency virus-associated wasting using beta-hydroxy beta-methyl butyrate, glutamine, and arginine: A randomized, double-blind, placebo-controlled study. JPEN J Parenter Enteral Nutr. 2000 May–Jun;24(3):133–139.
[31]Wilmore DW. The effect of glutamine supplementation in patients following elective surgery and accidental injury. J Nutr. 2001;131(suppl.):2543S–2549S.
[32]Nuesch R, Rossetto M, Martina B. Plasma and urine carnitine concentrations in well-trained athletes at rest and after exercise. Influence of L-carnitine intake. Drugs Exp Clin Res. 1999;25:167–171.
[33]Vecchiet L, Di Lisa F, Pieralisi G, et al. Influence of L-carnitine administration on maximal physical exercise. Eur J Appl Physiol Occup Physiol. 1990;61(5–6):486–490.
[34]Mingrone G. Carnitine in type 2 diabetes. Ann NY Acad Sci. 2004; 1033:99–107.
[35]Azain MJ, Hausman DB, Sisk MB, et al. Dietary conjugated linoleic acid reduces rat adipose tissue cell size rather than cell number. J Nutr. 2000;130:1548–1554.
[36]West DB, Delany JP, Camet PM, et al. Effects of conjugated linoleic acid on body fat and energy metabolism in the mouse. Am J Physiol. 1998;275:R667–R672.
[37]Miner JL, Cederberg CA, Nielsen MK, et al. Conjugated linoleic acid (CLA), body fat, and apoptosis. Obes Res. 2001;9:129–134.
[38]Kamphuis MM, Lejeune MP, Saris WH, Westerterp-Plantenga MS. Effect of conjugated linoleic acid supplementation after weight loss on appetite and food intake in overweight subjects. Eur J Clin Nutr. 2003;57:1268–1274.
[39]Blankson H, Stakkestad JA, Fagertun H, et al. Conjugated linoleic acid reduces body fat mass in overweight and obese humans. J Nutr. 2000;130:2943–2948.
[40]Riserus U, Arner P, Brismar K, Vessby B. Treatment with dietary trans10cis12 conjugated linoleic acid causes isomer-specific insulin resistance in obese men with the metabolic syndrome. Diabetes Care. 2002;25: 1516–1521.

[41]Wahle KW, Heys SD, Rotondo D. Conjugated linoleic acids: Are they beneficial or detrimental to health? Prog Lipid Res. 2004;43:553–587.
[42]Konrad T, Vicini P, Kusterer K, et al. Alpha-lipoic acid treatment decreases serum lactate and pyruvate concentrations and improves glucose effectiveness in lean and obese patients with type 2 diabetes. Diabetes Care. 1999;22:280–287.
[43]Jacob S, Henriksen EJ, Schiemann AL, et al. Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid. Arzneimittelforschung. 1995;45:872–874.
[44]Eason RC, Archer HE, Akhtar S, Bailey CJ. Lipoic acid increases glucose uptake by skeletal muscles of obese-diabetic ob=ob mice. Diabetes Obes Metab. 2002;4:29–35.
[45]Lee WJ, Song KH, Koh EH, et al. Alpha-lipoic acid increases insulin sensitivity by activating AMPK in skeletal muscle. Biochem Biophys Res Commun. 2005;332:885–891.
[46]Kim MS, Park JY, Namkoong C, et al. Anti-obesity effects of alpha-lipoic acid mediated by suppression of hypothalamic AMP-activated protein kinase. Nat Med. 2004;10:727–733.
[47]Burke DG, Chilibeck PD, Parise G, et al. Effect of alpha-lipoic acid combined with creatine monohydrate on human skeletal muscle creatine and phosphagen concentration. Int J Sport Nutr Exerc Metab. 2003; 13:294–302.
[48]Bahrke MS, Yesalis CE, Brower KJ. Anabolic-androgenic steroid abuse and performance-enhancing drugs among adolescents. Child Adolesc Psychiatr Clin N Am. 1998;7:821–838.
[49]Casaburi R, Bhasin S, Cosentino L, et al. Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004;170:870–878.
[50]Young NR, Baker HW, Liu G, Seeman E. Body composition and muscle strength in healthy men receiving testosterone enanthate for contraception. J Clin Endocrinol Metab. 1993;77:1028–1032.
[51]Storer TW, Magliano L, Woodhouse L, et al. Testosterone dose-dependently increases maximal voluntary strength and leg power, but does not affect fatigability or specific tension. J Clin Endocrinol Metab. 2003;88: 1478–1485.
[52]Niewoehner CB. Endocrine Pathophysiology. Madison, CT: Fence Creek Publishing, 1998.
[53]Tenover JS. Effects of testosterone supplementation in the aging male. J Clin Endocrinol Metab. 1992; 75:1092–1098.
[54]Urhausen A, Albers T, Kindermann W. Are the cardiac effects of anabolic steroid abuse in strength athletes reversible? Heart. 2004;90:496–501.
[55]Broeder CE, Quindry J, Brittingham K, et al. The Andro Project: Physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high-intensity resistance training program. Arch Intern Med. 2000;160:3093–3104.
[56]Villareal DT, Holloszy JO. Effect of DHEA on abdominal fat and insulin action in elderly women and men: A randomized controlled trial. JAMA. 2004;292:2243–2248.
[57]Kimura M, Tanaka S, Yamada Y, et al. Dehydroepiandrosterone decreases serum tumor necrosis factor-alpha and restores insulin sensitivity: Independent effect from secondary weight reduction in genetically obese Zucker fatty rats. Endocrinology. 1998;139:3249–3253.
[58]Morales AJ, Haubrich RH, Hwang JY, et al. The effect of six months treatment with a 100 mg daily dose of dehydroepiandrosterone (DHEA) on circulating sex steroids, body composition and muscle strength in age-advanced men and women. Clin Endocrinol (Oxf). 1998;49:421– 432.
[59]Healy ML, Gibney J, Russell-Jones DL, et al. High dose growth hormone exerts an anabolic effect at rest and during exercise in endurance-trained athletes. J Clin Endocrinol Metab. 2003;88:5221–5226.
[60]Taaffe DR, Pruitt L, Reim J, et al. Effect of recombinant human growth hormone on the muscle strength response to resistance exercise in elderly men. J Clin Endocrinol Metab. 1994;79:1361–1366.
[61]Kim KR, Nam SY, Song YD, et al. Low-dose growth hormone treatment with diet restriction accelerates body fat loss, exerts anabolic effect and improves growth hormone secretory dysfunction in obese adults. Horm Res. 1999;51:78–84.
[62]Yarasheski KE, Campbell JA, Smith K, et al. Effect of growth hormone and resistance exercise on muscle growth in young men. Am J Physiol. 1992;262(3pt1):E261–E267.
[63]Berggren A, Ehrnborg C, Rosen T, et al. Short-term administration of supraphysiological recombinant human growth hormone (GH) does not increase maximum endurance exercise capacity in healthy, active young men and women with normal GH-insulin-like growth factor I axes. J Clin Endocrinol Metab. 2005;90:3268–3273.
[64]Fogelholm GM, Naveri HK, Kiilavuori KT, Harkonen MH. Low dose amino acid supplementation: No effects on serum human growth hormone and insulin in male weightlifters. Int J Sport Nutr. 1993;3: 290–297.
[65]Yarasheski KE. Growth hormone effects on metabolism, body composition, muscle mass, and strength. Exerc Sport Sci Rev. 1994;22: 285–312.

[66]Kellis JT Jr, Vickery LE. Inhibition of human estrogen synthetase (aromatase) by flavones. Science. 1984;225:1032–1034.
[67]Dhawan K, Kumar S, Sharma A. Beneficial effects of chrysin and benzoflavone on virility in 2-year-old male rats. J Med Food. 2002;5:43–48.
[68]Lukaski HC, Bolonchuk WW, Siders WA, Milne DB. Chromium supplementation and resistance training: Effects on body composition, strength, and trace element status of men. Am J Clin Nutr. 1996; 63:954–965.
[69]Hasten LD, Rome EP, Franks BD, Hegsted M. Effects of chromium picolinate on beginning weight training students. Int J Sport Nutr. 1992;2:343–350, 1992.
[70]Kaats GR, Blum K, Fisher JA, Adelman JA. Effect of chromium picolinate supplementation on body composition: A randomized, double-masked placebo-control study. Curr Ther Res. 1996;57:747–755.
[71]Stanko RT, Robertson RJ, Galbreath RW, et al. Enhanced leg exercise endurance with a high-carbohydrate diet and dihydroxyacetone and pyruvate. J Appl Physiol. 1990;69:1651–1656.
[72]Medon PJ, Ferguson PW, Watson CF. Effects of Eleutherococcus senticosus extracts on hexobarbital metabolism in vivo and in vitro. J Ethnopharmacol. 1984;10:235–241.
[73]Dowling EA, Redondo DR, Branch JD, et al. Effect of Eleutherococcus senticosus on submaximal and maximal exercise performance. Med Sci Sports Exerc. 1996;28:482–489.
[74]Wang SM, Lee LJ, Lin WW, Chang CM. Effects of a water-soluble extract of Cordyceps sinensis on steroidogenesis and capsular morphology of lipid droplets in cultured rat adrenocortical cells. J Cell Biochem. 1998;69:483–489.
[75]Parcell AC, Smith JM, Schulthies SS, et al. Cordyceps sinensis (Cordy-Max Cs-4) supplementation does not improve endurance exercise performance. Int J Sport Nutr Exerc Metab. 2004;14:236–242.
[76]Gauthaman K, Ganesan AP, Prasad RN. Sexual effects of puncture vine (Tribulus terrestris) extract (protodioscin): An evaluation using a rat model. J Altern Complement Med. 2003;9:257–265.
[77]Antonio J, Uelmen J, Rodriguez R, Earnest C. The effects of Tribulus terrestris on body composition and exercise performance in resistance-trained males. Int J Sport Nutr Exerc Metab. 2000;10:208–15.

27

NATUROPATHIC MUSCULOSKELETAL PAIN MANAGEMENT

Controlling pain in patients is perhaps one of the physician's greatest challenges. Pain is not a disease, but a symptom of an underlying imbalance. Because pain tends to be the greatest motivator for a person to seek medical care, this symptom often takes precedence over any others. Pain, as discussed in this chapter, refers to that which is derived from the physical realm (to separate it from mental, emotional, and psychologic types of pain). One of the main tenets of naturopathic medicine is ''find the cause.'' However, this approach is easily overlooked by some physicians who help patients deal with symptoms of pain, regardless of duration. Many conventional pain medicines (many of which are derived from plant substances) offer strong and fast-acting modes of treatment and are quite useful in instances when pain is unbearable for patients (e.g., traumatic injuries, cancer).

NATUROPATHIC APPROACH TO TREATING PAIN

In the naturopathic tradition, in some instances, pain and disease may be the result of such factors as inadequate diet, improper care of the body (sedentary lifestyle), and other lifestyle overindulgences and excesses. This is based on the concept that an organism is more likely to be healthier than one that is deprived in some fashion. A healthier organism also will be able to resist disease and pain better even if both come from external causes. In addition, the early naturopathic doctors prescribed fresh air, sunshine, proper diet, exercise, ''scientific relaxation,'' (i.e., an early form of Western meditation designed to relax the mind), constructive thinking, and a positive mental attitude, with prayer and meditation to create a sound mind in a sound body. These extremely simplistic recommendations provide the basic framework for health; but striving for health when one has poor lifestyle habits is self-defeating at best. Thus, people need additional treatment using botanical medicines, nutraceuticals, or pharmaceuticals until a better state of health can be achieved. The technique of pain control with natural medicines involves identifying, treating, and, if possible, removing the source of the discomfort. In addition, when treatment is focused this way, ideally, a patient can avoid the addictive perils of pharmaceutical pain medicines as well as their sometimes strong and toxic side effects.

Most importantly, from the perspective of removing the cause, physicians perhaps do their greatest service by altering the course of a person's health away from a protracted period of pain and concomitant disability. The first intervention involves setting a course for healing the tissues that are the source of the pain. Removing dietary perils that prevent the body from being in its optimum state of health includes limiting refined carbohydrates and optimizing protein, micronutrient, and fatty-acid intakes. Excess carbohydrate intake exerts a negative effect on insulin metabolism, provoking weight gain and the inflammatory cascade. Insufficient protein intake, at levels less than 30% of the recommended daily allowance (0.8 g of protein per kg of body weight per day), may limit repair and regeneration. An excess of foods that contain arachidonic acid, a long-chain omega-6 fatty acid, is a known promoter of inflammation,

cancer, autoimmune conditions, and circulatory compromise.[1] Protein synthesis is compromised by a number of conditions, and protein-energy malnutrition is associated with impaired muscle function, immune dysfunction, decreased bone mass, impaired cognitive function, delayed wound healing (even wounds caused by surgical interventions), and increased morbidity.[2] Medical conditions, including gastrointestinal (GI) disease, malabsorption syndromes, and chronic and acute infections, can lead to micronutrient deficiencies as well as increased protein and energy requirements. Patients with chronic pain often use prescription medicines heavily, which can, in turn, compound nutrient malabsorption, GI conditions, and loss of appetite.

PROTEOLYTIC ENZYMES

Proteolytic enzymes have analgesic effects in addition to their well-recognized anti-inflammatory and antiedemic properties. Enzyme-derived analgesia is based on inhibition of the inflammatory cascade as well as exerting a direct influence on nociceptors.[3] Bromelain (pineapple; Ananas comosus) is used orally to treat acute swelling and inflammation following trauma. Bromelain is a grouping of proteolytic enzymes obtained from the stem and fruit of pineapple.[4] Bromelain is thought to exert its anti-inflammatory effect by altering leukocyte migration and activation. Other mechanisms of action include proteolysis at point of inflammation, fibrinolysis via the plasminogen-plasmin system, depletion of kininogen, inhibition of inflammatory prostaglandins, and induction of prostaglandin E1 (an anti-inflammatory prostaglandin). Side effects of taking bromelain may include GI upset with diarrhea. Immunoglobulin E (IgE)–mediated allergic reactions are possible but this has not yet been widely documented.[5]

Research on Efficacy

A three-month study was conducted on the anti-inflammatory and analgesic effects of bromelain in osteoarthritis (OA) and rheumatoid arthritis.[6] The researchers tested bromelain's effects on mild, acute knee pain at a dose of either 200 mg or 400 mg per day. Total pain symptom scores were reduced by 41% and 59%, respectively, in each treatment group. Additional scores for stiffness and physical function were significantly decreased in the high-dose (400 mg per day) group compared to the low-dose (200 mg per day) group. In addition, the researchers noticed that, compared to baseline, overall psychologic well-being was significantly improved in both groups following treatment, indicating a significant dose-response relationship. In another study, efficacy and tolerability of an oral enzyme preparation (Phlogenzym , MUCOS Pharma GmbH & Co., Geretsried, Germany) containing 90 mg of bromelain was compared to the non-steroidal anti-inflammatory drug (NSAID) diclofenac for treating OA.[7]

Figure 27–1. California poppy (Eschscholtzia californica).

This trial lasted three weeks and involved patients, ages 40–75 years, with active OA of the knee joint. Both groups experienced comparable reductions in joint tenderness, pain, swelling, and slight improvements in range of motion (ROM) at seven weeks' follow-up, with greater reduction of joint tenderness in the Phlogenzym-treatment group. The investigators concluded that the enzyme preparation was equally efficacious and as well-tolerated as diclofenac for treating active OA.

Enzymes, particularly bromelain, have been shown to be helpful for treating postsurgical pain and edema. An interesting study divided postsurgical fracture patients into two treatment groups; the first was treated with a standard antiedemic medication and the other group was given an oral proteolytic enzyme preparation.[8] Subjects who were treated with the enzyme preparation took it three times per day, in the first three days following surgery, then twice per day in the follow-up period. These patients experienced a continuous and significantly more rapid reduction in postoperative swelling compared to the control group (on the standard medication). Furthermore, the enzyme-treated group had an average reduction of limb fluid volume of 8% while the control group experienced an increase of 100% fluid volume. The investigators also noted an analgesic effect; the total amount of analgesics taken by the enzyme-treatment group was significantly lower (especially in the early postoperative period) compared to analgesic intake in the control group.

Bromelain is useful for treating athletic injuries (namely, bruising and edema) and for speeding healing time. Healing of musculoskeletal injuries, such as muscle strains and sprains, ligamentous tears, and contusions, is helped by bromelain's ability to decrease fibrin, thereby promoting circulation and assisting resorption of posttraumatic inflammatory factors. An in-office clinical study found that orthopedic patients treated with bromelain experienced reductions in swelling, pain at rest and during movement, and tenderness on all subsequent follow-up visits compared to baseline.[9] In addition, patient tolerance was noted to be very good. These studies highlight the positive effects of enzymes for treating pain, inflammation, and edema. In addition, enzymes increase speed of healing and pain relief, and decrease inflammation. These are all distinct advantages of enzymes for treating painful conditions; in addition, these effects promote the healing process.

BOTANICAL AND NUTRACEUTICAL MEDICINES

Several herbal medicines are useful for treating pain; the herbs addressed in the following section were selected because of their analgesic and anti-inflammatory effects. (There are several other herbs that are useful for treating painful conditions, so this coverage is not complete.) These herbs exert beneficial effects on pain via their analgesic, anti-inflammatory, anxiolytic, and sedative properties. Using a combination of herbs that are best suited for certain conditions produces the best result. It is important to consider how pain affects each individual when offering a course of treatment for each patient.

Jamaican Dogwood

Jamaican dogwood (Piscidia erythrina; piscidia) is a shrub found in tropical America and the West Indies. The medicine is derived from the bark. Jamaican dogwood has several pain-relieving effects. These include sedative, anti-inflammatory, and antispasmodic (smooth muscle) effects.[10] Historically, this herb has been used to treat neuralgia, migraine headaches, toothaches, insomnia, and smooth-muscle spasms (GI spasms). The herb has also been used for

Table 27–1. Botanicals for Treating Pain

Latin Bionomials	Common Names	Doses
Piscidia erythrina	Jamaican dogwood	Dried root bark: piscidia 2–4 g or via decoction per day Liquid extract: 1:1 in 30% alcohol, 1–2 mL per day Tincture: 5–15 mL per day
Corydalis cava	Corydalis	Infusion: 2–4 g of dried herb brewed, 1 time per day Tincture: 1–2 mL per day
Eschscholtzia californica	California poppy	Infusion: 1–2 tsp of herb in 1 cup water per day Tincture: 1–4 mL per day
Ananas comosus	Pineapple (contains bromelain)	300 mg, 3 times per day
Zingiber officinale	Ginger	200–300 mg, 3 times per day
Boswellia serrata	Indian frankincense	300–350 mg, 3 times per day
Curcuma longa	Turmeric	500 mg, 4 times per day
Salix spp.	Willow bark	240 mg of salicin
Capsicum spp.	Capsicum	Creams containing 0.025% to 0.075% capsaicin applied 3-4 times per day

treating insomnia resulting from neuralgia or nervous tension. Although Jamaican dogwood is a powerful sedative, relatively little research has been performed on this herb. Piscidia also acts as an antitussive and antipyretic. Because of its potent neuromuscular sedative effects, piscidia is considered to be a toxic herb. This herb's reputation as a toxin stems from its use as a fish poison. Crushed leaves were used to stupefy fish, enabling them to be caught easily. The constituent responsible for this, rotenone, interferes with oxygen consumption in cold-blooded animals, acting as a toxin to them. More specifically, rotenone is a complex I mitochondrial poison, with effects that overlap with the neurotoxicity found with Parkinson's disease. Due to the potential risk, piscidia should only be used short-term.

Corydalis and California Poppy

Corydalis (Corydalis cava) and California poppy (Eschscholtzia californica) are herbs with historical use in pain management. The medicinal parts of corydalis are the tuber and root. Typically, corydalis was used for treating nerve damage, tremors, and muscle spasms because of the herb's effects as a mild sedative and tranquilizer. Corydalis was also used to treat hypertension and intestinal spasms. Similarly, California poppy has been used historically to treat insomnia, aches and pains, nervous conditions, childhood enuresis, and bladder disorders. The dried stems and leaves are used. The active constituents of these two plants are thought to be isoquinoline alkaloids.[11] An active constituent in corydalis is tetrahydropalmatine, which can cause liver toxicity if not monitored carefully. California poppy is sometimes confused with the opium poppy (Papaver somniferum). These plants are distantly related, as well as corydalis (they are in the same family in different genera); Eschscholtzia does not produce opium. However, its primary alkaloid, protopine, is similar

in structure to morphine without morphine's addictive properties. Several studies on these plants have been performed in combination because of their similar effects. Alkaloids derived from the corydalis rhizome (protoberberine alkaloids) have been shown to bind positively to gamma aminobutyric acid (GABA) receptors in vitro.[12] GABA receptors in the human brain, when activated, typically facilitate down-regulatory functions. That is, when stimulated, activation of GABA receptors leads to down-regulation of certain neural activities. This activity is correlated with a calming=sedative effect. A grouping of peptide structures in the brain—endorphins and enkephalins—have pain-modulating effects. These molecules are thought to bear much of the responsibility for altering pain responses in humans under a number of physical stressors. Typically, these peptides bind to opioid receptors in the nociceptive areas of the brain, thereby altering pain perception. In one study, extracts of corydalis and California poppy have inhibited a particular degradation process (dimerization) of certain pain-modulating peptides in the brain, as well as inhibited dopamine beta-hydroxylase and monoamine oxidase (MAO) and the synthesis of adrenaline. This effect is thought to prolong the activity of these pain-relieving molecules.[13] Corydalis, in this investigation, appeared to have positive modulatory effects on human endogenous pain-relieving molecules to a greater degree than California poppy. This effect is thought to explain the two herbs' sedative, hypnotic, and antidepressive activities. These studies have demonstrated the unique effects of these herbs and their influence on neurotransmitter metabolism. While much research into the exact mechanisms of these herbs needs to be conducted, existing studies provide some information on the pain-modulating effects of these plant medicines.

Ginger

Ginger (Zingiber officinale) is one of the more widely used herbal medicines. It acts as an antipyretic, antiemetic, antitussive, cardiac inotropic, antibiotic, antifungal, sedative, and analgesic.[14] These effects are varied and are dependent on the particular herb preparation used. The active constituents of ginger (gingerols and gingerdione) are derived from the rhizome and root of the plant. Ginger is used for pain management because the herb is an analgesic and antioxidant, and inhibitor of inflammatory prostaglandins, thromboxanes, and leukotriene synthesis.[15] Ginger also produces anti-platelet-aggregation effects,[16] thereby speeding healing of contusions and bruises. The analgesic effect of ginger may be related to one of its constituents known as shogaol. This substance has inhibitory effects on the release of substance P, a neurotransmitter that is used by the sensory neurons involved in the perception of intense pain.[17] Ginger has been shown to have a mild effect on OA-related pain. Patients with moderate to severe OA pain were given a ginger supplement twice per day in a placebo-controlled, double-blind study for six weeks.[18] At the end of the study, the researchers concluded that the ginger extract's effects on OA pain were statistically significant for reducing symptoms of knee pain, producing a moderate effect. Subjects who were treated with ginger reported less pain on standing and following walking. Adverse effects in the treatment group included mild GI upset. Ginger is a botanical medicine that can modulate pain via several effects. It has been shown to be an effective medicine for treating mild pain; side effects are limited and are of short duration.

Boswellia

Boswellia serrata, also known as Indian frankincense, has anti-inflammatory, analgesic, and antiarthritic activity. It is believed that the mechanism of action for the anti-inflammatory

activity of the Boswellic acids is the ability to inhibit 5-lipoxygenase and leukotriene synthesis. In a randomized, double-blind, placebo-controlled crossover study in 30 patients with osteoarthritis of the knee, Boswellia serrata extract or placebo was given. All of the patients receiving Boswellia supplementation reported decrease in knee pain and frequency of swelling, and increased knee flexion and walking distance.[19]

Cetylated Fatty Acids

Cetylated fatty acids (CFA) have been examined for their effects on patients with osteoarthritis. Cetylated fatty acids include cetyl myristoleate, cetyl myristate, cetyl palmitoleate, cetyl laureate, cetyl palmitate, and cetyl oleate. There are several proposed mechanisms including inhibition of 5-lipoxygenase, acting as a surfactant lubricating joints and muscles, or modulation of the immune system and mediating inflammatory processes. In one study, 64 patients with chronic knee osteoarthritis were given CFA (Celadrin) or a placebo for 68 days. The patients treated with CFA exhibited significant increase in knee flexion and responses to the Lequesne Algofunctional Index indicated a significant shift toward functional improvement for the CFA group after 68 days compared to the placebo group.[20] In a similar study, topical cream consisting of CFA was used to examine the effects on functional performance in patients diagnosed with osteoarthritis of one or both knees. Patients were evaluated after 30 minutes and after 30 days of treatment. The results showed that the treatment group exhibited a significant decrease in time for stair-climbing ability and the up-and-go test, increased supine range of motion of the knees, and improvement in the medial step-down test and in the unilateral anterior reach compared to the placebo.[21]

Turmeric

Turmeric (Curcuma longa) is used for numerous inflammatory conditions as it has anti-inflammatory, antioxidant, and anti-cancer activity. The primary constituent is curcumin, which is believed to exert anti-inflammatory properties via inhibition of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase.[22] Preliminary studies have supported the efficacy of turmeric in several conditions such as rheumatoid arthritis, inflammatory eye diseases, inflammatory bowel disease, chronic pancreatitis, psoriasis, hyperlipidemia, and cancers.[23]

Willow Bark (Salix spp.)

Willow bark is the bark from the salix tree species, and is used medicinally for analgesic, anti-inflammatory, and antipyretic effects. The active constituent of willow bark is salicin, which is metabolized to salicylic acid. The mechanism in which salicin exerts analgesic activity is believed to be inhibition of COX-2 mediated prostaglandin release. Additional constituents may also have lipoxygenase-inhibiting and antioxidant effects. One study compared the effects of willow bark containing 240 mg of salicin to 12.5 mg of the synthetic COX-2 inhibitor rofecoxib in patients with acute exacerbations of low back pain. The results showed comparable improvements in the two groups showing 60% of the patients in each group improved greater or equal to 30% in the Total Pain Index relative to baseline.[24] In an additional double-blind, randomized placebo-controlled trial, Willow bark extract of 240 mg salicin per day was compared to a placebo for two weeks in patients with osteoarthritis. A statistically significant difference between the willow bark supplementation group and the placebo group was

observed in the WOMAC Osteoarthritis Index, with the pain score reduced by 14% from the baseline level after two weeks of supplementation.[25]

Capsicum (Capsicum spp.)

Capsicum (Capsicum spp.) is used frequently as a counterirritant to decrease pain perception. When used topically, the constituent capsaicin binds to nociceptors in the skin, initially causing neuronal excitation and heightened sensitivity as well as cutaneous vasodilation. It is believed that this is the result of selective stimulation of afferent C fibers, which act as thermoreceptors and nociceptors, and release of substance P, which is then followed by a refractory period with reduced pain sensitivity. Substance P is a sensory neurotransmitter that mediates pain. Repeated applications of capsaicin can induce a persistent desensitization, which is believed to be the result of depletion of substance P. Capsicum has been shown to decrease pain in numerous conditions including fibromyalgia and rheumatic diseases,[26] back pain,[27] headaches,[28] osteoarthritis,[29] postherpetic neuralgia,[30] psoriasis,[31] and diabetic neuropathy.[32] Camphor (Cinnamomum camphora) is also a commonly used counterirritant.

PHYSICAL MEDICINE=MODALITIES

Physical medicines, the application of therapies to the body externally, are numerous and are excellent for identifying, treating, and resolving pain and its sources. While beyond the scope of this chapter, therapies such as traditional hydrotherapy, electronic therapies such as ultrasound and electric stimulation in all of its forms, myofascial trigger-point injections, acupuncture, and manual (osseous manipulation) medicine all provide excellent pain relief in and of themselves. Each of these modalities has a long history of use as well as an excellent record of safety and efficacy for pain treatment. Used in various combinations, the previously mentioned therapies are powerful tools for moving patients from states of helpless pain to health and pain-free vitality.

PROLOTHERAPY AND REGENERATIVE INJECTION THERAPY

Another form of physical medicine, prolotherapy, is an excellent technique for treating musculoskeletal pain. Prolotherapy generally uses intra-articular injection of a proliferating agent that causes growth of normal cells or tissue—ligamentous and tendinous tissues at the fibro-osseous junction—leading to stronger, more taut tendons, thereby disrupting pain patterns. Regenerative injection therapy (RIT) is a modernized form of prolotherapy that utilizes injections into the fibro-osseous junction of the tendon or ligament that is causing the pain. Prolotherapy originated in the 1930s and is based on the theory that ligament and tendon laxity result in the generation of pain at the fibro-osseous junction; this was postulated by one of the technique's pioneers, George Hackett, M.D., who was a consulting surgeon at Mercy Hospital, in Canton, Ohio. Dr. Hackett is credited with bringing the technique to mainstream medicine via his large clinical trial during which he observed 656 patients ranging in age from 15 to 88 years old with various forms of ligamentous joint pain. Dr. Hackett followed this patient population for 12 years and it is estimated that he administered 18,000 prolotherapy injections over this time period. He observed that 82% of his patients considered themselves cured during the follow-up period. In addition, Dr. Hackett mapped common pain-referral patterns from tendon and ligamentous instability that are still applicable today.

As noted previously, the RIT technique involved injection of a proliferative substance into the fibro-osseous junction in the tendon or ligament that caused pain. A large body of supportive research has examined different types of proliferative substances. The most often-researched and utilized substance today is dextrose solution. Dextrose produces several proliferative effects, including elevation of extracellular glucose levels to as little as 0.5%. This has been shown to raise levels of insulin-like growth factor 1, insulin-like growth factor 2, and transforming growth factor-beta in a variety of human cell types.[33,34] The cellular response to extracellular glucose is quite rapid; levels of DNA rise within minutes to hours following exposure.[35] It is thought that as many as 15 different genes are induced, with exposure to elevated concentrations of glucose, to produce various cellular proteins associated with growth and repair.[36] There is a great deal of research that explains the mechanism of action of dextrose on connective tissue; a search through the literature will offer more information on prolotherapy.

Research on Efficacy

In addition to investigations of RIT's effectiveness for inducing connective tissue regeneration, other studies have explored the effectiveness of RIT for relieving musculoskeletal joint–related pain. Several studies explored the ability of RIT to lessen joint-specific pain. One study investigated RIT's effect on anterior cruciate ligament (ACL) laxity from treatment through three years post-injection.[37] Subjects were enrolled if they had suffered from six or more months of knee pain in addition to documented ACL laxity (defined by a KT1000 anterior displacement difference [ADD] of 2 mm or more). Injections into the fibro-osseous junction (RIT) was performed, using 6–9 cc of 10% or 25% dextrose, every 2 months over a 10-month period. At follow-up, pain at rest, pain on walking, and pain on stair use were reduced by 45%, 43%, and 35% respectively. Subjective measurements showed a 63% reduction in swelling, knee ROM improved by 10.5 degrees, and the anterior displacement difference was reduced by 71%. RIT also produced clinically and statistically significant reductions in ACL pain. RIT was also effective for treating pain related to knee OA. Patients with grade 2 or more joint narrowing and=or grade 2 or more osteophytic changes in any knee compartments were treated with RIT, using a 10% dextrose solution.[38] After treatment with one injection every two months over the course of one year, RIT-treated patients had a 44% decrease in pain, a 63% decrease in swelling, and an 85% decrease in knee buckling. Flexion ROM was increased by 148. In addition, radiographic variables (lateral patello-femoral cartilage thickness and distal femur width in mm) remained stable at one year and ACL laxity was also reduced. This study showed that RIT relieved OA complications such as pain and swelling. Perhaps even more importantly, this therapy stabilized joint degradation while reducing pain-related symptoms.

This is a key factor in using preventive medicine techniques in pain medicine; the cause of pain is addressed and modulated. RIT is used to treat numerous ligament- and tendon-related pain syndromes. Clinical studies have demonstrated efficacy for treating OA-related pain in the finger joints,[39] cervicothoracic pain and cervicogenic headaches,[40] and low-back pain.[41] RIT has generated much interest in recent years in the realm of interventional pain management. The use of steroidal and nonsteroidal medications have limited appeal for treating degenerative connective-tissue conditions while RIT offers a preventive and curative form of therapy. (The treatment is also relatively inexpensive when one considers the savings in reduced office visits, pain medicine prescriptions cost, and life and work-related disability.)

MESOTHERAPY

Mesotherapy involves the injection of small amounts of combinations of natural and pharmaceutical medicines in the superficial tissues of the skin. Defined mainly by its unique style of injection, mesotherapy protocols are wide-ranging. Intracutaneous injections of medicines allow them to remain in the injected area longer. These injected solutions continue to penetrate deeper tissues in a time-release manner. Mesotherapy is indicated primarily for treating pain that originates from injured musculoskeletal tissues, including both overlying muscles and connective tissues within injured joints. The technique was founded in France in the late 1950s; it continues to be widely used in that country for a variety of purposes today. Considered to be a part of mainstream medicine in France, mesotherapy is used by approximately 16,000 practitioners there, primarily for sports medicine and pain management.[42]

Mesotherapy has gained popularity in numerous other countries around the world today with many established national organizations. However, although primarily used for pain reduction, mesotherapy is just gaining recognition in the United States as a form of cosmetic medicine. Originated by Michel Pistor, M.D., who practiced in France, mesotherapy is based on treating the tissues that originated from the mesoderm. The name of the therapy was based on Dr. Pistor's reasoning that: "[t]he action on the tissues originating from the mesoderm is so extensive that these treatments should be called mesotherapy." He advocated using the smallest dose of medicine, as infrequently as possible, in the correct location in order to achieve a clinical effect. An analysis of the mesotherapy technique via radioisotope serial scanning has shown that the more superficial the injection, the longer the solution remained in the treatment area.[43] Another study utilizing measurement of the injected medicine via venous blood draws showed that at one and three hours post-injection, lesser amounts of the injected medicine were found in the venous circulation according to the respective depth of injection.[44] Overall, the mechanism of action of mesotherapy in pain medicine is derived from the novel form of injection whereby the dermis acts as a time-release dosing system, allowing relatively minute amounts of medicine to be absorbed both locally and systemically over a prolonged period of time. A typical procedure involves using injection depths ranging from 2 to 4 mm directly over pain-affected structures or in corresponding acupuncture points. The amount of medicine injected at each point is only 0.02–0.05 cc of solution. Classical mesotherapy solutions contain a base solution comprised of a local anesthetic and a vasodilatory pharmaceutical drug. Other medicines are added depending on individual indications. Common examples include glucosamine sulfate, methylsulfonylmethane (MSM), B vitamins (methylcobalamin, pantothenic acid, pyridoxine, and folic acid), magnesium, and various homeopathic medicines. Vasodilators are used in order to increase microcirculation over the injured area, thereby assisting with delivery of mesotherapeutic solutions and general improvement of circulatory delivery of oxygen and micronutrients. Naturally derived vasodilatory medicines may be used as well; examples of these include sweet clover (Melilotus officinalis) or witch hazel (Hamamelis virginiana).

Research on Efficacy

Currently, the majority of research on mesotherapy is derived from case studies; other more-rigorous studies are under way. One case series revealed beneficial effects of mesotherapy treatment in 65 patients with chronic thoracic pain. The subjects' pain had various causes, including arthritis, spinal stenosis, and various sprains and strains.[45] These patients' pain had not been adequately controlled with NSAIDs, narcotic analgesics, or muscle relaxants. In

another case series, 267 patients with degenerative arthritic pain were treated with mesotherapy; this was deemed as an ''effective and reasonable treatment option'' and no adverse side effects= reactions were noted in the treatment group.[46] Another case series determined mesotherapy to be a promising treatment option that was safe and efficacious for 132 patients with back and neck pain that was not lessened by at least three months of conventional treatments.[47] Interestingly, mesotherapy appears to be amenable to the use of several different forms of medicines; combinations of pharmaceutical and natural medicines make this an especially effective form of pain resolution and management. Additional research is being performed on this technique, and its popularity as a pain therapy in the United States is expected to grow.

CONCLUSIONS

Naturopathic pain management entails numerous aspects of preparing the body to heal (using nutrition), alleviating pain (proteolytic enzymes and botanical medicines), and prevention of further tissue degradation (prolotherapy and nutrition). All methods mentioned in this article are applicable to nearly all forms of musculoskeletal pain. Enzyme and botanical therapies are useful for treating visceral pain as well. The magnificence of natural medicines is their ability to modulate perception of pain, prevent continuous degradation of bodily structures, and limit the duration of pain by addressing its causative factors.

REFERENCES

[1]Simopoulos AP. The importance of the ratio of omega-6=omega-3 essential fatty acids. Biomed Pharmacother. 2002;56:365–379.

[2]Gallagher HJ, Daly JM. Malnutrition, injury, and the host immune response: Nutrient substitution. Curr Opin Gen Surg. 1993;92–104.

[3]Klein G, Kullich W. Reducing pain by oral enzyme therapy in rheumatic diseases. Wien Med Wochenschr. 1999;149(21–22):577–580.

[4]Hale LP, Greer PK, Sempowski GD. Bromelain treatment alters leukocyte expression of cell surface molecules involved in cellular adhesion and activation. Clin Immunol. 2002;104:183–190.

[5]Nettis E, Napoli G, Ferrannini A, Tursi A. IgE-mediated allergy to bromelain. Allergy. 2001;56:257–258.

[6]Walker AF, Bundy R, Hicks SM, Middleton RW. Bromelain reduces mild acute knee pain and improves well-being in a dose-dependent fashion in an open study of otherwise healthy adults. Phytomedicine. 2002; 9:681–686.

[7]Tilwe GH, Beria S, Turakhia NH, Daftary GV, Schiess W. Efficacy and tolerability of oral enzyme therapy as compared to diclofenac in active osteoarthrosis of knee joint: An open randomized controlled clinical trial. J Assoc Physicians India. 2001;49:617–621.

[8]Kamenicek V, Holan P, Franek P. Systemic enzyme therapy in the treatment and prevention of post-traumatic and postoperative swelling. Acta Chir Orthop Traumatol Cech. 2001;68:45–49.

[9]Masson M. Bromelain in the treatment of blunt injuries to the musculoskeletal system: A case observation study by an orthopedic surgeon in private practice. Fortschr Med. 1995;113:303–306.

[10]Newall CA, Anderson LA, Philpson JD. Herbal Medicine: A Guide for Healthcare Professionals. London: The Pharmaceutical Press, 1996.

[11]Kleber E, Schneider W, Schafer HL, Elstner EF. Modulation of key reactions of the catecholamine metabolism by extracts from Eschscholtzia californica and Corydalis cava. Arzneimittelforschung. 1995;45: 127–131.

[12]Halbsguth C, Meissner O, Haberlein H. Positive cooperation of protoberberine type 2 alkaloids from Corydalis cava on the GABA(A) binding site. Planta Med. 2003;69:305–309.

[13]Reimeier C, Schneider I, Schneider W, Schafer HL, Elstner EF. Effects of ethanolic extracts from Eschscholtzia californica and Corydalis cava on dimerization and oxidation of enkephalins. Arzneimittelforschung. 1995;45:132–136.

[14]Langner E, Greifenberg S, Gruenwald J. Ginger: History and use. Adv Ther. 1998;15:25–44.

[15]Srivastava KC, Mustafa T. Ginger (Zingiber officinale) and rheumatic disorders. Med Hypoth. 1989; 29:25–28.
[16]Srivastava KC. Effect of onion and ginger consumption on platelet thromboxane production in humans. Leukot Essent Fatty Acids. 1989;35:183–185.
[17]Onogi T. Capsaicin-like effect of (6) shogaol on substance P-containing primary afferents rats: A possible mechanism of its analgesic action. Neuropharmacology. 1992;31:1165–1169.
[18]Altman RD, Marcussen KC. Effects of a ginger extract on knee pain in patients with osteoarthritis. Arthritis Rheum. 2001;44:2531–2538.
[19]Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee—a randomized double blind placebo controlled trial. Phytomedicine. 2003 Jan;10(1):3–7.
[20]Hesslink R Jr, Armstrong D 3rd, Nagendran MV, Sreevatsan S, Barathur R. Cetylated fatty acids improve knee function in patients with osteoarthritis. J Rheumatol. 2002 Aug;29(8):1708–1712.
[21]Kraemer WJ, Ratamess NA, Anderson JM, Maresh CM, Tiberio DP, Joyce ME, Messinger BN, French DN, Rubin MR, Gómez AL, Volek JS, Hesslink R Jr. Effect of a cetylated fatty acid topical cream on functional mobility and quality of life of patients with osteoarthritis. J Rheumatol. 2004 Apr;31(4):767–774.
[22]Menon VP, Sudheer AR. Antioxidant and anti-inflammatory properties of curcumin. Adv Exp Med Biol. 2007;595:105–125.
[23]Hsu CH, Cheng AL. Clinical studies with curcumin. Adv Exp Med Biol. 2007;595:471– 480.
[24]Chrubasik S, Künzel O, Model A, Conradt C, Black A. Treatment of low back pain with a herbal or synthetic anti-rheumatic: A randomized controlled study. Willow bark extract for low back pain. Rheumatology (Oxford). 2001 Dec;40(12):1388–1393.
[25]Schmid B, Lüdtke R, Selbmann HK, Kötter I, Tschirdewahn B, Schaffner W, Heide L. Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: randomized placebo-controlled, double blind clinical trial. Phytother Res. 2001 Jun;15(4):344–350.
[26]McCarty DJ, Csuka M, McCarthy G, et al. Treatment of pain due to fibromyalgia with topical capsaicin: A pilot study. Semin Arthr Rheum. 1994;23:41– 47.
[27]Frerick H, Keitel W, Kuhn U, Schmidt S, Bredehorst A, Kuhlmann M. Topical treatment of chronic low back pain with a capsicum plaster. Pain. 2003;106:59–64.
[28]Fusco BM, Marabini S, Maggi CA, Fiore G, Geppetti P. Preventative effect of repeated nasal applications of capsaicin in cluster headache. Pain. 1994 Dec;59(3):321–325.
[29]McCarthy GM, McCarty DJ. Effect of topical capsaicin in the therapy of painful osteoarthritis of the hands. J Rheumatol. 1992 Apr;19(4):604–607.
[30]Watson CP, Tyler KL, Bickers DR, Millikan LE, Smith S, Coleman E. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. Clin Ther. 1993 May–Jun;15(3):510–526.
[31]Reimann S, Luger T, Metze D. [Topical administration of capsaicin in dermatology for treatment of itching and pain]. Hautarzt. 2000 Mar;51(3):164–172.
[32]Biesbroeck R, Bril V, Hollander P, Kabadi U, Schwartz S, Singh SP, Ward WK, Bernstein JE. A double-blind comparison of topical capsaicin and oral amitriptyline in painful diabetic neuropathy. Adv Ther. 1995 Mar–Apr;12(2):111–120.
[33]DiPaolo S, Gesualdo E, Grandaliano G, Schena FP. High glucose concentration induces the over-expression of transforming growth factor-beta through the activation of a platelet-derived growth factor loop in human mesangial cells. Am J Pathol. 1996;149:2095–2106.
[34]Pugliese G, Pricci F, Locuratolo N, Romeo G, Romano G, Giannini S, Cresci B, Galli G, Rotella CM, Di Mario U. Increased activity of the insulin-like growth factor system in mesangial cells cultured in high glucose conditions: Relation to glucose-enhanced extracellular matrix production. Diabetologia. 1996;39: 775–784.
[35]Ongley MJ, Klein RG, Dorman TA, Eek BC, Hubert LJ. A new approach to the treatment of chronic low back pain. Lancet. 1987;ii:143–146.
[36]Murphy M, Godson C, Cannon S, Kato S, Mackenzie HS, Martin F, Brady HR. Suppression subtractive hybridization identifies high glucose levels as a stimulus for expression of connective tissue growth factor and other genes in human mesangial cells. J Biol Chem. 1999;274:5830–5834.
[37]Reeves KD, Hassanein KM. Long-term effects of dextrose prolotherapy for anterior cruciate ligament laxity. Altern Ther Health Med. 2003;9:58–62.
[38]Reeves KD, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. Altern Ther Health Med. 2000;6:68–74, 77–80.
[39]Reeves KD, Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: Evidence of clinical efficacy. J Altern Complement Med. 2000;6:311–320.

[40]Linetsky FS, Miguel R, Torres F. Treatment of cervicothoracic pain and cervicogenic headaches with regenerative injection therapy. Curr Pain Headache Rep. 2004;8:41–48.
[41]Yelland M, Mar C, Pirozzo S, Schoene M, Vercoe P. Prolotherapy injections for chronic low-back pain. Cochrane Database Syst Rev. 2004;2:CD004059.
[42]9th International Mesotherapy Conference [held by the French Society of Mesotherapy; proceedings]. Paris, France, October 20–22, 2000.
[43]Kaplan A. Marks of pain produced by four different ways of injection [in French]. Bulletin SFM. 1985:in vol. 62.
[44]LeCoz J. and Dupont, J-Y. Injection in eye of the knee by way of mesotherapy provides good concentrations intra-articularly [in French]. Quotidien du Medecin. 1983 Sep 20.
[45]Smail H. Anterior thoracic pain with vertebral origins [in French]. 9th International Mesotherapy Conference [held by the French Society of Mesotherapy; proceedings]. Paris, France, October 20–22, 2000.
[46]Leah da Silva J, Mesquita ME. Evaluation results of two methods of treatment with mesotherapy for chronic degenerative rheumatic pain [in French]. 9th International Mesotherapy Conference [held by the French Society of Mesotherapy; proceedings]. Paris, France, October 20–22, 2000.
[47]Messedi-Kamoun, N., Ben Salah FZ, Dziri C. Mesotherapy in the treatment of 132 cases of spinal pain matters [in French]. 9th International Mesotherapy Conference [held by the French Society of Mesotherapy; proceedings]. Paris, France, October 20–22, 2000.

28

OPTIMIZING WELLNESS FOR PEAK PHYSICAL PERFORMANCE

Exercise is not dead, by any means, in the United States. The usual headlines highlighting the disturbing infrequency of exercise by U.S. citizens, as well as the dismal percentages of Americans who are obese, tend to produce a negative view regarding exercise. However, consider the following statistics that demonstrate clearly the vigor with which Americans engage in physical activity:

> In the United States, approximately 30 million children and adolescents participate in some form of organized sport, and approximately 30 million people in the United States enjoy running, with 10 million people running on a regular basis.[1]
>
> Americans place maintaining good physical health and keeping up their physical appearance among the top of their personal priorities, with 97% of Americans saying these are essential. An annual consumer report determined that the 33 million Americans who currently belong to health clubs visited gyms an average of 89 times per year, translating into nearly 3 billion visits in 2001.[2]
>
> The total number of health-club patrons, including both members and nonmembers, climbed 7%, from 54.5 million in 2000 to 58.3 million people in 2001.[2]

The positive benefits of exercise are well-studied at this time. Performing regular exercise on most days of the week reduces the risk of developing (or dying from) some of the conditions that are the leading causes of illness and death in the United States. (See the box on page 317 entitled ''Benefits of Activity.'') It is clear that keeping fit is an important part of life for many people. In addition to getting in shape, people are increasingly looking for ways to maintain a competitive edge in sports. The use of supplements as ergogenic supports is increasingly popular among all athletes. Using natural medicines can help athletes to maintain their health and can help to prevent exercise-related injuries. Many natural medicines that athletes use counteract the prooxidative effects of exercise, limit joint wear, decrease inflammation, and increase energy, thereby positioning athletes, whether they are professionals or amateurs, for optimal wellness.

ANTIOXIDANTS

Despite the clear benefits of exercise, it does induce oxidative stress, which is potentially injurious to cellular macromolecules, such as lipids, proteins, and nucleic acids. Free radicals such as superoxide and hydroxyl radicals are by-products of aerobic metabolism. Reducing molecular oxygen to water creates aerobically generated cell energy. The cytochrome C oxidase-catalyzed reaction, as well as other energy-generating enzymatic processes, such as the flavin enzyme systems, produces partially reduced oxygen species. Approximately 1%–2% of total oxygen consumption is converted to one such reactive oxygen species, the superoxide anion. Formation of the superoxide anion radical leads to a cascade of other reactive oxygen species, namely hydroxyl and peroxyl radicals. The initial reaction spawns a second reactive

oxygen, which, in turn, reacts with another macromolecule, propagating the chain reaction. Reactive oxygen species affect the structure and function of polyunsaturated fatty acids adversely because of lipid peroxidation. And, individual nucleotide bases of proteins are modified in such a way that unwanted single-strand breakage and cross-linking occurs. The effects of oxidative stress have been associated with decreased physical performance, muscular fatigue, muscle damage, and overtraining syndrome.[3]

Benefits of Activity

Reduces the risk of dying prematurely
Reduces the risk of dying from heart disease
Reduces the risk of developing diabetes
Reduces the risk of developing high blood pressure
Helps to reduce blood pressure
Reduces the risk of developing colon cancer
Reduces feelings of depression and anxiety
Helps to control weight
Helps to build and maintain healthy bones, muscles, and joints
Helps older adults to maintain and develop strength so that they are able to move about without falling
Promotes psychologic well-being.

When examining the physiologic effects of exercise and the resultant increase in overall metabolism, an astute clinician can focus on decreasing potentially damaging metabolic ''side effects'' of exercise (i.e., increased free-radical damage). Such free-radical damage from aerobic exercise can be quantified in the form of oxidative stress-related biomarkers. These include lipid peroxidation, protein oxidation (in the form of protein carbonyls), and total antioxidant levels in the blood following exhaustive aerobic exercise. Indirect measurements of free-radical activity include mitochondrial membrane damage, conjugated dienes, hydroperoxides, thiobarbituric-acid reactive substances, short-chain hydrocarbons, and oxidized nucleosides.

Several studies have implicated elevated volume of oxygen (VO_2) consumption caused by aerobic exercise as a contributor to the body's total oxidative stress.[4] There may be a number of other sources of this oxidative stress, including mitochondrial superoxide production, ischemia-reperfusion mechanisms, and autoxidation of catecholamines. The exact role of exercise in free-radical processes is not clear; however, a large body of evidence suggests that elevated oxygen consumption may lead to an increase in free-radical activity.[5] An athlete's training status and exercise type, duration, and intensity will affect the biomarkers of free-radical activity as well. Because severe or prolonged exercise can overwhelm antioxidant defenses, it is hypothesized that the body's physiologic amount of antioxidants is not sufficient to prevent exercise-induced oxidative stress and that additional antioxidants are needed to reduce oxidative stress, muscular damage, and inflammation. By bolstering the athlete's store of antioxidant defenses, such long-term supplementation may ameliorate exercise-induced free-radical damage.[6]

Some studies have reported that antioxidant vitamins such as C and E, as well as other antioxidants, or antioxidant mixtures can reduce the symptoms or indicators of oxidative stress resulting from exercise. Ingestion of antioxidant vitamins (592 mg of alpha-tocopherol equivalents, 1,000 mg of ascorbic acid, and 30 mg of beta-carotene) resulted in significantly lower resting and postexercise levels of expired pentane and serum malondialdehyde, both of which are markers of lipid peroxidation.[7] In addition, older men, when exposed to exercise-induced oxidative stress, had significantly lower levels of lipid peroxides in urine compared to placebo controls after receiving vitamin E supplements for 48 days.[8] Thus, antioxidants, such as arginine, citrulline, creatine, glutathione, taurine, selenium, zinc, vitamin E, vitamin C, vitamin A, and green tea (Camellia sinensis) polyphenols are likely to provide beneficial effects against exercise-induced oxidative damage.[9] Using any of the preceding antioxidants is indicated for competitive athletes who are routinely engaged in strenuous exercise. Supplementation of an athlete's diet with antioxidants may serve as a potent therapeutic tool. Efforts to determine athletes' individual needs, and to ensure consumption of a balanced diet that is rich in antioxidants, are highly recommended.

Glucosamine's pain-relieving effects appear to be the result of its cartilage-rebuilding properties.

PREVENTION OF PHYSICAL WEAR AND TEAR

While many health care providers experience frustration in trying to motivate their patients to exercise, the problem is often amplified when such patients return with complaints of exercise-related aches and pains. Most exercise-related injuries occur from overuse stress on the muscles, tendons, bones, or joints. Sporting activities with major risk for creating pain are, not surprisingly, those that include repetitive, high-intensity, high-impact forces going through the affected joints, especially when there is a high association of the activities with risks of injury. Various nutritional supplements can mitigate the effects of exercise-induced wear-and-tear on the body. (See Table 28–1 on page 319.) The mechanism of action for these supplements focuses on ligamentous and cartilaginous tissue repair and maintenance.

Glucosamine

Glucosamine is comprised of glucose and glutamine, is the key precursor for the manufacture of joint glycosaminoglycans, and comprises 50% of hyaluronic acid, the core protein from which cartilage and proteolglycans are formed. The three most common commercial forms are glucosamine sulfate (as the sodium or potassium salts), glucosamine hydrochloride, and N-acetylglucosamine, the acetylated derivative. The majority of clinical trials have used a chemically bonded glucosamine sulfate. In vitro studies have revealed that glucosamine increases sulfate uptake by cartilage and stimulates glycosaminoglycan synthesis by cartilage cells (chondrocytes).[10] Glucosamine has been shown to have both anti-inflammatory and antioxidant activities. Its anti-inflammatory activity is independent of an effect on cyclooxygenase (COX) or the inflammatory mediators bradykinin or histamine.[11] In a three-year study of glucosamine sulfate in subjects with osteoarthritis of the knee, radiography was used to determine structural changes in the knee joint while pain reduction was assessed in comparing a single

daily dose of 1,500 mg of glucosamine to a placebo. Radiography studies of the knee indicated that joint damage had progressed in the placebo group but not in the glucosamine sulfate group. Pain worsened slightly among members of the placebo group while improvements of 20%–25% occurred in the treatment group.[12] Another study compared 1.2 g of ibuprofen per day to 1.5 g of glucosamine sulfate per day for reducing pain. The results of this study showed that glucosamine sulfate's efficacy is similar to that of ibuprofen.[13] Earlier studies had yielded positive clinical effects and the absence of significant adverse effects. However, the relief of pain occurred more slowly than with non-steroidal anti-inflammatory drugs (NSAIDs) but appeared to be longer lasting.[14] Glucosamine's pain-relieving effects appear to be the result of its cartilage-rebuilding properties; conventional analgesic therapy does not produce the disease-modifying effects of glucosamine supplementation. For the active athlete, glucosamine can be used as an alternative to anti-inflammatory drugs and analgesics or as a useful adjunct to standard analgesic therapy while supporting cartilage repair and regeneration.

Methylsulfonylmethane

Methylsulfonylmethane (MSM) is a sulfur-containing substance that is currently utilized primarily for pain control and for its antiarthritic and anti-inflammatory properties. It is a metabolite of dimethylsulfoxide. MSM is found in certain plants, algae, fruits, vegetables, and grains. MSM is a precursor source of sulfur for the amino acids cysteine and methionine, which are building blocks for cartilage. Preliminary research suggests MSM might inhibit the degenerative changes of osteoarthritis.[15] In a randomized, double-blind, parallel, placebo-controlled study, 118 patients with mild to moderate osteoarthritis were randomized to receive either glucosamine 500 mg, MSM 500 mg, glucosamine and MSM, or placebo capsules three times daily for 12 weeks. According to the results, glucosamine, MSM, and their combination produced an analgesic and anti-inflammatory effect in osteoarthritis with improved signs and symptoms such as pain and swelling of osteoarthritis compared with the placebo.[16] In a similar randomized, double-blind, placebo-controlled trial, 50 patients aged 40–76 years with knee osteoarthritis pain were given MSM 3 g or placebo twice a day for 12 weeks. MSM produced significant decreases in pain and physical function impairment measured by the Western Ontario and McMaster University Osteoarthritis Index visual analogue scale (WOMAC). The

Table 28–1. Supplements for Building Peak Physical Performance

Antioxidants	Dosages
Vitamin A	5,000 IU per day, with food
Vitamin C	2,000–6,000 mg, in divided doses, per day
Vitamin E	400–800 IU per day, with food
Selenium	50–60 mg per day
Zinc	50 mg per day
Cartilage Supports	**Dosages**
Glucosamine sulfate	500 mg, 3 times per day (4 times per day for patients more than 200 lbs)
Methylsulfonlymethane	1,000–3,000 mg per day, with meals

IU international unit.

MSM supplementation group also showed improvement in performing activities of daily living when compared to the placebo.[17]

The clinician who cares for athletes must emphasize the importance of preventive and protective measures for the joints. Protecting against joint destruction and providing the essential materials that are necessary for cartilage maintenance and repair can prevent both short-term aches and long-term disability. In addition, the athlete must be attentive to correct posture and positioning while participating in both high- and low-impact activities. Limiting high-impact contact with excessively hard surfaces, such as gym floors and concrete, is also important. Finally, athletes must be made aware of their physical limitations and be taught to recognize the early symptoms of overuse injuries associated with their athletic endeavors.

ACHES AND PAINS

Even when they observe appropriate preventive measures, athletes are susceptible to aches and pains resulting from physical activity. Alleviation of these symptoms is important for two reasons: (1) a prompt reduction in pain is necessary for the athlete to continue performing at his or her desired level; and (2) the pain-inciting inflammatory process must be halted before a chronic inflammatory condition develops. Tendonitis, bursitis, arthritis, sprains, strains, and other inflammatory conditions that result from athletic activity have been treated conventionally with over-the-counter or prescription non-steroidal anti-inflammatory drugs (NSAIDs). However, these medications do not provide the most desirable results for patients with inflammatory injuries because NSAIDs are associated with increased cartilage degeneration via inhibitory effects on cartilage proteoglycan metabolism. In addition, NSAIDs exert inhibitory effects on the production of gastrointestinal mucosal prostaglandins, resulting in deleterious modulation of prostaglandin-related cellular mechanisms that are important for mucosal defenses.[18] More specifically, by inhibiting PGE1 production in the gut, NSAIDs cause gastric erosions and ulcers, as well as increase permeability in the small intestines.

Various plant-derived anti-inflammatories can be used to achieve immediate prevention of inflammatory cascade by-products in the injured athlete. (See Table 28–2 below.)

Bromelain

Bromelain is a proteolytic enzyme derived from pineapple (Ananas comosus). Recent investigations have revealed that bromelain exerts a significant effect on T-cell response by inhibiting

Table 28–2. Anti-Inflammatory Treatment for Athletes

Supplements	Dosages
Bromelain[a]	1,800–2,400 GDU or MCU or 350–750 mg, 3 times per day, between meals
Curcumin[a]	1500–3,000 mg, 3 times per day, between meals
Mixed blend of flavonoids (quercitin, hesperidin, and rutin)	1,000 mg, 3 times per day
Essential fatty acids	500–1,000 mg, 3 times per day

GDU gelatin-dissolving unit, MCU milk-clotting unit.
[a]Do not use in patients who have gastrointestinal ulcers or esophagitis; monitor patients who are on blood thinners carefully.

T-cell signal transduction and can ameliorate the inflammatory process by reducing the number of CD4 cells and by diminishing interferon-gamma mRNA levels.[19] In vitro bromelain treatment has selectively removed certain cell-surface molecules that affect lymphocyte migration and activation on a broad range of cell-surface molecules and on lymphocytes, monocytes, and granulocytes. These cell-surface molecules, which are altered by bromelain, are involved in leukocyte homing, cellular adhesion, and activation.[20] These effects on the inflammatory pathways suggest a decrease in the creation of pro-inflammatory by-products of exercise, pain, swelling, and edema, making bromelain an optimal choice for treating sports injuries. However, bromelain does have side effects. Although the interaction is theoretical, because this pineapple-stem–derived medicine acts proteolytically, caution should be used when treating athletes who are prone to gastric mucosal irritation or ulceration, or patients who are on anticlotting regimens, because bromelain can amplify the effects of blood-thinning pharmaceuticals.

Curcumin

Curcumin (Curcuma longa) is the yellow pigment of the spice turmeric. Curcumin has various properties that are beneficial for the athlete. Curcumin behaves as an inhibitor of the transcription factor NF-kappaB, which allows it to act as a stimulator of muscle regeneration after traumatic injury. One recent study showed that in-vivo muscle regeneration is greatly enhanced after the systemic administration of curcumin. Biochemical and histologic analyses indicated this effect in subjects after four days of curcumin administration compared to controls who required more than two weeks to attain fully restored muscle-tissue architecture.[21] Because of curcumin's role in regulating myogenesis, it is an appropriate treatment for sports-related muscle injuries.

In addition, the anti-inflammatory effect of curcumin is most likely mediated by curcumin's ability to inhibit cyclooxygenase-2 (COX-2), lipoxygenase (LOX), and inducible nitric oxide synthase (iNOS),[22] working to inhibit leukotriene synthesis, platelet aggregation, and neutrophil reactivity. Like bromelain, curcumin produces side effects such as the potential to cause gastric irritation and antiplatelet activity and, therefore, has the same contraindications.

Flavonoids

Flavonoids comprise a group of plant pigments numbering in the thousands with remarkable antioxidant and anti-inflammatory activities. Hesperidin, rutin, and quercitin are among the plant flavonoids that attenuate inflammation via inhibiting important regulatory enzymes. Certain flavonoids are potent inhibitors of the production of pro-inflammatory prostaglandins. Studies have shown that this effect is the result of flavonoids inhibiting key enzymes involved in eicosanoid biosynthesis, such as lipoxygenase, phospholipase, and COX. Flavonoids also inhibit cyclic nucleotide phosphodiesterases, affecting both cGMP and cAMP, which is involved in inflammatory-type cell activity, namely, manufacturing protein cytokines that mediate adhesion of circulating leukocytes to sites of injury.[23] Interactions with various protein kinases, depending on the particular flavonoid and cell, are another class of regulatory enzymes affected by flavonoids. These various modes of inhibitory action provide the mechanisms by which flavonoids inhibit the inflammation response.

Two specific types of bioflavonoids, proanthocyanidin and quercetin, are potentially useful for treating musculoskeletal conditions. Evidence suggests that these flavonoids may be beneficial for connective tissue because of their ability to limit inflammation and associated tissue degradation, improve local circulation, and promote the manufacture of a strong col-

lagen matrix.[24] In addition, other anti-inflammatory effects of quercetin are attributable to its inhibition of leukotriene and prostaglandin production and activity and inhibition of basophil and mast-cell histamine release.[25] Another flavonoid, hesperidin, appears to exert anti-inflammatory effects via inhibiting cell-activating enzyme systems, such as phosphodiesterase A2 and protein kinase C. In addition, hesperidin inhibits inflammatory cellular processes by preventing the production of eicosanoid-synthesizing enzymes, such as phospholipase, cyclooxygenase, and lipoxygenase. Hesperidin also seems to exert its anti-inflammatory effect by inhibiting cyclic nucleotide phosphodiesterases, thereby increasing intracellular cyclic adenosine monophosphate levels, which causes decreased production of inflammatory prostaglandins E2 and F2 and thromboxane B2.[26]

Essential Fatty Acids

Omega-3 fatty acids produce anti-inflammatory and antithrombotic effects because of their ability to compete with arachidonic acid (AA) for binding sites on cyclooxygenase and lipoxygenase enzyme systems. Consequently, essential fatty acids (EFAs) inhibit the synthesis of inflammatory prostaglandins and leukotrienes from the precursor AA. Prostaglandins are derived from dietary EFAs via short biochemical pathways. Synthesis of inflammatory prostaglandins can be manipulated by modifying EFA intake. Prostaglandins of the 1 and 3 series have desirable (i.e., anti-inflammatory) or neutral actions while those of the 2 series are mixed, with some being desirable and others being highly undesirable (i.e., pro-inflammatory). By supplementing the diet with omega-3 fatty acids, several aspects of neutrophil, monocyte, and lymphocyte functions, including the production of inflammatory mediators, can be reduced. The majority of studies indicating reduced inflammatory functions used a minimum of 1.2 g per day of eicosapentaenoic acid and docosahexaenoic acid for six weeks.[27] The anti-inflammatory effects produced by EFAs influence inflammatory cell-activation processes, such as signal transduction and protein expression at the genomic level, decreasing cytokine-induced adhesion molecule expression (thereby reducing inflammatory leukocyte-endothelium interactions), and influencing leukocyte migration.[28] Using fish oils and other EFA oils for preventive management of inflammatory processes is well-supported and can modulate unwanted and excessive inflammatory responses to athletic activities.

ADAPTOGENIC BOTANICALS

The term adaptogen is used to characterize the medicinal plants that can improve the nonspecific response to stress and promote recovery from stress. Because the body interprets exercise as an essentially stressful event, responding, for example, with increased pulse, respiration, and blood pressure, athletes can benefit from incorporating adaptogenic herbs into supplement regimens. (See Table 28–3 on page 323.)

Licorice (Glycyrrhiza glabra) retains modest glucocorticoid activity via its cortisol-sparing effect. Glycyrrhizin, a component of licorice, inhibits the activity of 11-beta-hydroxy-steroid dehydrogenase, which leads to an increase in cortisol half-life.[29] Glycyrrhizin can bind to glucocorticoid and mineralocorticoid receptors, exerting a weak mimetic effect.[30] In addition, licorice inhibits phospholipase A2, which then lowers inflammatory prostaglandin and leukotriene production.

Ashwagandha (Withania somnifera) has active components, withanolides, which have a sterol structure and are thought to be the main inducers of the herb's glucocorticoid-like effects.

Table 28–3. Adaptogenic Herbal Supports

Latin Binomials	Common Names	Parts Used and Dosages
Glycyrrhiza glabra[a]	Licorice	Dried root: 1,000–2,000 mg per day[a] Fluid extract: 2–4 mL per day[a]
Withania somnifer[a]	Ashwaganda	Fluid extract: 1–2 mL per day Dried herb: 3,000–4,000 mg per day
Panax ginseng	Korean ginseng	Fluid extract: 1–2 mL per day Dried herb: 3,000–4,000 mg per day
Eleutherococcus senticosus	Siberian ginseng	Fluid extract: 1–2 mL per day Dried root: 400 mg 2–4 times per day

NOTE: Caution must be taken to cycle herbs to avoid side effects caused by long-term supplementation that are not yet well-defined in studies. These effects may include habituation, development of allergic sensitivity, or disturbance of innate physiologic pathways.
[a]Monitor blood pressure.

Given to animals exposed to experimental physical stress, ashwagandha produces anti-stress and anabolic activity similar to that of Asian ginseng (Panax ginseng).[31] When administered to animals, Siberian ginseng, more accurately known as eleuthero, (Eleutherococcus senticosus) inhibited many of the biologic changes accompanying extreme stress, such as adrenal weight changes, increasing cortisol levels, and blood-sugar levels.[32] A large body of research has demonstrated an enhanced response to physical or chemical stress in animals that have been given Asian ginseng or its active components.[33] In a double-blind study, an Asian ginseng root extract that was added to the base of a multivitamin improved subjective parameters in a population exposed to the stress of high physical and mental activity, suggesting an adaptogenic or anti-stress ability of this combination in humans.[34] A review of the body of literature regarding the clinical trials of eleuthero's anti-stress effects on more than 2,100 healthy human subjects ranging in age from 19 to 72, suggested that the subjects who took this botanical had an increased ability to accommodate to adverse physical conditions, had improved mental performance, and enhanced quality of work under stressful conditions.[31] Another study demonstrated increased exercise time to exhaustion in swimming rats that had been given this herb, as well as attenuated changes of the hypothalamic-pituitary-adrenal axis under extreme conditions in the animals.[35] (See Chapter 1 on adrenal fatigue.)

CONCLUSIONS

Given that there are only a few standard conventional medicines for preventing exercise-induced injury and wear, natural medicines provide an extensive armamentarium which practitioners can offer athletes for attenuating the effects of excessive exercise and increasing their performance to optimal levels.

REFERENCES

[1]Requa RK, DeAvilla LN, Garrick JG. Injuries in recreational adult fitness activities. Am J Sports Med. 1993;21:461–467.
[2]International Health and Racquet and Sportsclub Association=American Sports Data, Inc. (IHRSA=ASD). Health Club Trend Report. Boston: IHRSA=ASD, 2002.

[3]Konig D, Wagner KH, Elmadfa I, Berg A. Exercise and oxidative stress: Significance of antioxidants with reference to inflammatory, muscular, and systemic stress. Exerc Immunol Rev. 2001;7:108–133.
[4]Alessio HM, Hagerman AE, Fulkerson BK, Ambrose J, Rice RE, Wiley RL. Generation of reactive oxygen species after exhaustive aerobic and isometric exercise. Med Sci Sports Exerc. 2000;32:1576–1581.
[5]Alessio HM. Exercise-induced oxidative stress. Med Sci Sports Exerc. 1993;25:218–224.
[6]Packer L. Oxidants, antioxidant nutrients and the athlete. J Sports Sci. 1997;15:353–363.
[7]Kanter MM, Nolte LA, Holloszy JO. Effects of an antioxidant vitamin mixture on lipid peroxidation at rest and postexercise. J Appl Physiol. 1993;74:965–969.
[8]Meydani M. Vitamin E requirement in relation to dietary fish oil and oxidative stress in elderly. Experientia. 1992;62:411– 418.
[9]Fang Y, Yang S, Wu G. Free radicals, antioxidants, and nutrition. Nutrition. 2002;Oct;18:872.
[10]Thie NM, Prasad NG, Major PW. Evaluation of glucosamine sulfate compared to ibuprofen for the treatment of temporomandibular joint osteoarthritis: A randomized double blind controlled 3-month trial. J Rheumatol. 2001;28:1347–1355.
[11]Shikhman, AR et al. N-acetylglucosamine prevents IL-1B-mediated activation of human chondrocytes. J Immunol. 2001;166:5155–5160.
[12]Reginster, JY, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: A randomized, placebo-controlled clinical trial. Lancet. 2001;357:251–256.
[13]Ruane R, Griffiths P. Glucosamine therapy compared to ibuprofen for joint pain. Br J Community Nurs. 2002;7:148–152.
[14]Vaz, AL. Double-blind clinical evaluation of the relative efficacy of ibuprofen and glucosamine sulphate in the management of osteoarthritis of the knee in outpatients. Curr Med Res Opin. 1982;8:145–149.
[15]Murav'ev IV, Venikova MS, Pleskovskaia GN, et al. Effect of dimethyl sulfoxide and dimethyl sulfone on a destructive process in the joints of mice with spontaneous arthritis [in Russian]. Patol Fiziol Ekspp Ter. 1991;5:37–39.
[16]Usha PR, Naidu MU. Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. Clin Drug Investig. 2004;24(6):353–363.
[17]Kim LS, Axelrod LJ, Howard P, Buratovich N, Waters RF. Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: A pilot clinical trial. Osteoarthritis Cartilage. 2006 Mar;14(3):286–294. Epub 2005 Nov 23.
[18]Rainsford KD. Profile and mechanisms of gastrointestinal and other side effects of nonsteroidal anti-inflammatory drugs (NSAIDs). Am J Med. 1999:13;107(6 suppl.A):27S–35S; discussion 35S–36S.
[19]Hale LP, Greer PK, Sempowski GD. Bromelain treatment alters leukocyte expression of cell surface molecules involved in cellular adhesion and activation. Clin Immunol. 2002;104:183–190.
[20]Leung AY, Foster S. Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics, 2nd Edition. New York: John Wiley & Sons, 1996.
[21]Thaloor D, Miller KJ, Gephart J, Mitchell PO, Pavlath GK. Systemic administration of the NF-kappa B inhibitor curcumin stimulates muscle regeneration after traumatic injury. Am J Physiol. 1999;277(2pt.1): C320–C329.
[22]Menon VP, Sudheer AR. Antioxidant and anti-inflammatory properties of curcumin. Adv Exp Med Biol. 2007;595:105–125.
[23]Manthey JA. Biological properties of flavonoids pertaining to inflammation Microcirculation. 2000; 7(suppl.pt.2):S29–S34.
[24]Teixeira S. Bioflavonoids: Proanthocyanidins and quercetin and their potential roles in treating musculoskeletal conditions. J Orthop Sports Phys Ther. 2002;32:357–363.
[25]Grimm H, Mayer K, Mayser P, Eigenbrodt E. Regulatory potential of n-3 fatty acids in immunological and inflammatory processes. Br J Nutr. 2002;87(suppl.1):S59–S67.
[26]Kelley DS. Modulation of human immune and inflammatory responses by dietary fatty acids. Nutrition. 2001;17:669–773.
[27]Konig D, Berg A, Weinstock C, Keul J, Northoff H Essential fatty acids, immune function, and exercise. Exerc Immunol Rev. 1997;3:1.
[28]Horrobin DF, Manku MS, Huang YS. Effects of essential fatty acids on prostaglandin biosynthesis. Biomed Biochim Acta. 1984;43(suppl.8–9): S114–S120.
[29]Armanini D, Karbowiak I, Funder J. Affinity of licorice derivatives for mineralocorticoid and glucocorticoid receptors. Clin Endocrinol. 1983;19:609–612.
[30]Kuroyanagi T, Sato M. Effect of prednisolone and glycyrrhizin on passive transfer of experimental allergic encephalomyelitis. Allergy. 1966;15:67–75.
[31]Grandhi A, Mujumdar AM, Patwardhan B. A comparative pharmacological investigation of ashwagandha and ginseng. J Ethnopharmacol. 1994;44:131–135.

[32]Farnsworth NR, Kinghorn AD, Soejarto D, Waller DP. Siberian ginseng (Eleutherococcus senticosus): Current status as an adaptogen. Econ Med Plant Res. 1985;156–215.
[33]Saito H, Yoshida Y, Takagi K. Effect of Panax ginseng root on exhaustive exercise in mice. Jpn J Pharmacol. 1974;24:119–127.
[34]Banerjee U, Izquierdo JA. Antistress and antifatigue properties of Panax ginseng: Comparison with piracetam. Acta Physiol Lat Am. 1982;277–285.
[35]Golotin VG, Gonenko VA, Zimina VV, et al. Effect of ionol and eleutherococcus on changes of the hypophysea-adrenal system in rats under extreme conditions. Vopr Med Khim. 1989;35:35–37.

29

NATURAL APPROACHES FOR TREATING POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS) is a complex medical condition involving multiple body systems. The etiology of this condition is unknown. In addition, there is currently no consensus on the diagnostic criteria for PCOS. It is accepted that hyperandrogenism, insulin resistance, and menstrual abnormalities are commonly present. An estimated 6%–10% of reproductive-age women have PCOS, making it one of the most common endocrine reproductive disorders.[1]

ETIOLOGY

The cause of PCOS is unknown. Many studies have indicated that either insulin resistance or endocrine dysfunction can cause the symptoms associated with this condition.[2] Many theories have been suggested to explain the primary defect that causes PCOS pathology. They include abnormal insulin action and secretion, endocrine abnormalities causing an increased luteinizing hormone (LH) pulse frequency and amplitude, increased androgen production from the ovaries, and abnormal cortisol metabolism.[2] There is also evidence that genetic factors play a role in PCOS.[3] Eating disorders, such as bulimia and binge eating, have also been associated with this condition.[4]

SYMPTOMS

PCOS involves metabolic, endocrine, and clinical manifestations. Studies have suggested that 75%–80% of women with PCOS have irregular menstrual cycles. These women typically have five to nine menstrual cycles per year, ranging from 40–65 days in length. Increased androgens cause hirsutism in 60%–80%—as well as alopecia in 40%–70%—of these women. Acne is also increased and prevalent in 40%–60% of women with PCOS. Obesity is common in this condition, and studies have suggested that 75% of women with PCOS are overweight or obese.[5] These women often have increased abdominal adiposity with an average waist-to-hip ratio of 0.86.[6] Of these overweight women, an estimated 10% have acanthosis nigricans, commonly found in the axilla, nape of the neck, and skin folds. Increased prolactin can also cause breast discharge in 8%–10% of affected women. Finally, sleep apnea may also occur in approximately 8% of women with PCOS.[5] Other endocrine diseases with similar symptoms must be ruled out in order to diagnose PCOS.

PATHOPHYSIOLOGY

Insulin Resistance

Insulin resistance can be caused by increased peripheral insulin resistance of the target tissue, increased pancreatic sensitivity, or decreased hepatic insulin clearance. Studies have shown

that insulin resistance and hyperinsulinemia are common in women with PCOS. In addition, obese women with PCOS have had decreased insulin sensitivity compared to lean women with the condition.[7] However, some studies have not found abnormal insulin action in lean women with PCOS.[8]

Pancreatic beta-cell dysfunction similar to that of type 2 diabetes has also been found in women with this condition.[9] In addition, studies have shown excessive serine phosphorylation at the insulin receptor causing an inhibition of signaling. Serine phosphorylation of insulin-receptor substrate-1 is also associated with the tumor necrosis factor–alpha-mediated insulin resistance seen with obesity. It is also important that serine phosphorylation increases the activity of the enzyme P450c17 in adrenal and ovarian tissue. This enzyme is a key regulatory molecule in androgen synthesis, and serine phosphorylation has been shown to increase androgen synthesis. Research has indicated that serine phosphorylation causes insulin resistance in at least 50% of women with PCOS.[10]

Hyperandrogenism

Although studies have yielded conflicting results, current evidence suggests that hyperinsulinemia causes the hyperandrogenism seen in women with PCOS. Studies have indicated that insulin increases the amplitude of the LH pulse in obese women with PCOS.[11] In addition, insulin decreases the synthesis of sex–hormone binding globulin (SHBG) from the liver, which increases the bioavailability of androgens. Insulin also decreases the production of insulin-like growth factor (IGF) binding protein-1 (IGFBP-1) in the liver and the ovaries, which causes an increase in available IGF-1.[12] Studies have shown that insulin and IGF-1 increase thecal androgen response to LH and that high levels of insulin can bind the IGF receptor leading to an increase in androgen production.[13]

Diabetes and Glucose Intolerance

Interestingly, studies have shown that 82% of women with type 2 diabetes had polycystic ovaries (shown via ultrasound tests). Yet, only 52% of these women had symptoms of hyperandrogenism or menstrual abnormalities. Thus, it is clear that insulin resistance is only one factor causing PCOS. Studies have indicated that glucose intolerance is found in 31% of patients with PCOS, and type 2 diabetes is found in 7.5% of obese women with PCOS. Approximately 10% of nonobese women with PCOS have glucose intolerance, and 1.5% of these women have type 2 diabetes.[9] In addition, women with PCOS have a fivefold to tenfold rate increase in converting from glucose intolerance to type 2 diabetes.[14]

Cardiovascular Disease

Metabolic syndrome and its individual components are common in women with PCOS. There is an increased risk of cardiovascular disease (CVD) among women with PCOS. Studies have shown that, although atherosclerosis is not specifically increased in women with PCOS, carotid artery intima media thickness is increased significantly in these women, suggesting subclinical atherosclerotic changes.[15] In addition, hyperandrogenic insulin-resistant women with PCOS have abnormal endothelial function. Endothelin-1 (ET-1) is a potent vasoconstrictor molecule that has been shown to be elevated in women with PCOS regardless of obesity, which appears to be indicative of abnormal vascular reactivity, endothelial injury, and increased risk for CVD.[16]

Women with PCOS have increased risk for abnormal lipid levels as well. Studies have shown increases in triglycerides and low-density lipoprotein cholesterol, and decreased high-density lipoprotein cholesterol.[17] Women with PCOS have also been shown to have increased levels of plasminogen activator inhibitor (PAI-1).[18] Insulin resistance and increased risk of thrombotic vascular events is associated with increased PAI-1.[19]

Endocrine Abnormalities

Many endocrine abnormalities are seen in PCOS. One significant finding is the increase in LH surge amplitude and frequency seen in approximately one-third of women with this condition.[20] Follicle-stimulating hormone (FSH) levels are usually normal or low. The LH diurnal secretion pattern is also abnormal, peaking in late afternoon instead of at night. Gonadotropin-releasing hormone (GnRH) secretion is also atypical in these women. GnRH is secreted in a rapid pulse frequency that increases LH synthesis, increases androgens, and inhibits the maturation of follicles.[21] Progesterone supplementation to anovulatory women with PCOS also causes a slower GnRH pulse frequency and increased FSH secretion and follicle maturation.[21] In addition, it has been shown that the hypothalamus GnRH pulse generator is less sensitive to inhibition by estradiol and progesterone in women with this condition, requiring higher levels to decrease the pulse frequency than controls.[22]

Ovarian Abnormalities

Studies have suggested that women with PCOS may have increased 17alpha-hydroxyprogesterone and androstenedione as a result of abnormal enzyme regulation in the ovaries. In vitro studies of thecal cells from polycystic ovaries show that androstenedione production per cell is increased with or without LH stimulation compared to normal thecal cells.[23] Additional studies have shown an abnormal steroid synthesis in the ovaries, possibly caused by the ovarian P450c17 enzyme, which is a key enzyme in the biosynthesis of androgens. Researchers have also investigated abnormalities in ovarian enzymes involved in testosterone synthesis. This research showed an increase of P450 17 alpha-hydroxylase (P450c17) activity by 500% and 3-beta-hydroxysteroid dehydrogenase (3bHSD) by 1000% in thecal cells from polycystic ovaries, causing an increase in production of testosterone precursors.[24] Decreasing insulin levels and weight loss causes a decrease in the activity of the P450c17 enzyme and decreases testosterone levels in obese and in nonobese women with PCOS.[25]

Adrenal Abnormalities

Adrenal androgen synthesis is increased in 26% of women who have symptoms consistent with PCOS.[26] Studies have shown an increase in 5-alpha-reductase activity in women with PCOS, which could cause an inactivation of cortisol, as well as increased production of dihydrotestosterone causing increase in acne and hirsutism. The enzyme 11-beta-hydroxysteroid dehydrogenase type 1 (11b-HSD1), which converts cortisone to cortisol, is decreased in women with this condition.[27] These enzyme abnormalities would lead to an increase in adrenocorticotropic hormone secretion to maintain normal cortisol levels and, thus, an increase in adrenal androgen production. Also, total cortisol metabolites measured in the urine have been found to be higher in women with PCOS.[28]

Some research indicates that women with PCOS have an increased incidence of uterine cancer.

Genetics and Prenatal Exposure

Studies have shown that first-degree relatives of women with PCOS have an increased incidence of this condition. Research has demonstrated that 40% of women with PCOS have sisters with the condition and that 35% have mothers with PCOS.[3] A twin study done on women with PCOS showed that androgen levels, insulin levels, and body mass index (BMI) were influenced genetically, and the researchers proposed that PCOS is possibly X-linked or influenced by polygenic factors.[29] More specifically, evidence has shown that PCOS is linked to polymorphism of the regulatory region CYP11a, which codes for an important enzyme in the steroidogenic pathway. PCOS has also been associated with the class III allele in a satellite regulation region of the insulin gene called the INSVNTR.[30]

Studies with rhesus monkeys have demonstrated that intrauterine exposure to increased androgens can cause the symptoms associated with PCOS in adults, such as hyperandrogenism, insulin resistance, increased LH levels, and anovulation.[31] Human studies suggest that obese women with PCOS have increased ovarian secretion of androgens and have increased birth weight and maternal obesity, while thin women with PCOS have abnormal LH secretion as a result of prolonged gestation.[32]

Cancer

Chronic anovulation, obesity, and hyperinsulinemia are all associated with both PCOS and endometrial carcinoma. Anovulatory menstrual cycles cause increased levels of unopposed estrogen, which, in turn, can lead to endometrial hyperplasia and possibly to endometrial cancer. Although there are some studies with conflicting results, some research indicates that women with PCOS have an increased incidence of uterine cancer.[33] In addition, one small study suggested that most young women with uterine cancer have PCOS.[34] Studies showing that women with PCOS have a threefold increased incidence of breast cancer are controversial.[35]

DIAGNOSIS

Currently, there is no consensus on the diagnostic criteria for PCOS. It is generally accepted that oligo-ovulation and hyperandrogenism are present and other diseases with similar symptoms have been excluded. Polycystic ovaries found on transvaginal ultrasound are present in only approximately 80%–90% of women with PCOS.[36] Polycystic ovaries are also found in many women without any symptoms of PCOS; thus, this finding is associated with the condition but is not considered to be diagnostic. Ultrasound criteria for PCOS are variable; however, generally the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter or an increased ovarian volume (>10 mL) is correlated with a diagnosis of PCOS.[37]

Women with PCOS have inappropriate gonadatropin secretion. Increases in LH, abnormal LH pulse frequencies, and elevated LH to FSH ratios are frequently seen.[2] However, LH levels

are suppressed with increasing BMI and obesity, making it less useful as a diagnostic tool. Elevated circulating total testosterone or free testosterone levels have been the most useful hormone indicators that can be tested to correlate with PCOS. Testing for insulin resistance is done initially with fasting glucose and insulin levels. However, an oral glucose tolerance test is frequently necessary. Studies have indicated that approximately 40% of women with PCOS are glucose-intolerant.[38] Conditions with similar presentation that need to be ruled out include Cushing's disease, adrenal 21-hydroxylase deficiency, hyperprolactinemia, and androgen-producing tumors.

CONVENTIONAL TREATMENTS

Conventional medical treatments involve a number of pharmaceuticals because of the many body systems affected by the condition, which causes a vast array of symptoms.

Metformin

Metformin hydrochloride is commonly prescribed to treat insulin resistance and glucose intolerance. This drug reduces fasting glucose levels and improves oral glucose tolerance in patients with type 2 diabetes, possibly by reducing glucose output from the liver. Studies performed on women with PCOS showed that metformin not only improved glucose tolerance but also reduced total testosterone and free testosterone, and increased the levels of SHBG.[39] However, conflicting results in similar studies demonstrated that weight and obesity also play roles in the effectiveness of metformin, showing decreased effectiveness with increasing weight.[40] A study on women with PCOS and oligo-ovulation showed that treatment with metformin caused 23% of the patients to ovulate.[41] When metformin was combined with clomiphene citrate, the ovulation rate jumped to nearly 90% compared to 12% of women who took a placebo.[42] Continuing metformin while pregnant has also been shown to decrease the rate of spontaneous abortions in women with PCOS.[43] Metformin treatment may also provide cardiovascular benefits as studies have indicated that the drug decreases ET-1, PAI-1, and lipoprotein(a).[16,44]

Estrogen-Progestin Combinations

Oral contraceptives are commonly used to treat symptoms associated with hyperandrogenism, such as acne, hirsutism, and hair loss. An estrogen-progestin combination suppresses LH, which, in turn, decreases androgen levels and increases SHBG levels. Increasing SHBG decreases the amount of bioavailable testosterone. Estrogen also suppresses sebaceous cell function directly. The form of progestin is an important consideration because some forms are more androgenic than others. Desogestrel and norgestimate are both low androgenic forms of progesterone and are commonly used for women with PCOS.[45]

Antiandrogens

Antiandrogens, such as spironolactone, are used to treat symptoms such as acne and hirsutism. This drug can cause menstrual abnormalities; thus, it is commonly used in conjunction with oral contraceptives. Other antimineralcorticoids, such as flutamine and cyproterone acetate (not available in the United States), have been effective for treating symptoms associated with androgen excess.[45] Newer oral contraceptives, such as Yasmin, which contains

drospirenone (a synthetic progestin/spirolactone analogue), is often prescribed for anti-androgenic activity.

GnRH Agonists

GnRH agonists, such as leuprolide, are used to suppress the pituitary-ovarian axis. This causes a decrease in ovarian secretion of estrogen and androgens. This drug is usually used for short periods of time because of the bone loss associated with hypoestrogenism.

Eflornithine

Eflornithine is a topical treatment for hirsutism. It inhibits the enzyme ornithine decarboxylase in the skin. This causes a decrease in the rate of hair growth.

Clomiphene

Clomiphine citrate is an antiestrogen used to increase LH and FSH to induce ovulation for enhancing fertility. Studies have shown that this agent can induce ovulation in approximately 80% of oligo-ovulatory women.[46]

NUTRIENTS AND HERBAL INTERVENTIONS

Several herbal and nutrient interventions are recommended because of the complexity of this condition. Some therapies can improve ovulation and insulin sensitivity and reduce hyper-androgenism. (See Table 29–1 below.)

Table 29–1. Nutrient and Herbal Interventions for Polycystic Ovary Syndrome

Nutrient	Dose
Research strongly supports these interventions	
Vitamin C	400–2,000 mg per day
Chromium picolinate	400 mcg per day
D-chiro-inositol	600 mg per day
N-acetyl-cysteine	1.2 g per day
Some research supports these interventions	
Stinging nettle (Urtica dioica)	300–900 mg per day
Zinc	25–50 mg per day
Momordica (bitter melon; Momordica charantia)	900–1,800 mg per day
a-lipoic acid	600 mg per day
Clinical or historical use supports these interventions	
Soy (Glycine spp.) protein extract	20–40 g per day
Gymnema (Gymnema sylvestre)	400 mg per day
Essential fatty acids	1–3 g per day
Saw palmetto (Serenoa repens)	320 mg per day

Chromium

Chromium is a trace element commonly used for blood-sugar balancing. Chromium in the trivalent form is found in many foods such as whole-grain products, egg yolks, coffee, nuts, brewer's yeast, meat, green beans, and broccoli. Chromium deficiency often presents with impaired glucose, insulin, and lipid metabolism. Research has demonstrated that chromium supplementation reduces glucose intolerance and relieves symptoms of type 1 and type 2 diabetes, as well as those of gestational diabetes.[47] The proposed mechanism of action for the insulin response to chromium is focused on the insulin receptor. Chromium activates the insulin receptor tyrosine kinase and inhibits the insulin receptor phosphotyrosine phosphatase enzyme. This causes increased phosphorylation of the insulin receptor and increased insulin sensitivity and may facilitate glucose transport into cells.[48] In addition, chromium may augment insulin binding, insulin receptor number, and beta-cell sensitivity.[49] A study performed on women with PCOS showed that chromium supplementation improved glucose tolerance in this population.[50]

Vitamin C

Vitamin C has multiple functions including antioxidant and collagen-stimulating properties. A study performed on anovulatory women for whom clomiphene failed showed that oral supplementation with vitamin C (400 mg per day) increased ovulation both with and without clomiphene citrate.[51] In addition, a study indicated that vitamin C supplementation for infertile women with luteal-phase defects may increase progesterone levels.[52] Vitamin C has also been shown to improve endothelial-dependent vasodilation, which has been shown to be abnormal in women with PCOS.[53]

N-Acetyl-Cysteine

N-acetyl-cysteine (NAC) is a derivative of the amino acid L-cysteine. NAC is the precursor to glutathione and is commonly used for its antioxidant, anti-inflammatory, and mucolytic actions. A study performed on women with PCOS whose conditions are resistant to clomiphene showed that NAC supplementation of 1.2 g per day plus clomiphene significantly increased ovulation and pregnancy rates.[54]

Zinc

Zinc is an essential trace mineral and is a required cofactor for numerous biochemical reactions. Zinc has been shown to affect glucose transport and insulin levels. Evidence suggests that zinc supplementation can improve glucose tolerance and increase insulin-induced glucose transport into cells.[55] In addition, some research indicates that zinc may be deficient in individuals with type 2 diabetes.[56]

Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) is a coenzyme used in carbohydrate metabolism and adenosine triphosphate (ATP) production, and is a potent free-radical scavenger. ALA has been shown to improve insulin sensitivity, and several studies on patients with type 2 diabetes have demonstrated that ALA supplementation increases metabolic clearance of glucose by as much as 50%.[57]

ALA supplementation can also increase glucose uptake into skeletal muscle by 40%–300%.[58] Research has demonstrated that ALA stimulates adenosine monophosphate–activated protein kinase in skeletal muscle, which causes a decrease in triglyceride accumulation. Studies have suggested that triglyceride accumulation in skeletal muscle contributes to insulin resistance.[59]

Essential Fatty Acids

Essential fatty acids cannot be made by the body and thus need to be consumed in the diet. Omega-3 fatty acids such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) and omega-6 fatty acids such as gamma-linolenic acid (GLA) are often taken as supplements because of their strong anti-inflammatory action. EPA and DHA are present in high amounts in fish oils and produce anti-inflammatory and antithrombotic effects. Specifically, EPA has cardioprotective effects, such as decreasing triglycerides and increasing high-density lipoprotein (HDL).[60] As previously mentioned, women with PCOS often have hyperlipidemia with elevated triglyceride levels and low HDL levels. EPA and DHA decrease inflammatory eicosanoids by competing with arachidonic acid (AA) in the lipo-oxygenase and cyclooxygenase pathways. GLA is commonly found in borage (Borago officinalis) seed oil, evening primrose (Oenothera spp.) oil, and black currant (Ribes nigrum) oil. GLA metabolites decrease the inflammatory response by inhibiting the production of inflammatory leukotrienes from AA.[61]

Momordica

Momordica (Momordica charantia) fruit, commonly known as bitter melon, has historically been used to improve blood-sugar control. A study demonstrated that supplementation with bitter melon improved glucose tolerance in 73% of patients with diabetes who were treated with the supplement.[62] Another study also showed that treatment with bitter melon improved both fasting and two-hour postprandial glucose levels in 86% of individuals with type 2 diabetes.[63]

Gymnema

Gymnema (Gymnema sylvestre) is a tropical plant used medicinally to treat hyperglycemia. Research has shown that gymnema supplementation decreases glucose levels in hyperglycemic rats. Other studies have shown that using this herb as a supplement decreases glucose absorption in the intestines, stimulates pancreatic beta-cell growth, and stimulates insulin release from beta cells.[64,65]

Stinging Nettle

Medicinal use of stinging nettle (Urtica dioica) involves both the root and leaf of this plant. Studies have shown that the lignans in the root competitively bind SHBG. This binding may cause a decrease in SHBG ability to bind its receptors.[66]

Figure 29–1. Stinging nettle (Urtica dioica).

Saw Palmetto

Figure 29–2. Saw palmetto (Serenoa repens).

Saw palmetto (Serenoa repens) is an herb commonly used, because of its antiandrogen and anti-inflammatory properties, for treating benign prostate hypertrophy (BPH). The lipid portion of the berries is used medicinally to produce these effects. Studies have shown that saw palmetto inhibits 5 alpha-reductase in the prostate, which decreases conversion of testosterone to the more potent form dihydrotestosterone.[67] Although saw palmetto has not been studied as a PCOS treatment, the herb's antiandrogenic activity may be beneficial for patients with the condition.

Soy

Soy (Glycine spp.) protein extracts and isoflavones produce many beneficial effects to treat PCOS symptoms. There is evidence that using soy products as supplements to treat individuals with type 2 diabetes decreases fasting glucose, fasting and postprandial insulin, insulin resistance, triglycerides, low-density lipoprotein, and hemoglobin A1c.[68–70] In addition, studies have indicated that increased soy intake decreases risks of endometrial cancer, hypertension, and hyperlipidemia.[71,72]

D-Chiro-Inositol

Women with PCOS are believed to have a deficiency of a D-chiro-inositol-containing-inositolphosphoglycan (DCI-IPG), causing insulin resistance and hyperinsulinemia. Research has shown that D-chiro-inositol supplementation in women with PCOS increases insulin action; improves ovulation rates; and decreases androgen levels, blood pressure, and hypertriglyceridemia.[73,74]

A study done with obese women who had PCOS showed that treatment with metformin improved insulin action by increasing the insulin-mediated release of DCI-IPG mediators.[75] DCI-IPG functions to stimulate the rate limiting-enzymes pyruvate dehydrogenase phosphatase (involved in insulin-induced lipogenesis) and glycogen synthase phosphatase (involved in insulin-induced glycogenesis).[76]

LIFESTYLE CHANGES

Dietary changes and weight loss have been shown to have profound effects on the symptoms of PCOS. Research has indicated that even modest weight loss improves insulin sensitivity, menstrual-cycle regularity, and fertility; increases SHBG; and decreases circulating androgens.[77] In addition, weight loss has been shown to decrease ovarian volume, number of follicles, and spontaneous abortion rates.[78]

Dietary changes can affect blood-sugar control and weight loss. Diets focused on low-glycemic-index carbohydrates, low saturated fats, and high fiber have benefited women with

PCOS.[79] Fasting and postprandial insulin levels were improved in women with PCOS on a moderately low carbohydrate diet.[80] Another study with women with PCOS showed that a low-carbohydrate ketogenic diet for six months led to a decrease in fasting insulin levels, percent of free testosterone, LH=FSH ratio, and weight.[81] Diets high in fiber have been shown to decrease insulin resistance in overweight or obese women as well as in healthy adults.[82,83]

CONCLUSIONS

PCOS is a complex condition for which the symptoms are variable and the cause is unknown. This makes both diagnosis and treatment of this condition challenging. Although additional research on nutrient and herbal interventions is necessary, studies have provided evidence that such supplements are effective for treating PCOS.

REFERENCES

[1]Knochenhauer ES, Key TJ, Kahsar-Miller M, et al. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: A prospective study. J Clin Endocrinol Metab. 1998;83:3078–3082.

[2]Tsilchorozidou T, Overton C, Conway GS. The Pathophysiology of Polycystic Ovary Syndrome. Online document at: www.medscape.com=viewarticle=466573_1. Accessed April 27, 2006.

[3]Kahsar-Miller MD, Nixon C, Boots LR, et al. Prevalence of polycystic ovary syndrome (PCOS) in first-degree relatives of patients with PCOS. Fertil Steril. 2001;75:53–58.

[4]Jahanfar S, Eden JA, Nguyent TV. Bulimia nervosa and polycystic ovary syndrome. Gynecol Endocrinol. 1995;9:113–117.

[5]Futterweit W, Ryan G. A Patient's Guide to PCOS: Understanding and Reversing Polycystic Ovary Syndrome. New York: Henry Holt & Co., 2006.

[6]Strowitzki T, Halser B, Demant T. Body fat distribution, insulin sensitivity, ovarian dysfunction and serum lipoproteins in patients with polycystic ovary syndrome. Gynecol Endocrinol. 2002;16:45–51.

[7]Dunaif A. Insulin resistance and the polycystic ovary syndrome: Mechanism and implications for pathogenesis. Endocr Rev. 1997;18:774–800.

[8]Ovesen P, Moller J, Ingerslev HJ, et al. Normal basal and insulin-stimulated fuel metabolism in lean women with the polycystic ovary syndrome. J Clin Endocrinol Metab. 1993;77:1636–1640.

[9]Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: A prospective, controlled study in 254 affected women. J Clin Endocrinol Metab. 1999;84:165–169.

[10]Dunaif A, Xia J, Book CB, et al. Excessive insulin receptor serine phosphorylation in cultured fibroblasts and in skeletal muscle: A potential mechanism for insulin resistance in the polycystic ovary syndrome. J Clin Invest. 1995;96:801–810.

[11]Adashi EY, Hsueh AJ, Yen SS. Insulin enhancement of luteinizing hormone and follicle-stimulating hormone release by cultured pituitary cells. Endocrinology. 1981;108:1441–1449.

[12]De Leo V, La Marca A, Orvieto R, Morgante G. Effect of metformin on insulin-like growth factor (IGF) I and IGF-binding protein I in polycystic ovary syndrome. J Clin Endocrinol Metab. 2000;85:1598–1600.

[13]Bergh C, Carlsson B, Olsson JH, et al. Regulation of androgen production in cultured human thecal cells by insulin-like growth factor I and insulin. Fertil Steril. 1993;59:323–331.

[14]Norman RJ, Masters L, Milner CR, et al. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non–insulin dependent diabetes mellitus in polycystic ovarian syndrome. Hum Reprod. 2001;16:1995–1998.

[15]Guzick DS, Talbott EO, Sutton-Tyrrell K, et al. Carotid atherosclerosis in women with polycystic ovary syndrome: Initial results from a case-control study. Am J Obstet Gynecol. 1996;174:1224–1229;discussion: 1229–1232.

[16]Diamanti-Kandarakis E, Spina G, Kouli C, Migdalis I. Increased endothelin-1 levels in women with polycystic ovary syndrome and the beneficial effect of metformin therapy. J Clin Endocrinol Metab. 2001; 86:4666– 4673.

[17]Ehrmann DA, Liljenquist DR, Kasza K, et al., and PCOS=Troglitazone Study Group. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2006;91:48–53.

[18]Sampson M, Kong C, Patel A, et al. Ambulatory blood pressure profiles and plasminogen activator inhibitor (PAI-1) activity in lean women with and without the polycystic ovary syndrome. Clin Endocrinol (Oxf). 1996;45:623–629.

[19]Tarkun I, Canturk Z, Arslan BC, et al. The plasminogen activator system in young and lean women with polycystic ovary syndrome. Endocr J. 2004;51:467–472.

[20]Balen AH. Hypersecretion of luteinizing hormone in the polycystic ovary syndrome and a novel hormone ''gonadotrophin surge attenuating factor.'' J R Soc Med. 1995;88:339P–341P.

[21]Christman GM, Randolph JF, Kelch RP, Marshall JC. Reduction of gonadotropin-releasing hormone pulse frequency is associated with subsequent selective follicle-stimulating hormone secretion in women with polycystic ovarian disease. J Clin Endocrinol Metab. 1991;72:1278–1285.

[22]Pastor CL, Griffin-Korf ML, Aloi JA, et al. Polycystic ovary syndrome: Evidence for reduced sensitivity of the gonadotropin-releasing hormone pulse generator to inhibition by estradiol and progesterone. J Clin Endocrinol Metab. 1998;83:582–590.

[23]Gilling-Smith C, Willis DS, Beard RW, Franks S. Hypersecretion of androstenedione by isolated thecal cells from polycystic ovaries. J Clin Endocrinol Metab. 1994;79:1158–1165.

[24]Nelson VL, Qin K-N, Rosenfield RL, et al. The biochemical basis for increased testosterone production in theca cells propagated from patients with polycystic ovary syndrome. J Clin Endocrinol Metab. 2001;86: 5925–5933.

[25]Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. N Engl J Med. 1996;335: 617–623.

[26]Turner EI, Watson MJ, Perry LA, White MC. Investigation of adrenal function in women with oligomenorrhoea and hirsutism (clinical PCOS) from the north-east of England using an adrenal stimulation test. Clin Endocrinol (Oxf). 1992;36:389–397.

[27]Tsilchorozidou T, Honour JW, Conway GS. Altered cortisol metabolism in polycystic ovary syndrome: Insulin enhances 5 alphareduction but not the elevated adrenal steroid production rates. J Clin Endocrinol Metab. 2003;88:5907–5913.

[28]Stewart PM, Shackleton CH, Beastall GH, Edwards CR. 5 Alphareductase activity in polycystic ovary syndrome. Lancet. 1990;335:431–433.

[29]Jahanfar S, Eden JA, Warren P, et al. A twin study of polycystic ovary syndrome. Fertil Steril. 1995;63: 478–486.

[30]Franks S, Gharani N, McCarthy M. Genetic abnormalities in polycystic ovary syndrome. Ann Endocrinol (Paris). 1999;60:131–133.

[31]Xita N, Tsatsoulis A. Fetal programming of polycystic ovary syndrome by androgen excess: Evidence from experimental, clinical and genetic association studies [review]. J Clin Endocrinol Metab. 2006; 91: 1660–1666.

[32]Cresswell JL, Barker DJ, Osmond C. Fetal growth, length of gestation, and polycystic ovaries in adult life. Lancet. 1997;350:1131–1135.

[33]Pillay OC, Te Fong LF, Crow JC, et al. The association between polycystic ovaries and endometrial cancer. Hum Reprod. 2006;21:924–929.

[34]Farhi DC, Nosanchuk J, Silverberg SG. Endometrial adenocarcinoma in women under 25 years of age. Obstet Gynecol. 1986;68:741–745.

[35]Coulam CB, Annegers JF, Kranz JS. Chronic anovulation syndrome and associated neoplasia. Obstet Gynecol. 1983;61:403–407.

[36]Atiomo WU, Pearson S, Shaw S. Ultrasound criteria in the diagnosis of polycystic ovary syndrome (PCOS). Ultrasound Med Biol. 2000;26:977–980.

[37]The Rotterdam ESHRE=ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19:41–47.

[38]Legro RS, Gnatuk CL, Kunselman AR, Dunaif A. Changes in glucose tolerance over time in women with polycystic ovary syndrome: A controlled study. J Clin Endocrinol Metab. 2005;90:3236–3242.

[39]Diamanti-Kandarakis E, Kouli C, Tsianateli T, Bergiele A. Therapeutic effects of metformin on insulin resistance and hyperandrogenism in polycystic ovary syndrome. Eur J Endocrinol. 1998;138:269–274.

[40]Maciel GA, Soares Junior JM, Alves da Motta EL, et al. Nonobese women with polycystic ovary syndrome respond better than obese women to treatment with metformin. Fertil Steril. 2004;81:355–360.

[41]Fleming R, Hopkinson ZE, Wallace AM, et al. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. J Clin Endocrinol Metab. 2002;87:569–574.

[42]Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. N Engl J Med. 1998;338:1876–1880.
[43]Thatcher SS, Jackson EM. Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin. Fertil Steril. 2006;85:1002–1009.
[44]Velazquez EM, Mendoza SG, Wang P, Glueck CJ. Metformin therapy is associated with a decrease in plasma plasminogen activator inhibitor-1, lipoprotein(a), and immunoreactive insulin levels in patients with the polycystic ovary syndrome. Metabolism. 1997;46:454–457.
[45]Ehrmann DA, Rychlik D. Pharmacologic treatment of polycystic ovary syndrome. Semin Reprod Med. 2003;21:277–283.
[46]Hammond MG, Halme JK, Talbert LM. Factors affecting the pregnancy rate in clomiphene citrate induction of ovulation. Obstet Gynecol. 1983;62:196–202.
[47]Cefalu WT, Hu FB. Role of chromium in human health and in diabetes. Diabetes Care. 2004;27:2741–2751.
[48]Davis CM, Sumrall KH, Vincent JB. A biologically active form of chromium may activate a membrane phosphotyrosine phosphatase (PTP). Biochemistry. 1996;35:12963–12969.
[49]Anderson RA. Nutritional factors influencing the glucose=insulin system: Chromium. J Am Coll Nutr. 1997;16:404–410.
[50]Lucidi RS, Thyer AC, Easton CA, et al. Effect of chromium supplementation on insulin resistance and ovarian and menstrual cyclicity in women with polycystic ovary syndrome. Fertil Steril. 2005;84:1755–1757.
[51]Igarashi M. Augmentative effect of ascorbic acid upon induction of human ovulation in clomiphene-ineffective anovulatory women. Int J Fertil. 1977;22:168–173.
[52]Henmi H, Endo T, Kitajima Y, et al. Effects of ascorbic acid supplementation on serum progesterone levels in patients with a luteal phase defect. Fertil Steril. 2003;80:459–461.
[53]Natali A, Sironi AM, Toschi E, et al. Effect of vitamin C on forearm blood flow and glucose metabolism in essential hypertension. Arterioscler Thromb Vasc Biol. 2000;20:2401–2406.
[54]Rizk AY, Bedaiwy MA, Al-Inany HG. N-acetyl-cysteine is a novel adjuvant to clomiphene citrate in clomiphene citrate-resistant patients with polycystic ovary syndrome. Fertil Steril. 2005;83:367–370.
[55]Tang X, Shay NF. Zinc has an insulin-like effect on glucose transport mediated by phosphoinositol-3-kinase and Akt in 3T3-L1 fibroblasts and adipocytes. J Nutr. 2001;131:1414–1420.
[56]Blostein-Fujii A, DiSilvestro RA, Frid D, et al. Short-term zinc supplementation in women with non–insulin-dependent diabetes mellitus: Effects on plasma 5$^{\beta}$-nucleotidase activities, insulin-like growth factor I concentrations, and lipoprotein oxidation rates in vitro. Am J Clin Nutr. 1997;66:639–642.
[57]Jacob S, Henriksen EJ, Schiemann AL, et al. Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid. Arzneimittelforschung. 1995;45:872–874.
[58]Eason RC, Archer HE, Akhtar S, Bailey CJ. Lipoic acid increases glucose uptake by skeletal muscles of obese-diabetic ob=ob mice. Diabetes Obes Metab. 2002;4:29–35.
[59]Lee WJ, Song KH, Koh EH, et al. Alpha-lipoic acid increases insulin sensitivity by activating AMPK in skeletal muscle. Biochem Biophys Res Commun. 2005;332:885–891.
[60]Erkkila AT, Lehto S, Pyorala K, Uusitupa MI. n-3 Fatty acids and 5-y risks of death and cardiovascular disease events in patients with coronary artery disease. Am J Clin Nutr. 2003;78:65–71.
[61]Fan YY, Chapkin RS. Importance of dietary gamma-linolenic acid in human health and nutrition. J Nutr. 1998;128:1411–1414.
[62]Welihinda J, Karunanayake EH, Sheriff MH, Jayasinghe KS. Effect of Momordica charantia on the glucose tolerance in maturity onset diabetes. J Ethnopharmacol. 1986;17:277–282.
[63]Ahmad N, Hassan MR, Halder H, Bennoor KS. Effect of Momordica charantia (Karolla) extracts on fasting and postprandial serum glucose levels in NIDDM patients. Bangladesh Med Res Counc Bull. 1999; 25:11–13.
[64]Persaud SJ, Al-Majed H, Raman A, Jones PM. Gymnema sylvestre stimulates insulin release in vitro by increased membrane permeability. J Endocrinol. 1999;163:207–212.
[65]Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS. Systematic review of herbs and dietary supplements for glycemic control in diabetes. Diabetes Care. 2003;26:1277–1294.
[66]Schottner M, Gansser D, Spiteller G, et al. Lignans from the roots of Urtica dioica and their metabolites bind to human sex hormone binding globulin (SHBG). Planta Med. 1997;63:529–532.
[67]Di Silverio F, Monti S, Sciarra A, et al. Effects of long-term treatment with Serenoa repens (Permixon) on the concentrations and regional distribution of androgens and epidermal growth factor in benign prostatic hyperplasia. Prostate. 1998;37:77–83.
[68]Jayagopal V, Albertazzi P, Kilpatrick ES, et al. Beneficial effects of soy phytoestrogen intake in post-menopausal women with type 2 diabetes. Diabetes Care. 2002;25:1709–1714.
[69]Tsai AC, Vinik AI, Lasichak A, Lo GS. Effects of soy polysaccharide on postprandial plasma glucose, insulin, glucagon, pancreatic polypeptide, somatostatin, and triglyceride in obese diabetic patients. Am J Clin Nutr. 1987;45:596–601.

[70]Hiroyuki F, Tomohide Y, Kazunori O. Efficacy and safety of Touchi extract, an alpha-glucosidase inhibitor derived from fermented soybeans, in non–insulin-dependent diabetic mellitus. J Nutr Biochem. 2001; 12:351–356.

[71]Goodman MT, Wilkens LR, Hankin JH, et al. Association of soy and fiber consumption with the risk of endometrial cancer. Am J Epidemiol. 1997;146:294–306.

[72]He J, Gu D, Wu X, et al. Effect of soybean protein on blood pressure: A randomized, controlled trial. Ann Intern Med 2005;143:1–9.

[73]Nestler JE, Jakubowicz DJ, Reamer P, et al. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. N Engl J Med. 1999;340:1314–1320.

[74]Iuorno MJ, Jakubowicz DJ, Baillargeon JP, et al. Effects of D-chiroinositol in lean women with the polycystic ovary syndrome. Endocr Pract. 2002;8(6):417– 423.

[75]Baillargeon JP, Iuorno MJ, Jakubowicz DJ, et al. Metformin therapy increases insulin-stimulated release of D-chiro-inositol-containing inositolphosphoglycan mediator in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2004;89:242–249.

[76]Larner J. D-chiro-inositol—its functional role in insulin action and its deficit in insulin resistance. Int J Exp Diabetes Res. 2002;3:47–60.

[77]Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: Role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab. 1999;84:1470–1474.

[78]Crosignani PG, Colombo M, Vegetti W, et al. Overweight and obese anovulatory patients with polycystic ovaries: Parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. Hum Reprod. 2003;18:1928–1932.

[79]Marsh K, Brand-Miller J. The optimal diet for women with polycystic ovary syndrome? Br J Nutr. 2005;94:154–165.

[80]Douglas CC, Gower BA, Darnell BE, et al. Role of diet in the treatment of polycystic ovary syndrome. Fertil Steril. 2006;85:679–688.

[81]Mavropoulos JC, Yancy WS, Hepburn J, Westman EC. The effects of a low-carbohydrate, ketogenic diet on the polycystic ovary syndrome: A pilot study. Nutr Metab (Lond). 2005;2:35.

[82]Weickert MO, Mohlig M, Schofl C, et al. Cereal fiber improves whole-body insulin sensitivity in overweight and obese women. Diabetes Care. 2006;29:775–780.

[83]Fukagawa NK, Anderson JW, Hageman G, Young VR, Minaker KL. High-carbohydrate, high-fiber diets increase peripheral insulin sensitivity in healthy young and old adults. Am J Clin Nutr. 1990;52:524–528.

30

RHEUMATOID ARTHRITIS

Etiology and Naturopathic Treatments

Rheumatoid arthritis (RA) is a complex, multifactorial disease that affects approximately 1% of the United States population. According to the National Institutes of Health (NIH), 2.1 million Americans, or approximately 1% of the adult population, have been diagnosed with RA.[1] Across all age groups, RA predominates in females over males in a ratio of 2–3:1, although, in reproductive years, the ratio may be as high as 5:1.[2] Within joints, the autoimmune mediated course of RA is characterized by four stages: (1) inflammation of the synovial membrane and joint capsule, (2) formation of a pannus (granulation tissue) that first covers and then invades cartilage and bone, (3) fibrous invasion of the pannus, and (4) calcification of the fibrous tissue. It is important to view RA, however, not only as a disease process that affects the joints, but as a systemic disorder that may include vasculitis, rheumatoid nodules in the pleural space, and blood-clotting abnormalities. (See Table 30–1 on page 340.) Moreover, some common comorbidities of RA include cardiovascular disease, infections, malignancies, gastrointestinal (GI) disease, and osteoporosis.[3] In fact, a prospective study has indicated that the average life span for patients with RA is shortened by seven years in men and three years in women.[4]

There are various factors that may precede the clinical manifestation of RA and=or exacerbate the clinical course of RA in a susceptible individual. Such a multifactorial disease process lends itself comfortably to a naturopathic plan of treatment that is also multifactorial and includes dietary modification, botanical support, counseling, and appropriate physical medicine.

THE COMPLEX ETIOLOGY AND PATHOGENESIS OF RHEUMATOID ARTHRITIS

This review focuses on several factors that may predispose a patient to the development of RA and=or intensify symptoms that are characteristic of the disease, specifically, gut microflora influences, hormonal alterations, impairment in regulation of T-cell subsets, chronic exposure to environmental toxins, genetic influences, and total levels of oxidative stress.

Gut Microflora Influences

As discussed by Kjeldsen-Kragh,[5] there are several ways in which the ecology of the gut flora may make an impact on the course of RA. For example, the bacteria Proteus mirabilis, a normal intestinal species that can also give rise to urinary tract infections, contains in one of its surface-membrane proteins a sequence of six amino acids that is only two amino acids different from a sequence found on several types of human leukocyte antigen (HLADR) associated with RA. Antibody activity against a synthetically prepared peptide containing the sequence from Proteus was increased in patients with rheumatoid arthritis compared to healthy controls or patients with ankylosing spondylitis.[6,7] In addition, the sequence occurring on the HLA has been shown to be the target of elevated levels of autoantibodies in a study of Japanese patients with RA.[8]

Table 30–1. Revised American Rheumatism Association Criteria for Classification of Rheumatoid Arthritis[a]

Sign or Symptom	Definition
Morning stiffness	Stiffness in or around the affected joints for at least one hour after initiating movement before maximal improvement
Arthritis of three or more joint areas	Three or more of the following joints noted to be fluid-filled or have soft tissue swelling: wrist, PIP, MCP, elbow, knee, ankle, MTP
Hand joint involvement	Wrist, MCP, or PIP joints among the symptomatic joints observed
Symmetric arthritis	Right and left joints involved for one or more of the following: wrist, PIP, MCP, elbow, knee, ankle, MTP[b]
Rheumatoid nodules	Subcutaneous nodules in regions surrounding joints, extensor surfaces, or bony prominences
Serum rheumatoid factor positive	Positive result using any laboratory test that has a positive predictive value of 95% or more (i.e., is positive in no more than 5% of patients without rheumatoid arthritis)
Radiographic changes	Radiographic erosions and=or periarticular osteopenia in hand and=or wrist joints

[a]Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315–324.
[b]PIP, MCP, and MTP joints need not be absolutely symmetrical.
LR positive likelihood ratio, LR negative likelihood ratio, PIP proximal interphalangeal, MCP metacarpophalangeal, MTP metatarsophalangeal.

Moreover, when patients with RA fasted for one week and then were placed on a vegetarian diet (see sections on treatment) there was a significant reduction in anti-Proteus immunoglobulin G activity among the subjects who responded most to the diet, which correlated with a decrease in the activity of the patients' disease.[9] No such changes were seen in the level of antibody activity against Escherichia coli. P. mirabilis, however, may not be the only floral species with the potential to contribute to the pathogenesis of RA. There are several studies demonstrating that injection of cell-wall fragments of Eubacterium aerofaciens or Bifidobacterium breve in rats results in a form of arthritis that is similar to RA.[10] In addition, an increase of Clostridium perfringens in the bowels of patients with RA has been shown, although this effect might also be attributed to the effects of treatment with anti-inflammatory drugs.[11–13]

In one study, serum testosterone levels were consistently decreased in the men with rheumatoid arthritis versus the controls.

It is perhaps not surprising that, among the numerous possible species of bowel microbes living along the thin epithelium separating outside world from gut-associated lymphatic tissue, there exists an antigenic potential to trigger an immune response that may become misdirected at the self. The presence and effect of mycoplasma on the pathogenesis of RA should also be considered within the confines of the clinical presentation.

Hormonal Alterations

Another lens through which to view the pathophysiology of RA is to explore the significance of changes in glucocorticoid and sex hormones both before and during the course of RA. This area is exceedingly complex as researchers try to decipher which changes may actually be causes of RA and which changes may be secondary to the already established inflammatory process of RA. A review by Masi et al.,[14] published in 1995, analyzed collective results of controlled trials measuring sex hormones in patients with RA who had not been previously treated with glucocorticoids. The findings did indicate that dehydroepiandrosterone (DHEA) sulfate was significantly decreased in premenopausal and postmenopausal women with RA, although the magnitude of difference was more pronounced in the premenopausal subjects (a 39% decrease in premenopausal versus a 19% decrease in postmenopausal subjects). Among the men, the clearest finding was that serum testosterone levels were consistently decreased in the men with RA versus the controls.

Perhaps one of the most valuable hormonal studies of patients with RA is one in which serum was actually collected in subjects 4–20 years before any of the subjects had developed RA.[15] For each subject that eventually developed RA, samples from four controls matched for race, age, and menopausal status at study entry were included. This study found significantly lower levels of DHEA-sulfate among the youngest group of premenopausal women who years later developed RA compared to controls who did not. This youngest group (mean age of 29 at study entry with a mean onset of RA at 41 years) also showed a significant dissociation between DHEA sulfate and cortisol levels, a dissociation that was not seen among the older subjects who also went on to develop RA. The interpretation of these results was that dysfunction of the adrenal cortex may be a long-term marker for RA in a minority of women or that such dysfunction may actually lead to RA onset in some younger women.

Other hormonal alterations may occur both at the onset and throughout the course of RA. For example, while research indicates that, in patients with recent onset of RA (less than one year), cortisol levels are actually elevated compared to controls,[16] there is also a theory suggesting that ''normal'' cortisol levels seen in other studies of patients with RA are, in fact, inadequate considering the amount of chronic inflammation.[17] An additional study showed that women with RA had elevated inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and IL-6. Growth hormone half-life was shorter, and insulin-like growth factor-1 (IGF-I) and IGF-binding protein (IGFBP)-3 was lower in patients with active RA. Also, a relatively diminished diurnal cortisol and DHEA secretion for their state of inflammation was seen in these patients.[18] In addition, it has long been observed that pregnancy, a time of increased estrogen, progesterone, and cortisol, is a time during which many women experience remission of RA symptoms. Estriol is thought to exhibit anti-inflammatory properties, and progesterone is thought to contribute to the down-regulation of autoimmune tendencies, suggesting possible modalities in which these hormones provide benefit for RA symptoms.[19] These hormone changes of pregnancy are associated with increased level of anti-inflammatory cytokines interleukin (IL)-4 and IL-10 and a decrease in production of pro-inflammatory cytokines interferon-gamma and IL-2.[20]

While still controversial, there are several studies linking exposure to crystalline silica with rheumatoid arthritis.

Regulation of T-Cell Subsets

Figure 30–1. Yucca (Yucca glauca) has a rich history of use as an antiarthritic.

An imbalance between subsets of T-cells, with a resulting loss of immunologic tolerance to self, is another perspective from which to view RA.[21] In fact, RA may be considered a disease process in which an immune response based on the action of Th1 cells predominates over Th2 cells, characterized by an increase in levels of interferon-gamma and a cellular immune response.[22] There continues to be debate over the precise role and ultimate significance of this theory. In one recent study that may open new avenues of research in this area,[23] researchers found a decrease of a T-cell regulatory subset, Tr1, which produces the anti-inflammatory cytokine IL-10, in the blood of patients with RA compared to controls. IL-10 inhibits Th1 cytokine expression. The reduced levels of Tr1 were inversely correlated with levels of Th1 cells in the synovial fluid, with C-reactive protein levels, and with a score of disease activity. Additionally, CD4 CD25 T cells play a major role in the maintenance of tolerance. In RA, the CD4 CD25 regulatory T-cell subset represents 5%–10% of the CD4 T-cell population, which has been shown to suppress the in vitro proliferation of autologous CD4 T cells. CD4 CD25 regulatory T cells isolated from patients with active RA are defective in their ability to suppress cytokine production and in their ability to convey a suppressive phenotype to CD4 effector T cells.[24] Research shows that the regulatory function of CD4 CD25 T cells is mediated by the induction of anti-inflammatory Tr1 cell differentiation.[25]

Environmental Toxins and Genetic Predisposition

While still controversial, there are several studies linking exposure to crystalline silica with RA.[26,27] The most recent of these is a study by the Occupational Health and Safety Administration, examining a cohort of 4,626 workers in the industrial-sand industry.[28] By examining available death records of workers, which may have mentioned multiple diseases on a death certificate (RA is often listed as a contributory cause or other significant condition), a standard mortality ratio was calculated by comparing the cohort with the U.S. population. The standard mortality ratio (SMR) of arthritis in the cohort was 4.36 (95%; confidence interval [CI] 2.76–6.54). Also, this data demonstrated a positive correlation between cumulative silica exposure and the incidence of RA.

A final factor that may influence the severity of the clinical course of RA is that of genetics, specifically HLA-DBR1 alleles. It is interesting to note, however, that while twin studies do indicate a significant increased risk for one twin acquiring RA if the other twin is exhibiting symptoms, these studies also suggest that the maximum level of genetic contribution to the concordance rate of twins with RA is about 15%.[29] Indeed, genetic contribution is one significant factor, but there are still other factors, such as those outlined previously, which also

deserve careful attention, and that, at this time, may be more amenable to therapeutic intervention.

Oxidative Stress

In a recent review by Darlington and Stone,[30] an overview is provided of the pro-oxidative scene present in RA. Of key importance is the production of nitric oxide (NO), which can generate peroxynitrite and hydroxyl radicals. Hydroxyl radicals generated via this or other mechanisms can then break hyaluronic acid down, interfere with proteoglycans, and limit the functioning of proteinase inhibitors.[31,32] In addition, the synovial fluid of patients with RA may contain iron, which is capable of catalyzing the production of hydroxyl radicals from superoxide and hydrogen peroxide. The activated macrophages and neutrophils present in the pannus are themselves a source of pro-oxidants that lead to joint damage.[33]

An epidemiologic study involving a Finnish cohort of 18,709 subjects, of whom 122 developed RA, found that both low selenium and alpha-tocopherol could be risk markers for RA.[34] The interesting findings showed that low selenium was probably a risk factor specifically for Rf negative RA, while low alpha-tocopherol levels probably represented a risk factor that was independent of Rf status. An additional report on 1,400 people whose levels of the key antioxidants beta-carotene, vitamin E, and selenium were measured before any of the volunteers had symptoms of RA indicated a significantly reduced antioxidant status in the 14 patients who later developed RA.[35]

Numerous studies have also shown that cigarette smoking increases the risk of RA. In a study with postmenopausal women, women who were current or who had quit 10 years or less before the study were at increased risk of rheumatoid arthritis. Both the duration and intensity of smoking were associated with rheumatoid arthritis.[36] Additional studies have shown that patients with RA who smoke displayed the disease at a younger age than nonsmokers, the smokers presented at disease onset with more prominent features of articular involvement, and had a higher frequency of IgM and IgA rheumatoid factors as compared to nonsmokers. Overall, the RA patients who smoked exhibited more active and severe disease as evaluated by the higher total number of tender and swelling joints and more frequently had rheumatoid nodules than the ex-smokers and nonsmokers.[37] One proposed theory to explain this finding is that smoking is related to RA through induction of oxidative stress.

> Addressing gastrointestinal integrity and ecology is essential when autoimmune-modulated responsiveness to potential antigens can serve as triggers.

OVERALL NATUROPATHIC APPROACH

It is of fundamental importance when dealing with any autoimmune condition to address, as completely as possible, the underlying causes that allow sufficient disturbance to homeostasis to occur and result in a self-attack being triggered. Nevertheless, this limited review of factors contributing to the etiology and pathogenesis of RA partially demonstrates the complexity of

the disease process. It may even be the case that, while one individual's RA is based largely in adrenal cortex dysfunction, another patient's RA may develop after an immune response to Proteus, and still another patient's RA may result from prolonged exposure to silica. And, even when etiologic factors are identified, we still must consider the issue of susceptibility; after all, not everyone with some adrenal dysfunction, some exposure to Proteus, or some time working in the industrial-sand industry will develop RA. Thus, the overall aspect of health and human frame (human frame refers to human tissues, mind, and spirit) must be addressed and a naturopathic approach including clinical nutrition, botanical medicines, counseling, and appropriate physical medicine has a good deal to offer.

CLINICAL NUTRITION

Fasting

There is some evidence that, for many patients, a week of fasting followed by a vegetarian diet will reduce the symptoms of RA over the course of a year.[38] During the fasting period of the study cited, subjects were allowed to eat garlic, vegetable broth, a decoction of potatoes and parsley, herbal teas, and the juices of carrots, beets, and celery. (Note that, in addition to potentially suppressing the immune system because of hypocaloric intake, this fasting diet also provides an excellent source of phytochemicals that assist in detoxification and is itself rich in antioxidants.) Following the fasting, subjects introduced new foods one at a time, discontinuing them if any increase in pain, stiffness, or joint swelling was noticed. If, after a week of waiting, reintroduction resulted in a repeat exacerbation, then that item was removed for the rest of the study period. New food items being introduced excluded gluten, meat, fish, eggs, dairy foods, refined sugar, citrus, salt, strong spices, preservatives, alcohol, tea, and coffee for three to five months. After that time, dairy products and gluten were allowed to be introduced one at a time. Over the course of the year, the group of 27 dieters noted statistically significant decreases in pain, duration of morning stiffness, number of tender and swollen joints, sedimentation rate, C-reactive protein (CRP), and white-blood-cell count, compared to the 26 controls. The magnitude of the difference between the two groups at the end of the study was appreciable. For example, the dieters reported an average duration of morning stiffness of approximately 1.5 hours compared to more than 2.5 hours reported in the control group. The average CRP at the end of the year was roughly 30 mg=L in the control group and less than 20 mg=L in the dieters.

A more recent study of fasting by patients with RA also has produced some interesting results.[39] Specifically, after a week of vegetable-juice fasting, this study found significant decreases in sedimentation rate, CRP, and tender-joint count, as well as experiencing a 37% decrease in the pro-inflammatory cytokine IL-6. In addition, there was a significant increase in DHEA-sulfate levels, which was also seen in patients who were placed on a ketogenic diet.

One of the ways in which this dietary approach may have been beneficial to dieters was via the alteration of their gut flora. Stool samples from the 27 fasting=vegetarian subjects and 26 controls were analyzed for their content of various fatty acids, which are components of the cell walls of intestinal bacteria. Significant changes were found between the fatty-acid profiles of dieters who were ''high-responders'' to the diet and those who were ''low-responders.''[40] Hence, addressing GI integrity and ecology is essential when autoimmune-modulated responsiveness to potential antigens can serve as triggers. From a nutritional perspective, the prudent clinician must scrutinize GI health closely, for the alimentary tract is the most crucial boundary

between the external macroworld and the well-defined and well-ordered and sometimes precariously balanced internal microworld.

With regard to the study, there were no significant changes seen within the control group throughout the year. Within the dieting group, changes in fatty-acid profile, and thus changes in gut flora, were apparent at each of the stages of the diet when major changes were made (i.e., the fasting period versus the period of food introduction versus the lactovegetarian period of study). Given the potential for fasting and strict diet to alter bowel flora in ways correlating with improvement in the course of RA, and the possibility that, in some cases, flora may play a causative role in RA, it makes sense to discuss this approach with patients who are considering clinical options.

HORMONAL SUPPORT

Because adrenal dysfunction may play an underlying role in RA development, it seems logical, in some cases, to provide support with the androgen DHEA. The reasons for DHEA supplementation are based at this point in an idea that arose from viewing several sets of study results. First, as already reviewed, androgen hormones were commonly decreased in women and men patients with RA (DHEA in women and testosterone in men). Second, the results of recent research showed that patients with chronic RA experienced significantly increased levels of cortisol and epinephrine under the very acute mental stress of a presurgical setting and that these levels were significantly depressed under general anesthesia. Such a pattern was not seen in controls with osteoarthritis.[41] This pattern suggests to us that, at least in some patients with RA, attempting to deal with stress creates an increased demand for glucocorticoids, which, even if successfully met, may be incompletely coordinated with the control of androgen secretion. As a result, a healthy relationship between these two groups of hormones is not maintained. Moreover, whether such events are primary or secondary to the development of RA, it would seem that such supplementation could have benefit being that DHEA-sulfate has been shown to decrease the expression of the gene coding for the pro-inflammatory IL-6,[42] high levels of which predispose patients to a worsening course of RA.

SUPPLEMENTAL ANTIOXIDANT= ANTI-INFLAMMATORY SUPPORT

There is certainly theoretical support in several ways for the use of omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), in the treatment of patients with RA. Not only do omega-3 acids compete with omega-6 acids for metabolism by lipoxygenase and cyclooxygenase, the former can become incorporated in membrane phospholipids at the expense of arachidonic acid.[43,44] Several trials, some open and others controlled, have demonstrated benefit for patients with RA who consumed fish oils, with dosages of EPA in the range of anywhere from 2 to 20 g per day, for lengths of time from 6 to 24 weeks.[45–49]

A reasonable therapeutic trial may be a dose of from 3 to 6 g per day of fish oils providing a natural mix of EPA and DHA, stabilized with vitamin E and=or the fat soluble form of vitamin C, ascorbyl palmitate. Other oils, such as olive oil and gamma-linolenic acid (GLA), may also provide anti-inflammatory benefit for patients with RA.[50–52] Particularly noteworthy and reflective of the potential benefits of essential fatty acids, GLA has been positively highlighted in research for its therapeutic benefit. GLA can be converted to arachidonic acid, thus, high

doses of GLA should be taken with EPA to block this conversion. Not only may therapy with fatty acids be helpful in the treatment of RA, there is also evidence that regular consumption of fish reduces the risk of developing RA. Epidemiologic research suggests that baked or broiled fish consumption, at least two servings per week, was associated with a significant decrease in the risk of RA (odds ratio, 0.57; confidence interval, 0.35–0.93) compared to less than one serving per week.[53]

Several trials have demonstrated benefit for patients with rheumatoid arthritis who consumed fish oils.

Given the ongoing oxidative stress present in RA, there is certainly a rationale for supplementation with the common antioxidants, vitamins A, C, and E. In fact, levels of retinol and its binding protein have been shown to be lower in patients with RA than in matched controls.[54] In addition to being an antioxidant, vitamin C is also required to hydroxylate proline and lysine in order to produce collagen, which is gradually destroyed in RA, narrowing the joint space and eventually damaging bone. In one double-blind study of subjects given 600 international units of vitamin E two times per day for 12 weeks, there was a small, but significant, analgesic effect compared to controls.[55] While the extent of the analgesic effect attributable to vitamin E is clearly not as great as that derived from non-steroidal anti-inflammatory drug (NSAID) use, it should be remembered that one of the comorbidities of RA is cardiovascular disease. If vitamin E is included in treatment for this reason alone, its use would be justified and, if it also provides some pain relief without the side effects of NSAID use, so much the better. It would also seem that selenium, which is reduced in the serum of patients with RA,[56] and is a required coenzyme for glutathione peroxidase, would be beneficial as a supplement. In this case, however, long-term (26 weeks) supplementation failed to increase the depressed activity of glutathione peroxidase found in patients with RA.[57] Additionally, greater intake of vitamin D was inversely associated with risk of RA.[58]

BOTANICAL MEDICINES

One of the most supportive botanical medicines for the patient with RA may well be curcumin or turmeric (Curcuma longa). Notable for its ability to act as an antioxidant and anti-inflammatory,[59–61] curcumin seems well suited for treating this condition. More recent research suggests that curcumin is a potent inhibitor of the signaling pathway utilized by a specific type of IL-6, called oncostatin M.[62] Specifically, curcumin decreases the pro-inflammatory pathways induced by oncostatin M. If not inhibited via this pathway, oncostatin M signaling results in the transcription=translation of metalloproteinases and their inhibitors. An imbalance between metalloproteinases and their inhibitors may represent one of the mechanisms of joint damage in RA. To be able to slow down metalloproteinase expression may represent one of the many recently discovered mechanisms of efficacy of an ancient herb.

A second botanical option recently reported in the botanical literature is the Ayurvedic herbal combination Maharasnadhi Quathar (MQR). In a three-month study that involved 45 patients with RA treated with this herbal combination and a second group of RA patients treated with another traditional preparation, the patients in the MQR-treated group

demonstrated significant increases in the activity of the antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase, which is important as reactive oxygen species are believed to be one of the mediators of inflammation and responsible for the pathogenesis of tissue destruction in RA.[63] Another finding of the study was that lipid peroxidation was reduced by 34% in the MQR-treated group. MQR is a combination of 26 herbs, with the bulk (70%) of its composition accounted for by alpinia galangal (Alpinia calcarata), but also including a variety of other plants, such as ginger (Zingiber officinale), tropical almond (Terminalia chebula), tribulus (Tribulus terrestris), ashwagandha (Withania somnifera), and coriador also called Chinese parsley (Coriandrum sativum).

Oleoresin gum extracts of boswellia (Boswellia serrata), with 37.5%–65% boswellic acid, exert potent anti-inflammatory actions via inhibition of inflammatory mediators such as leukotrienes. The recommended boswellia dose is 150 mg three times per day.[64] Bromelain, a commonly used proteolytic enzyme, has direct clinical application for treating RA, as do other enzymes. Select results have yielded upward of 73% positive results, ranging from good to excellent.[65] Ginger (Zingiber officinale) extracts have demonstrated benefit as well, with good pain relief in preliminary studies.[66] Ginger suppresses prostaglandin synthesis through inhibition of cyclooxygenase-1 and cyclooxygenase-2 and leukotriene biosynthesis by inhibiting 5-lipoxygenase.[67] These herbs and numerous others show promise for alleviating symptoms and potentially modulating pathophysiologic changes.

Other select herbs that have been used in the treatment of RA include the following:

Oleoresin gum extracts of boswellia, with 37.5%–65% boswellic acid, exert potent anti-inflammatory actions via inhibition of pro-inflammatories such as leukotrienes.

Cayenne (Capsicum frutescens)

Topical cayenne application acts specifically by depleting stores of substance P from sensory neurons. In a placebo-controlled study, arthritis patients were instructed to apply 0.025% capsaicin cream to painful joints. After four weeks of capsaicin treatment, the mean reductions in pain in the RA patients were 57% and 33% in OA patients. The global evaluations showed that 80% of the capsaicin-treated patients experienced a reduction in pain after two weeks of treatment.[68] In vitro analysis has also shown that high doses of capsaicin also works on the cellular levels as it has been shown to decrease the synthesis of collagenase and prostaglandin E2.[69]

Thunder God Vine (Tripterygium wilfordi)

In a prospective, double-blind, placebo-controlled study in patients with long-standing RA in whom conventional therapy had failed, low-dose (180 mg per day) or high-dose (360 mg per day) extract of thunder god vine was supplemented for 20 weeks, followed by an open-label extension period. The results indicated that more than half of the patients who completed the trial showed therapeutic benefit in the treatment group.[70] In another study, 6 of 10 patients treated with 180 mg per day of ethyl acetate extract of Tripterygium wilfordi (EA) extract showed disease improvement, and 8 of the 9 patients who received EA extract at doses greater

than 360 mg per day experienced improvement in both clinical manifestations and laboratory findings. One patient met American College of Rheumatology criteria for remission.[71] Research has elucidated that Tripterygium wilfordii Hook f suppresses immune responses by inhibiting transcription of cytokine genes, including interleukin-2 and gamma interferon.[72] In addition, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is currently conducting a phase II trial to evaluate the safety and effectiveness of thunder god vine for rheumatoid arthritis.[73]

Cat's Claw (Uncaria tomentosa)

Forty patients with active RA treated with sulfasalazine or hydroxychloroquine were supplemented with highly purified extract from the pentacyclic chemotype of Uncaria tomentosa. The results showed a reduction of the number of painful and swollen joints by 53% after 24 weeks of treatment.[74]

> Effective treatment tools from clinical nutrition, botanical medicine, counseling, and physical medicine should significantly help many patients with RA to live with less pain.

COUNSELING

While many general practitioners will not have the same level of counseling skill as a trained psychologist or counselor, this is an area that deserves greater attention in the treatment of a patient with RA. In a preliminary, controlled study of group therapy sessions with patients of RA, in which the patients decided on their own topics of discussion in a series of 12 weekly sessions, the area of greatest concern was that of lost self-esteem.[75] Patients reported feeling unable to meet self-set expectations of productivity and rewards in their relationships with others, and reported difficulties in communicating adequately regarding the problems they faced with those around them, including their families and physicians. It is noteworthy that, within the group of patients participating in group counseling, there were significant improvements in scores of self-concept, specifically in the categories of self-satisfaction and family-self. Developing and implementing quality communication skills, such as restating a patient's concerns, asking if there is anything else that needs to be discussed, and expressing empathy appropriately will help to create an atmosphere in which both the patient and physician are understood and honored. In addition, assisting the patient in identifying stress triggers and teaching stress-reduction techniques, such as abdominal breathing, may help to reduce the load placed on a beleaguered hypothalamic-pituitary-adrenal axis.

PHYSICAL MEDICINE

A final therapy of benefit to patients with RA is hydrotherapy (defined here as the combination of water immersion and exercise). In a study of 139 patients with chronic RA, subjects were randomly divided into groups receiving hydrotherapy, seated immersion, land exercise, or progressive relaxation.[76] Subjects attended two 30-minute sessions per week for four weeks

and were assessed using the Arthritis Impact Measurement Scales 2 questionnaire. The group showing the greatest improvement (although all the therapies were somewhat helpful) was the hydrotherapy-treated group, with subjects reporting significant reductions in joint tenderness and improved knee range of motion. Some patients may also find benefit from the application of alternating hot and cold compresses.

CONCLUSIONS

Patients with RA experience the symptoms of a disease process that is exceedingly complex. There are a number of possible etiologic factors, perhaps some as yet undiscovered, and the exact causes of the autoimmune-driven inflammation characteristic of the disease may vary from one susceptible individual to another. The presence and effect of mycoplasma on the pathogenesis of RA should also be considered within the confines of the clinical presentation. A comprehensive treatment strategy using effective treatment tools from clinical nutrition, botanical medicine, counseling, and physical medicine, together, should significantly help many patients with RA to live with less pain and with an increased sense of well-being.

REFERENCES

[1]National Institute of Arthritis and Musculoskeletal and Skin Diseases. Rheumatoid Arthritis. Available at: www.niams.nih.gov=Health_Info=Rheumatic_Disease=default.asp#ra_3. Accessed November 17, 2007.

[2]Masi AT Incidence of rheumatoid arthritis: Do the observed age–sex interaction patterns support a role of androgenic-anabolic (AA) steroid deficiency in its pathogenesis? Br J Rheumatol. 1994;33:697–699.

[3]Mikuls TR, Saag KG. Comorbidity in rheumatoid arthritis. Rheum Dis Clin North Am. 2001;27(2): 283–303.

[4]Vandenbroucke J, Hazevoet H, Cats A. Survival and cause of death in rheumatoid arthritis: A 25-year prospective follow-up. J Rheumatol. 1984;11:158–161.

[5]Kjeldsen-Kragh J. Rheumatoid arthritis treated with vegetarian diets. Am J Clin Nutr. 1999;70(suppl.): 594S–600S.

[6]Wilson C, Ebringer A, Ahmadi K, et al. Shared amino acid sequences between major histocompatibility complex class II glycoproteins, type XI collagen and Proteus mirabilis in rheumatoid arthritis. Ann Rheum Dis. 1995;54:216–220.

[7]Tani Y, et al. Antibodies to Klebsiella, Proteus, and HLA-B27 peptides in Japanese patients with ankylosing spondylitis and rheumatoid arthritis. J Rheumatol. 1997;24(1):109–114.

[8]Takeuchi F, Kosuge E, Matsuta K, et al. Antibody to a specific HLA DR b1 sequence in Japanese patients with rheumatoid arthritis. Arthritis Rheum. 1990;33:1867–1868.

[9]Kjeldsen-Kragh J, Rashid T, Dybwad A, et al. Decrease in anti–Proteus mirabilis but not anti–Escherichia coli antibody levels in rheumatoid arthritis patients treated with fasting and a one-year vegetarian diet. Ann Rheum Dis. 1995;54:221–224.

[10]Hazenberg MP, Klasen IS, Kool J, Ruselervan-Embden JG, Severijnen AJ. Are intestinal bacteria involved in the etiology of rheumatoid arthritis? APMIS. 1992;100(1):1–9.

[11]Olhagen B, Månsson I. Intestinal Clostridium perfringens in rheumatoid arthritis and other collagen diseases. Acta Med Scand. 1968;184(5):395–402.

[12]Shinebaum R, Neumann VC, Cooke EM, Wright V. Comparison of faecal florae in patients with rheumatoid arthritis and controls. Br J Rheumatol. 1987;26(5):329–333.

[13]Dearlove M, Barr K, Neumann V, Bird HA, Gooi HC, Wright V. The effect of nonsteroidal antiinflammatory drugs on faecal flora and bacterial antibody levels in rheumatoid arthritis. Br J Rheumatol. 1992;31:443–447.

[14]Masi AT, Feigenbaum SL, Chatterton RT. Hormonal and pregnancy relationships to rheumatoid arthritis: Convergent effects with immunologic and microvascular systems. Semin Arthritis Rheum. 1995;25(1):1–27.

[15]Masi AT, Chatterton RT, Aldag JC. Pertubations of hypothalamic-pituitary-gonadal axis and adrenal andgrogen functions in rheumatoid arthritis: An odyssey of hormonal relationships to the disease. Ann NY Acad Sci. 1999;876:53–62.

[16]Green R, Godaert GLR, et al. Experimentally induced stress in rheumatoid arthritis of recent onset: Effects on peripheral blood lymphocytes. Clin Exper Rheumatol. 1998;16:553–559.
[17]Foppiani L, et al. Desmopressin and low-dose ACTH test in rheumatoid arthritis. Eur J Endocrinol. 1998;138(3):294–301.
[18]Blackman MR, Muniyappa R, Wilson M, Moquin BE, Baldwin HL, Wong KA, Snyder C, Magalnick M, Alli S, Reynolds J, Steinberg SM, Goldbach-Mansky R. Diurnal secretion of growth hormone, cortisol, and dehydroepiandrosterone in pre- and perimenopausal women with active rheumatoid arthritis: A pilot case-control study. Arthritis Res Ther. 2007 Jul 28;9(4):R73:[Epub ahead of print].
[19]Hench PS. The ameliorating effect of pregnancy on chronic atrophic (infectious rheumatoid) arthritis, fibrositis, and intermittent hydrarthrosis. Proc Staff Meet Mayo Clin. 1938;13:161–167.
[20]Østensen M. Sex hormones and pregnancy in rheumatoid arthritis and systemic lupus erythematosus. Ann NY Acad Sci. 1999;876:131–143.
[21]Romagnani S. Lymphokine production by human T cells in disease states. Annu Rev Immunol. 1994;12: 227–257.
[22]Dolhain RJEM, van der Heiden AN, ter Haar NT, Breedveld FC, Miltenburg AMM. Shift toward T lymphocytes with a T helper 1 cytokine-secretion profile in the joints of patients with rheumatoid arthritis. Arthritis Rheum. 1996;39:1961–1969.
[23]Yudoh K, Matsuno H, Nakazawa F, Yonezawa T, Kimura T. Reduced expression of the regulatory CD4 T cell subset is related to Th1=Th2 balance and disease severity in rheumatoid arthritis. Arthritis Rheum. 2000;43(3):617–627.
[24]Ehrenstein MR, Evans JG, Singh A, Moore S, Warnes G, Isenberg DA, Mauri C. Compromised function of regulatory T cells in rheumatoid arthritis and reversal by anti-TNFalpha therapy. J Exp Med. 2004 Aug 2;200(3):277–285. Epub 2004 Jul 26.
[25]Foussat A, Cottrez F, Brun V, Fournier N, Breittmayer JP, Groux H. A comparative study between T regulatory type 1 and CD4 CD25 T cells in the control of inflammation. J Immunol. 2003 Nov 15; 171(10):5018–5026.
[26]Parks C, Conrad K, Cooper G. Occupational exposure to crystalline silica and autoimmune disease. Environ Health Perspect. 1999;107(suppl.5):793–802.
[27]Streenland K, Goldsmith D. Silica exposure and autoimmune diseases. Am J Ind Med. 1995;28:603–608.
[28]Steenland K, Sanderson W, Clavert GM. Kidney disease and arthritis in a cohort study of workers exposed to silica. Epidemiology. 2001;12:405–412.
[29]Järvinen P, Aho K. Twin studies in rheumatic diseases. Semin Arthritis Rheum. 1994;24(1):19–28.
[30]Darlington GA, Stone TW. Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders. Br J Nutr. 2001;85:251–269.
[31]Grootveld M, Henderson EB, Farrell A, Blake DR, Parkes HG, Haycock P. Oxidative damage to hyaluronate and glucose in synovial fluid during exercise of the inflamed rheumatoid joint: Detection of abnormal low-molecular-mass metabolites by proton-NMR spectroscopy. Biochem J. 1991;273(pt.2):459–467.
[32]Cooper B, Creeth JM, Donald AS. Studies of the limited degradation of mucous glycoproteins—the mechanism of the peroxide reaction. Biochem J. 1985;228(3):615–626.
[33]Wasil M, Halliwell B, Moorhouse CP, Hutchinson DCS, Baum H. Biologically significant scavenging of the myeloperoxidase-derived oxidant hypochlorous acid by some antiinflammatory drugs. Biochem Pharmacol. 1987;36(22):3847–3850.
[34]Knekt P, et al. Serum selenium, serum alphatocopherol, and the risk of rheumatoid arthritis. Epidemiology. 2000;11(4):402–405.
[35]Heliovaara M, Knekt P, Aho K, Aaran R-K, Alfthan G, Aromaa A. Serum antioxidants and risk of rheumatoid arthritis. Ann Rheum Dis. 1994;53(1):51–53.
[36]Criswell LA, Merlino LA, Cerhan JR, Mikuls TR, Mudano AS, Burma M, Folsom AR, Saag KG. Cigarette smoking and the risk of rheumatoid arthritis among postmenopausal women: results from the Iowa Women's Health Study. Am J Med. 2002 Apr 15;112(6):465–471.
[37]Papadopoulos NG, Alamanos Y, Voulgari PV, Epagelis EK, Tsifetaki N, Drosos AA. Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients? Clin Exp Rheumatol. 2005 Nov–Dec;23(6):861—866.
[38]Kjeldsen-Kragh J, et al. Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. Lancet. 1991;338:899–902.
[39]Fraser DA, Thoen J, Djøseland Ø, Førre Ø, Kjeldsen-Kragh J. Serum levels of interleukin-6 and dehydroepiandrosterone sulphate in response to either fasting or a ketogenic diet in rheumatoid arthritis patients. Clin Exper Rheumatol. 2000;18:357–362.
[40]Peltonen R, et al. Changes of faecal flora in rheumatoid arthritis during fasting and one-year vegetarian diet. Br J Rheumatol. 1994;33:638–643.

[41]Hirano D, Masakazu N, Ogawa R, Yoshino S. Serum levels of interleukin 6 and stress related substances indicate mental stress condition in patients with rheumatoid arthritis. J Rheumatol. 2001;28:490–495.
[42]Bellido T, Jilka R, Boyce B. Regulation of interleukin-6 osteoclastogenesis, and bone mass by androgens: The role of the androgen receptor. J Clin Invest. 1995;2886–2895.
[43]Heller A, Koch Schmeck J, vanAckern K. Lipid mediators in inflammatory disorders. Drugs. 1998;55(4): 487–496.
[44]Sperling RI. Dietary omega-3-fatty acids: Effects on lipid mediators of inflammation and rheumatoid arthritis. Rheum Dis North Am. 1991;17(2):373–389.
[45]Esperson GT, Grunnet N, Lervang HH, Nielsen GL, Thomsen BS, Faarvang KL. Decreased interleukin-1 beta levels in plasma from rheumatoid arthritis patients after dietary supplementation with n-3 polyunsaturated fatty acids. Clin Rheumatol. 1992;11:393–395.
[46]Kremer JM, Lawrence DA, et al. Dietary fish oil and olive oil supplementation in patients with rheumatoid arthritis: Clinical and immunologic effects. Arthritis Rheum. 1990;33(6):810–820.
[47]Kremer J, Jubiz W, Michalek A, et al. Fish oil fatty acid supplementation in active rheumatoid arthritis. Ann Int Med. 1987;106:497–503.
[48]Sperling RI, et al. Effects of dietary supplementation with marine fish oil on leukocyte lipid mediator generation and function in rheumatoid arthritis. Arthritis Rheum. 1987;30:988–997.
[49]Kremer JM, Michalek AV, Lininger L. Effects of manipulation of dietary fatty acids on clinical manifestations of rheumatoid arthritis. Lancet. 1985;i:184–187.
[50]Whitehouse MW, Macrides TA, Kalafatis N, Betts WH, Haynes DR Broadbent J. Anti-inflammatory activity of a lipid fraction from the NZ green-lipped mussel. Inflammopharmacology. 1997;5:237–246.
[51]Leventhal LJ, Boyce EG, Zurier RB. Treatment of rheumatoid arthritis with gamma linolenic acid. Ann Int Med. 1993;119:867–873.
[52]Cleland LG, French JK, Betts WH, Murphy GA, Elliot MJ. Clinical and biochemical effects of dietary fish oil supplements in rheumatoid arthritis. J Rheumatol. 1988;15:1471–1475.
[53]Shapiro JA. Diet and rheumatoid arthritis in women: A possible protective effect of fish consumption. Epidemiology. 1996;7:256–263.
[54]Fairney A, Patel KV, Fish DE, Seifert MH. Vitamin A in osteo- and rheumatoid arthritis. Br J Rheumatol. 1988;27:329–330.
[55]Edmonds SE, Winyard PG, Guo R, Kidd B, Merry P, Langrish-Smith A, et al. Putative analgesic activity of repeated doses of vitamin E in the treatment of rheumatoid arthritis: Results of a prospective placebo controlled double blind trial. Ann Rheum Dis. 1997;56:649–655.
[56]Aaseth J, Haugen M, Førre Ø. Rheumatoid arthritis and metal compounds—perspectives on the role of oxygen radical detoxification. Analyst. 1998;123:3–6.
[57]Tarp U, Hansen JC, Overvad K, Thorling EB, Tarp BD, Grandal H. Glutathione peroxidase activity in patients with rheumatoid arthritis and in normal subjects: Effects of long-term selenium supplementation. Arthritis Rheum. 1987;30:1162–1166.
[58]Merlino LA, Curtis J, Mikuls TR, Cerhan JR, Criswell LA, Saag KG; Iowa Women's Health Study. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. Arthritis Rheum. 2004 Jan;50(1):72–77.
[59]Reddy AC, Cokesh BR. Studies on the inhibitory effects of curcumin and eugenol on the formation of reactive oxygen species and the oxidation of ferrous iron. Mol Cell Biochem. 1994;137(1):1–8.
[60]Srivastava KC, Bordia A, Verma SK. Curcumin, a major component of food spice tumeric (Curcuma longa), inhibits aggregation and alters eicosanoid metabolism in human blood platelets. Prostaglandins Leukot Essent Fatty Acids. 1995;52:223–227.
[61]Ammon HP, Wahl MA. Pharmacology of Curcuma longa. Planta Medica. 1991;57:1.
[62]Li WQ, Dehnade F, Zafarullah M. Oncostatin M-induced matrix metalloproteinase and tissue inhibitor of metalloproteinase-3 genes expression in chondrocytes requires janus kinase=STAT signaling pathway. J Immunol. 2001;166:3491–3498.
[63]Thabrew MI, Senaratna L, Samarawickrema N, Munasinghe C. Antioxidant potential of two polyherbal preparations used in Ayurveda for the treatment of rheumatoid arthritis. J Ethnopharmacol. 2001;76:285–291.
[64]Etzel R. Special extract of Boswellia serrata (H15) in the treatment of rheumatoid arthritis. Phytomed. 1996;3:91–94.
[65]Cohen A, Goldman J. Bromelain therapy in rheumatoid arthritis. Pennsylvania Med J. 1964;67:27–30.
[66]Srivastava KC, Mustafa T. Ginger (Zingiber officinale) in rheumatism and musculoskeletal disorders. Med Hypotheses. 1992 Dec;39(4):342–348.
[67]Grzanna R, Lindmark L, Frondoza CG. Ginger—an herbal medicinal product with broad anti-inflammatory actions. J Med Food. 2005 Summer;8(2):125–132.
[68]Deal CL, Schnitzer TJ, Lipstein E, Seibold JR, Stevens RM, Levy MD, Albert D, Renold F. Treatment of arthritis with topical capsaicin: A double-blind trial. Clin Ther. 1991 May–Jun;13(3):383–395.

[69] Matucci-Cerinic M, Marabini S, Jantsch S, Cagnoni M, Partsch G. Effects of capsaicin on the metabolism of rheumatoid arthritis synoviocytes in vitro. Ann Rheum Dis. 1990 Aug;49(8):598–602.

[70] Tao X, Younger J, Fan FZ, Wang B, Lipsky PE. Benefit of an extract of Tripterygium wilfordii Hook f in patients with rheumatoid arthritis: A double-blind, placebo-controlled study. Arthritis Rheum. 2002 Jul;46(7): 1735–1743.

[71] Tao X, Cush JJ, Garret M, Lipsky PE. A phase I study of ethyl acetate extract of the Chinese anti-rheumatic herb Tripterygium wilfordii hook F in rheumatoid arthritis. J Rheumatol. 2001 Oct;28(10):2160–2167.

[72] Lipsky PE, Tao XL. A potential new treatment for rheumatoid arthritis: Thunder god vine. Semin Arthritis Rheum. 1997 Apr;26(5):713–723.

[73] ClinicalTrials.gov. Treating Rheumatoid Arthritis with Tripterygium Wilfordi Hook F or Sulfasalazine. Available at: www.clinicaltrials.gov=ct=show=NCT00062465?order 1. Accessed December 5, 2007.

[74] Mur E, Hartig F, Eibl G, Schirmer M. Randomized double blind trial of an extract from the pentacyclic alkaloid-chemotype of uncaria tomentosa for the treatment of rheumatoid arthritis. J Rheumatol. 2002 Apr; 29(4):678–681.

[75] Kaplan S, Kozin F. A controlled study of group counseling in rheumatoid arthritis. J Rheumatol. 1981; 8:91–99.

[76] Hall J, Shevington SM, Maddison PJ, Chapman K. A randomized and controlled trial of hydrotherapy in rheumatoid arthritis. Arthritis Care Res. 1996;9(3):206–215

31

NATURAL REMEDIES FOR PROMOTING SKIN HEALTH

The skin is susceptible to many diseases and disorders. Skin disorders may be external manifestations of systemic illness. One example is the butterfly rash of systemic lupus erythematosus. Other skin conditions reflect topical exposure reactions, arising from localized responses. Skin disorders have a wide range of etiologies, ranging from infection (e.g., scabies, ringworm) to allergy (e.g., to drugs, foods, and cosmetics) to nutritional deficiency (e.g., vitamin A or essential fatty acid [EFA] deficiency may lead to follicular hyperkeratosis). Other causes of skin outbreaks include reactions to bites and stings and reactions to plants such as poison ivy or poison oak. This chapter examines applications of natural remedies for treating several common skin conditions.

The skin is a mirror of an individual's state of health. A skin condition often reflects a deeper state of imbalance. (See Table 31–1 on page 354.) Because the skin is an organ of elimination, if other organs of elimination (liver, kidneys, or bowels) are compromised, a skin outbreak may reflect the body's attempt to discharge wastes through an alternate route. Intestinal disturbances, such as constipation, may play a role in skin problems by increasing the amount of toxins circulating in the body. To ameliorate skin conditions, it is necessary to improve the health of these organs. For example, supporting liver health may help to improve acne conditions associated with hormonal imbalances.

GENERAL REQUIREMENTS FOR PROMOTING HEALTHY SKIN

Lifestyle factors are critical for maintaining healthy skin. Smoking can cause dryness and premature aging of the skin. Sun exposure is associated with an increased risk of skin cancer, premature aging, and hyperpigmentation of the skin, requiring a limit to sun exposure and the use of sunscreen during prolonged exposure. Clinically, exercise has been shown to help promote a radiant, glowing complexion.

Optimal intake and assimilation of nutrients is also essential for promoting healthy skin. A deficiency of EFAs often manifests as dry, flaky skin and a predisposition to inflammatory conditions, such as eczema. Vitamin A is a crucial nutrient for healing tissues and regenerating epithelial tissues including the skin. Vitamin A deficiency can manifest as follicular hyperkeratosis, poor wound healing, and acne. Vitamin E can prevent scarring from blemishes and incisions. Vitamin C is an important nutrient for the skin both internally and topically because the vitamin helps to inhibit free-radical damage and promotes collagen production. The B vitamins promote skin health and offer stress relief, with vitamin B_6 being particularly helpful for preventing premenstrual acne. Zinc deficiency is common in acne and other skin problems.

Probiotics, such as acidophilus and bifidobacteria, contribute to maintaining healthy and balanced gastrointestinal (GI) bacterial flora to enhance nutrient absorption and prevent the overgrowth of toxin-producing yeast and bacteria in the gut. Foods that contain sulfur, such as onions, garlic, and asparagus, provide the skin with this much-needed nutrient and support the liver's

Table 31–1. Skin and Nutritional Imbalances

Condition	Indications
Allergic shiners (dark circles under the eyes)	Allergies
Cheilosis	Low B vitamins (B_2)
Jaundice	Liver, increased bilirubin, hemolytic anemia
Pallor	Anemia, shock
Cyanosis	Hypoxia, cyanide poisoning
Dry skin	Dehydration, hypothyroid
Vitiligo	Autoimmune
Eczema	Low EFA=Allergy—internal or external
Psoriasis	Liver function
Liver spots (lipofuscin)	Low antioxidants, high free-radical burden

detoxification pathways. Finally, plenty of filtered or spring water also helps the body to remove wastes and keep the skin hydrated and healthy.

NATURAL REMEDIES FOR TREATING SKIN CONDITIONS

Eczema (Atopic Dermatitis)

Eczema, or atopic dermatitis, is a common skin condition characterized by a chronic, itchy red rash. Eczema is thought to affect approximately 9% of the population in the United States, mostly children, and appears to be increasing.[1] It is believed to be an allergic, immediate hypersensitivity disease also involving other immune responses. It often occurs as part of the ''atopic triad'' of asthma, hay fever, and eczema. A positive family history of allergies is found in two-thirds of patients who have eczema. Serum immunoglobulin E (IgE) levels are elevated in 80% of patients with eczema, and they often test positive on skin, radioallergoabsorbant (RAST), or other allergy tests.[2] White blood cells from patients with atopic dermatitis have decreased cyclic adenosine monophosphate (cAMP) levels as a result of increased AMP-phosphodiesterase activity. This lack of cAMP results in increased histamine release and decreased bactericidal activity.[3] Patients with atopic dermatitis appear to have altered EFA and prostaglandin metabolism as well.[4]

Food allergies play a major role in producing atopic dermatitis. Identifying and avoiding food allergens may be an essential component of a thorough treatment plan for treating eczema. Breast-feeding infants has been found to offer significant protection from developing atopic dermatitis and allergies in general.[2] In older or formula-fed infants, the most common offending food allergens are milk, eggs, peanuts, wheat, fish, and soybeans.[5] If breast-fed infants develop atopic dermatitis, it is usually the result of allergic antigens in the breast milk being transferred from the mother to the infant. The mother's avoidance of common allergens is helpful for resolving such cases.[6] Methods for diagnosing food allergy include the elimination diet, challenge, and the enzyme-linked immunoabsorbent assay and IgE and IgG assays. Food

allergens in the diet may also contribute to the "leaky gut" syndrome. This increased gut permeability causes an increased antigenic load on the immune system and can increase the likelihood of developing additional allergies.[7] Clinically, often replenishing beneficial GI flora with lactobacillus and bifobacterium strains along with fructo-oligosaccharides is helpful, particularly when a patient has a history of antibiotic use. An overgrowth of Candida albicans in the GI tract has been identified as a causative factor in allergic conditions, including atopic dermatitis. Therapy to address Candida overgrowth may ameliorate atopic dermatitis significantly.[8]

The active ingredient of coleus, forskolin, most often used orally, may be helpful both orally and topically for ameliorating eczema.

Essential fatty acids may be useful for treating eczema. Borage (Borago officinalis) oil, a rich source of the omega-6 fatty acid gamma-linolenic acid, has been found to reduce skin inflammation, dryness, scaliness, and itching.[9] Omega-3 fatty acids may be even more effective for relieving eczema symptoms. Fish oils appear to be a particularly good source of omega-3 fatty acids for patients with eczema because these oils contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[10] Consumption of cold-water fish, including salmon, mackerel, and herring, may also be useful. Zinc may also provide benefit for managing eczema due to the fact that zinc deficiency is common in atopic dermatitis and that zinc is crucial for proper fatty-acid metabolism.[11]

Plant-based therapies may also be indicated for managing eczema. Agents that stimulate cAMP production and=or inhibit cAMP phosphodiesterase may help to reduce the inflammatory process of atopic dermatitis by reducing shunting to histamine. Coleus (Coleus forskolhii) is a strong stimulant of cAMP.[12] The active ingredient of coleus, forskolin, most often used orally, may be helpful both orally and topically for ameliorating eczema. Flavonoids may help to reduce inflammation because of their ability to reduce mast-cell degranulation and inhibit cAMP phosphodiesterase. Helpful sources of flavonoids include quercitin, grape (Vitis vine fera) seed, pine (Pinus spp.) bark, green tea (Camellia sinensis), and ginkgo (Ginkgo biloba).[11,13] Licorice (Glycyrrhiza glabra) root, used either topically or internally, may also help to alleviate eczema symptoms.[14] Other herbs to consider for topical use are chamomile (Matricaria chamomilla), calendula (Calendula officinalis), and oak (Quercus alba), all of which are known for their anti-inflammatory properties.

Psoriasis

Psoriasis is a common skin disorder that affects between 2%–4% of the U.S. population. Psoriasis is a hyperproliferative skin disorder characterized by sharply bordered reddened rashes and silvery, scaly plaques on the skin. Eruptions often involve the scalp, the extensor surfaces of the extremities, the back, and the buttocks. Removal of the superficial scales typically causes pinpoint bleeding, or the Auspitz sign. The rate of cellular division in psoriatic lesions is very high, at approximately 1,000 times the rate of normal skin. Psoriasis predominately affects Caucasians and a family history of psoriasis is present in 35%–50% of patients. Genetic factors are likely to be involved. The rate at which cells divide is controlled by a

balance of cAMP and cyclic guanidine monophosphate (cGMP). Increased levels of cGMP are associated with increased cell proliferation while increased levels of cAMP are associated with cell maturation and decreased cell replication. Increased levels of cGMP and decreased levels of cAMP have been demonstrated in the skin of patients with psoriasis, resulting in excess cell replication.[15] Natural medicine interventions may help to rebalance the cyclic AMP:GMP ratio and thus improve the skin's condition.

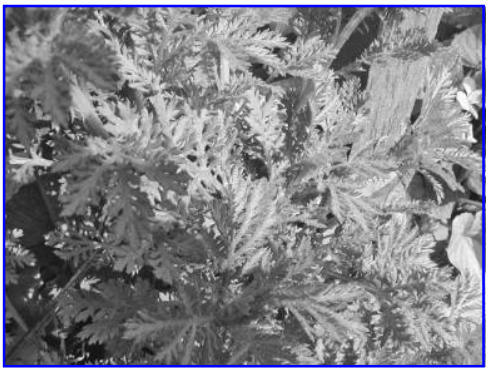

Figure 31–1. Matricaria chamomilla. Photo by Brian Hunter, huntergrafx.net.

Optimizing bowel and liver function may be useful for managing psoriasis. Individuals with psoriasis have increased levels of polyamines in the skin and blood, which are toxic by-products of incomplete protein digestion and assimilation. Polyamines inhibit the formation of cAMP and may, therefore, contribute to the excessive rate of skin-cell replication seen in psoriasis.[16,17] Several natural compounds may inhibit the formation of polyamines. These include vitamin A and the alkaloids from goldenseal (Hydrastis canadensis).[18,19] Another study investigated topical application of a 10% Mahonia aquifolium cream in patients with mild to moderate bilateral psoriasis. The results showed 84% of patients rated the Mahonia treatment as good to excellent compared with standard treatment, and 63% of patients rated Mahonia aquifolium equal to or better than the standard psoriatic treatment.[20]

One of the best ways to prevent polyamine formation is via evaluating digestive function with such tests as Heidelburg analysis or functional medicine assessments and then correcting problems with protein digestion or absorption by way of appropriate therapies. The Heidelburg analysis is a simple test that involves swallowing a radiotelemetry capsule that measures the stomach's pH at baseline and then after a pH-buffered test to see how the stomach compensates with acid production. Functional medicine tests include a closely monitored clinical trial of betaine hydrochloride. For patients who cannot get access to the Heidelburg analysis, the best second-line option is the betaine trial provided that there is no overt GI disease, such as ulcers or esophagitis, for example. Other intestinal toxins are implicated in psoriasis. These include endotoxins from gram-negative bacteria, C. albicans, and yeast compounds. These compounds lead to increased cGMP levels within skin cells.[21,22] Therefore, treating intestinal Candida or bacterial overgrowth may ameliorate psoriasis. A low-fiber diet is associated with increased levels of gut-derived toxins.[21] Thus, a fiber-rich diet helps to bind bowel toxins and promote their excretion. Patients with psoriasis need to consume plenty of beans, fruits, and vegetables.

Zinc supplements may help to reduce the severity of acne and assist in skin healing.

Improving liver function is often helpful for treating psoriasis. Silymarin, the flavonoid component of milk thistle (Silybum marianum) has been reported to be useful for treating psoriasis.[23] Silymarin improves liver function, inhibits inflammation, and reduces excessive cellular proliferation.[24] Alcohol consumption worsens psoriasis, presumably because such

consumption damages liver function and increases absorption of toxins from the gut,[25] thus, avoidance of alcohol is recommended for patients with psoriasis.

Manipulating dietary fats may also be useful. Several double-blind clinical studies have demonstrated that fish-oil supplements that are rich in EPA and DHA ameliorate the condition.[26,27] Yet some studies have shown less improvement, emphasizing the importance of selecting the proper nutraceutical interventions. Patients with the condition should generally be advised to minimize intake of arachidonic acid because of its pro-inflammatory effects.

Fumaric acid has been found, in some studies, to be effective. Fumaric acid is an intermediate of the Krebs cycle and is formed in the skin in response to ultraviolet rays. Patients with psoriasis may suffer from a biochemical defect that reduces their production of adequate amounts of fumaric acid. Controlled studies have demonstrated improvements in patients following the administration of oral dimethylfumaric acid combined with topical fumaric acid. However, side effects, including nausea, diarrhea, malaise, and liver and kidney disturbances, can occur,[28] requiring close medical supervision of such therapy.

Topical applications such as licorice root and chamomile may provide anti-inflammatory and antiallergic activity when used on dry, flaky, irritated skin.[29,30] Both topical and oral doses of vitamin D (in the form of calcitrol-1,25-dihydroxyvitamin D_3) have also been effective as a result of their ability to regulate terminal differentiation of basal cells of epidermal keratinocytes.[31]

Acne

Acne is the most common of all skin problems and will affect an estimated 85% of the population at some point during their lives. Comedones, papules, and pustules characterize Acne vulgaris. Acne conglobata is a more severe condition, with cyst formation and subsequent scarring. Lesions may occur on the face, shoulders, back, and chest. Teenagers and young adults are most commonly affected, with males being affected more often than females.

Excess androgen stimulation of the skin may play a role in the etiology of acne. Androgens stimulate keratin production. An overproduction of keratin can block skin pores. In addition, testosterone can stimulate the sebaceous glands to enlarge and increase their production of

General Guidelines for Healthy Skin

What to Tell Your Patients

- Limit sun exposure and use sunscreen.
- Drink plenty of filtered or spring water.
- Exercise regularly.
- Eliminate tobacco and alcohol.
- Avoid fried foods and hydrogenated fats.
- Consume a healthy diet.
- Take B vitamins and antioxidants, including vitamins A, C, and E.
- Include essential fatty acids in diet and supplement regime.
- Support healthy gastrointestinal, liver, and kidney function via diet, nutrients, and herbs.
- Consume foods and supplements that contain probiotics (acidophilus, bifidobacterium).

sebum, which also may block pores. This causes the formation of a comedone or a pustule. Bacteria can overgrow and release enzymes to break down sebum, resulting in inflammation. If this process occurs at the skin's surface, redness and pustules are created. Inflammation deeper in the skin can create nodules or cysts, causing greater damage to the skin and possible scarring.

Women who are or who may become pregnant must avoid therapeutic doses of vitamin A because of its teratogenicity.

Acne presents a clinical challenge to the practitioner and to the patient. Several nutrients and herbs may be helpful for managing acne. Zinc supplements may help to reduce the severity of acne and assist in skin healing. A dose of 30 mg, two to three times per day, is recommended.[32] Several months of zinc therapy may be required before improvement is noted. Long-term zinc therapy, in doses over 15 mg per day for more than three months, may lead to copper deficiency; thus, supplementation may become necessary and warrants close monitoring.

Large doses of vitamin A—such as 50,000 international units (IU) per day—have been used successfully for treating severe acne.[33] Although this dose can be used safely in healthy individuals for a treatment period of a few months, it is important to monitor patients for signs and symptoms of vitamin A toxicity. Running routine liver enzyme tests and determining serum vitamin A levels are recommended. Symptoms of vitamin A toxicity include headaches, fatigue, and muscle and joint pain. Women who are or who may become pregnant must avoid therapeutic doses of vitamin A because of its teratogenicity. It is advisable for young women who may become pregnant to avoid all vitamin A supplementation, with the exception of the amount in a prescribed prenatal vitamin. A prenatal supplement should not contain more than

Potential Therapeutic Dosing

Vitamin A—25,000–50,000 IU[a] per day for acne (with very close monitoring)
Vitamin C—1,000 mg per day
Vitamin B_6—25–50 mg per day
Vitamin B_5—25–500 mg, up to 10 g, per day for acne
Zinc—30–90 mg per day
Vitamin E—400–800 IU per day
Calcitrol—0.5 mcg orally and=or 0.5 mcg=g of base applied topically per day; calcium levels must be monitored[b]
Borage oil—1,000–3,000 mg per day
Fish oil—2,000 mg, up to 10 g per day, for psoriasis
Goldenseal—250–500 mg (with 18%–12% alkaloids) 3 times per day for psoriasis
Coleus—50 mg of extract, standardized to 18% forskolin, 2–3 times per day for eczema
Milk thistle—70–210 mg, 3 times per day, or standardized extract of 420 mg silymarin per day for psoriasis

[a]IU international unit. [b]Calcitrol should be started at lowest dose possible to prescribe and slowly increased after blood work is done.

5,000 IU to be on the safe side. In fact, prenatal vitamins that use natural beta-carotene instead of actual vitamin A are believed to be safer by nutritionally-oriented physicians.

Vitamin B_6 is often helpful for treating acne in affected women.[34] This may be the result of pyridoxine's role in metabolizing steroid hormones. Another B vitamin, vitamin B_5, may be valuable in high doses. One study demonstrated that 10 g per day of pantothenic acid, administered in divided doses, helped to reduce existing acne lesions and prevent the frequency of new eruptions.[35]

> Creating healthy skin requires a multifaceted approach that addresses dietary, lifestyle, and nutritional factors.

Topical treatment may also be useful. The goal of such applications is to reduce bacterial and inflammation levels. Tea tree (Melaleuca alternifolia) oil has antiseptic and antifungal properties. A 5% solution of tea tree oil demonstrated acne-fighting effects that were comparable to those produced by a 5% benzoyl peroxide solution.[36] Stronger concentrations of tea tree oil may produce even better effects; yet, caution must be used because skin irritation and damage can arise if the preparations are too concentrated.

Rosacea

Rosacea, or Acne rosacea, is a chronic skin disorder characterized by redness, papules, and pustules on the cheeks and nose. Rosacea typically occurs in adults between ages 30 and 50, with women being affected more often than men. Several factors have been suspected of causing rosacea. These include alcoholism, GI disorders, B-vitamin deficiencies, and menopausal flushing. Patients with rosacea have been found to have inadequate levels of gastric hydrochloric acid. Hydrochloric acid supplements have produced dramatic reductions in the rosacea of patients who are achlorhydric and hypochlorhydric.[37,38] A high incidence of gastric Helicobacter pylori infection has been found in patients with rosacea. Treatment of the H. pylori infection has been found to reduce rosacea significantly in many patients.[39] Dietary modification may also be helpful. Individuals with rosacea should be advised to avoid coffee,

Possible Causes of Skin Problems

- Infections, including fungal (ringworm), parasite (scabies), viral (warts), bacterial (abscess)
- Allergies (e.g., to foods, chemicals, cosmetics, detergents)
- Drug reactions
- Systemic disease (systemic lupus erythematosus, hypothyroidism)
- Excessive sun exposure
- Precancerous or cancerous lesions
- Hormonal imbalances (onset of puberty, premenstrual acne)
- Insect bites
- Vitamin or nutrient deficiencies

alcohol, hot beverages, and spicy foods. Eliminating refined sugars, hydrogenated oils, dairy products, and fried foods may also be helpful.

ADDITIONAL NUTRIENTS FOR SKIN

Hyaluronic Acid (HA)

Hyaluronic acid (HA) is a polypeptide chain of disaccharide units consisting of sodium acetyl glucosamine and sodium glucuronate. HA has a structural role in connective tissue as it is a component of the extracellular matrix and can be found predominately in skin, joints, and eyes. Hydrated matrices rich in hyaluronan expand the extracellular space, facilitating cell migration and wound healing. The viscoelastic properties of hyaluronan are also important for proper function of joints and cartilage. A study examined the effect of topical HA on experimentally induced wounds in hamsters. The results showed that wound size decreased almost twice as fast with HA compared with the control group and was believed to be due to HA favoring tissue hydration, which has a well-established beneficial effect on wound healing.[40] Additionally, HA protects granulation tissue from oxygen free-radical damage stimulating wound healing.[41]

Antioxidants

Numerous antioxidant preparations have been shown to benefit skin complaints. Antioxidants have the ability to quench damage-causing free radicals that lead to many skin problems. Studies using animal models have demonstrated that delayed wound healing in aged rats is related to low levels of antioxidants such as ascorbic acid, vitamin E, and glutathione, accompanied by elevated levels of markers of free-radical damage. Also, this study showed that in diabetic rats, decreased glutathione levels may have a contributory role in delaying the healing process.[42]

Vitamin C is known for its antioxidant action, photo-protective properties, and activity in the collagen biosynthetic pathway. Topical applications of vitamin C as a 3% ascorbic acid emulsion over 12 weeks was shown to significantly reduce oxidative stress in the skin, improve the epidermal-dermal microstructure, and reduce fine lines and wrinkles in aged skin.[43] Another study showed that a 5% ascorbic acid cream applied to the face in women with sun-induced photo damage showed positive results. The research found significant increase in the density of skin, decrease of the deep furrows, and evidence of elastic tissue repair.[44]

Vitamin E is a fat-soluble vitamin often used for its potent antioxidant activity. Studies have shown that a combination of vitamin E and vitamin C synergistically can suppress the inflammation reaction from solar simulated radiation.[45] Another study showed that vitamin E in the form of alpha-tocopherol reduced plasma malondialdehyde levels, increased glutathione peroxidase activity, and accelerated the rate of wound closure in rats.[46]

Glutathione is a potent antioxidant and its enzyme, glutathione peroxidase, is important in proper skin health and prevention of DNA damage in cells. Studies have shown that mice treated with esterified glutathione prior to ultraviolet-B exposure had increased cutaneous glutathione levels and decreased numbers of sunburned cells.[47] In a small study, a combination product of reduced glutathione and anthocyanins was shown to decrease radiation-induced dermatitis in women undergoing treatment for breast cancer, allowing for more consistent treatment.[48]

Curcumin, (Curcuma longa) is a potent antioxidant, anti-inflammatory, and anti-cancer agent. Studies indicate that topical curcumin improves wound healing. In one study, wounds

treated with topical curcumin were found to heal much faster as indicated by improved rates of cellular proliferation, wound contraction, and increased tensile strength. Also, there was a decrease in the levels of lipid peroxides, with significantly increased activity of superoxide dismutase, catalase, and glutathione peroxidase. Better maturation and cross-linking of collagen was demonstrated by increased stability of acid-soluble collagen, aldehyde content, shrinkage temperature, and tensile strength in the rats treated with curcumin.[49]

Alpha-lipoic acid (ALA) is both water and fat soluble and is a powerful free-radical scavenger preventing oxidative damage. Also, it is important as it can regenerate endogenous antioxidants including vitamin E, vitamin C, and glutathione. Topical treatment with ALA has been shown to increase collagen synthesis in the skin in animal models.[50] Additionally, in a randomized, double-blind placebo-controlled human study, a cream containing 5% ALA over 12 weeks showed significant improvement in clinical characteristics related to photoaging of facial skin.[51]

CONCLUSIONS

The skin is susceptible to many disorders because of its constant contact with environmental factors and because of its role in mirroring the state of GI and liver health. Creating healthy skin requires a multifaceted approach that addresses dietary, lifestyle, and nutritional factors. By working with patients to create optimal wellness, practitioners can help them improve skin health and ameliorate or eliminate skin and other underlying disorders.

REFERENCES

[1]American Academy of Allergy, Asthma, and Immunology. Allergy Statistics. Online document at: www.aaaai.org=media=resources=media_kit=allergy_statistics.stm. Accessed November 2, 2007.

[2]Soter N, Baden H. Pathophysiology of Dermatologic Disease. New York: McGraw-Hill, 1984.

[3]Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: Prospective follow-up study until 17 years old. Lancet. 1995;346(8982):1065–1069.

[4]Manku MS, Horrobin DF, Morse NL, et al. Essential fatty acids in the plasma phospholipids of patients with atopic eczema. Br J Dermatol. 1984;110(6):643–648.

[5]Burks AW, Williams LW, Mallory SB, et al. Peanut protein as a major cause of adverse food reaction in patients with atopic dermatitis. Allergy Proceed. 1989;10(4):265–269.

[6]Cant AJ, et al. Effect of maternal dietary exclusion on breast-fed infants with eczema. Two controlled studies. Br Med J. 1986;293(6541):231–233.

[7]Majamaa H, Isolauri E. Evaluation of the gut mucosal barrier: Evidence for increased antigen transfer in children with atopic eczema. J Allergy Clin Immun. 1996;97(4):985–990.

[8]Savolainen J, Lammintausta K, Kalimo K, et al. Candida albicans and atopic dermatitis. Clin Exp Allergy. 1993;(4)23:332–339.

[9]Landi G. Oral administration of borage oil in atopic dermatitis. J Appl Cosmetol. 1993;11:115–120.

[10]Soyland E, Funk J, Rajka G, et al. Dietary supplementation with very long-chain n-3 fatty acids in patients with atopic dermatitis: A double-blind, multicentre study. Br J Dermatol. 1994;130(6):757–764.

[11]David TJ. Serum levels of trace minerals in children with atopic eczema. Br J Dermatol. 1990;122(4): 485–489.

[12]Seamon K, Padgett W, Daly J. Forskolin: Unique determine activator of adenylate cyclase in membranes and intact cells. Proc Natl Acad Sci USA. 1981;78(6):3363–3367.

[13]Petkov E, Nikolov N, Uzunov P. Inhibitory effects of some flavonoids and flavonoid mixtures on cyclic AMP phosphodiesterase activity of rat heart. Planta Medica. 1981;43(2):183–186.

[14]Sheehan MP, Rustin MHA, et al. Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. Lancet. 1992;340(8810):13–17.

[15]Vorhees J, Duell E. Imbalanced cyclic AMP: Cyclic GMP levels in psoriasis. Adv Cyc Nuc Res. 1975; 5:755–757.

[16]Proctor M, Wilkenson D, Orenburg E, et al. Lowered cutaneous and urinary levels of polyamines with clinical improvement in treated psoriasis. Arch Dermatol. 1979;115(8):945–949.
[17]Editorial: Polyamines in psoriasis. J Invest Dermatol. 1983;81:385–387.
[18]Haddox M, Frassir K, Russell D. Retinol inhibition of ornithine decarboxylase induction and G1 progression in CHD cells. Cancer Res. 1979;39(12):4930–4938.
[19]Kuwano S, Yamauchi K. Effect of berberine on tyrosine decarboxylase activity of Streptococcus faecalis. Chem Pharm Bull. 1960;8:491–496.
[20]Gulliver WP, Donsky HJ. A report on three recent clinical trials using Mahonia aquifolium 10% topical cream and a review of the worldwide clinical experience with Mahonia aquifolium for the treatment of plaque psoriasis. Am J Ther. 2005 Sep–Oct;12(5):398–406.
[21]Rosenburg E, Belew P. Microbial factors in psoriasis. Arch Dermatol. 1982;118(3):143–144.
[22]Rao M, Field M. Enterotoxins and anti-oxidants. Biochem Soc Trans. 1984;12(2):177–180.
[23]Weber G, Galle K. The liver, a therapeutic target in dermatoses. Med Welt. 1983;34(4):108–111.
[24]Hikino H, Kiso Y, Wagner H, et al. Antihepatotoxic actions of flavanolignans from Silybum marianum fruits. Planta Medica. 1984;50(3):213–218.
[25]Monk BE, Neill SM. Alcohol consumption and psoriasis. Dermatologica. 1986;173(2):57–60.
[26]Bittiner SB, Tucker WFG, Cartwright I, et al. A double-blind, randomized, placebo-controlled trial of fish oil in psoriasis. Lancet. 1988;i:378–380.
[27]Maurice PDL, Allen BR, Barkley ASJ, et al. The effects of dietary supplementation with fish oil in patients with psoriasis. Br J Dermatol. 1987;117(5):599–606.
[28]Nieboer C, et al. Systemic therapy with fumaric acid derivates: New possibilities in the treatment of psoriasis. J Am Acad Dermatol. 1989;20(4):601–608.
[29]Evans FQ. The rational use of glycerrhetinic acid in dermatology. Br J Clin Pract. 1958;12:269–279.
[30]Mann C, Staba EJ. The chemistry, pharmacology, and commercial formulations of chamomile. Herbs, Spices, Medicinal Plants. 1984;1:235–280.
[31]Morimoto S, Yoshikawa K. Psoriasis and vitamin D_3: A review of our experience. Arch Dermatol. 1989; 125(2):231–234.
[32]Hillstrom L, et al. Comparison of oral treatment with zinc sulfate and placebo in Acne vulgaris. Br J Dermatol. 1977;97(6):681–684.
[33]Kligman AM, et al. Oral vitamin A in Acne vulgaris. Int J Dermatol. 1981;20:278–285.
[34]Snider B, Dieteman D. Pyridoxine therapy for premenstrual acne flare. Arch Dermatol. 1974;110(1): 130–131.
[35]Leung LH. Pantothenic acid deficiency as the pathogenesis of acne vulgaris. Med Hypoth. 1995;44(6): 490–492.
[36]Bassett IB, Pannowitz DL, Barnetson RSC. A comparative study of tea-tree oil versus benzoyl peroxide in the treatment of acne. Med J Australia. 1990;153(8):455–458.
[37]Ryle J, Barber H. Gastric analysis in Acne rosacea. Lancet. 1920;ii:1195–1196.
[38]Poole W. Effect of vitamin B complex and S factor on acne rosacea. S Med J. 1957;50:207–210.
[39]Utas S, Ozabakir O, Turasan A, Utas C. Helicobacter pylori eradication treatment reduce the severity of rosacea. J Am Acad Dermatol. 1999;40(3):433–435.
[40]King SR, Hickerson WL, Proctor KG. Beneficial actions of exogenous hyaluronic acid on wound healing. Surgery. 1991;109:76–84.
[41]Trabucchi E, Pallotta S, Morini M, Corsi F, Franceschini R, Casiraghi A, Pravettoni A, Foschi D, Minghetti P. Low molecular weight hyaluronic acid prevents oxygen free radical damage to granulation tissue during wound healing. Int J Tissue React. 2002;24(2):65–71.
[42]Rasik AM, Shukla A. Antioxidant status in delayed healing type of wounds. Int J Exp Pathol. 2000 Aug;81(4):257–263.
[43]Raschke T, Koop U, Düsing HJ, Filbry A, Sauermann K, Jaspers S, Wenck H, Wittern KP. Topical activity of ascorbic acid: From in vitro optimization to in vivo efficacy. Skin Pharmacol Physiol. 2004 Jul–Aug;17(4):200–206.
[44]Humbert PG, Haftek M, Creidi P, Lapière C, Nusgens B, Richard A, Schmitt D, Rougier A, Zahouani H. Topical ascorbic acid on photoaged skin. Clinical, topographical and ultrastructural evaluation: Double-blind study vs. placebo. Exp Dermatol. 2003 Jun;12(3):237–244.
[45]Fuchs J, Kern H. Modulation of UV-light-induced skin inflammation by D-alpha-tocopherol and L-ascorbic acid: a clinical study using solar simulated radiation. Free Radic Biol Med. 1998 Dec;25(9):1006–1012.
[46]Musalmah M, Fairuz AH, Gapor MT, Ngah WZ. Effect of vitamin E on plasma malondialdehyde, antioxidant enzyme levels and the rates of wound closures during wound healing in normal and diabetic rats. Asia Pac J Clin Nutr. 2002;11(suppl.7):S448–S451.

[47]Hanada K, Sawamura D, Tamai K, Hashimoto I, Kobayashi S. Photoprotective effect of esterified glutathione against ultraviolet B-induced sunburn cell formation in the hairless mice. J Invest Dermatol. 1997 May;108(5):727–730.

[48]Miko Enomoto T, Johnson T, Peterson N, Homer L, Walts D, Johnson N. Combination glutathione and anthocyanins as an alternative for skin care during external-beam radiation. Am J Surg. 2005 May;189(5): 627–630; discussion 630–631.

[49]Panchatcharam M, Miriyala S, Gayathri VS, Suguna L. Curcumin improves wound healing by modulating collagen and decreasing reactive oxygen species. Mol Cell Biochem. 2006 Oct;290(1–2):87–96. Epub 2006 Jun 13.

[50]Han B, Nimni ME. Transdermal delivery of amino acids and antioxidants enhance collagen synthesis: in vivo and in vitro studies. Connect Tissue Res. 2005;46(4–5):251–257.

[51]Beitner H. Randomized, placebo-controlled, double blind study on the clinical efficacy of a cream containing 5% alpha-lipoic acid related to photoageing of facial skin. Br J Dermatol. 2003 Oct;149(4): 841–849.

32

THERAPEUTIC USES OF AMINO ACIDS

The utility of amino acids in medicine today continues to be explored via clinical research and applications. Amino acids have several roles in the body; as the building blocks of protein, amino acids are found throughout the body. Muscle is by far the most protein- and amino acid–rich tissue in the body.[1] Health care practitioners are gaining more knowledge about amino acids, including their metabolism in the body, imbalances, and chemical structures. Therapeutic use of amino acids presents natural medicine with an important therapeutic option. Some of the most prominent therapeutic applications of amino acids are for treatment of imbalances of brain metabolism and neurotransmission. Other primary areas in which amino acids are important include gastrointestinal (GI) health, immune function, and cardiovascular health.

Amino acids are classified as essential, nonessential, or conditionally essential, according to whether the body is able to synthesize the amount that it needs for metabolic maintenance. Incomplete intake of amino acids may predispose a patient to many symptoms, the most obvious of which are growth retardation and weight loss. Overall, amino acids are required daily by the human body because they are not stored for long periods of time nor in adequate amounts to sustain health.

GLUTAMINE

One of the most freely available amino acids in the body, glutamine is derived mainly from skeletal muscles. The liver, kidneys, GI tract, and immune system utilize glutamine readily. Inside the organs, glutamine transports nitrogen and carbon.[1] Regarded mainly as nonessential (the body can manufacture some amount), glutamine is essential for proper immune system function and GI integrity (adequate amounts are produced by the intestinal mucosa, but not in amounts necessary in times of extreme physiologic stress), and plays a role in maintaining overall amino acid balance in the body. Because of these essential roles, glutamine should, more appropriately, be considered a conditionally essential amino acid.[2]

Gastrointestinal Health: Oral Mucositis

Oral ingestion of glutamine is useful for treating mucositis, an inflammatory condition of the mucous membranes that often results from chemotherapy or radiation therapy. Glutamine treatment can reduce the development and severity of mucositis and can shorten the duration of mouth pain in patients undergoing the aforementioned therapies.[3] Glutamine supplementation is a highly cost-effective treatment for patients who undergo cancer treatments. In addition to chemotherapy-induced anorexia, painful sores in the oral mucosa can make eating an unpleasant or even intolerable experience for these patients who desperately need good nutrition during the course of therapy. Providing glutamine for such patients, and healing their mucositis, can improve their quality of life at a time when such support is much needed. GI cells are some of the most rapidly dividing cells in the body, and chemotherapy (as a side effect) targets these rapidly dividing cells, thus patients are at an increased risk of developing GI problems.

Glutamine supplementation can help prevent GI toxicity induced by chemotherapy and radiation, thereby assisting normal GI function.[4] In animal models, glutamine supplementation reduced whole-body protein breakdown rate during chemotherapy in tumor-bearing rats. In addition, glutamine supplementation in patients with esophageal cancer demonstrated enhanced lymphocyte mitogenic function and reduced permeability of the intestines during radiochemotherapy.[5] Glutamine is a preferential metabolic substrate for the enterocytes and is thought to play a regulatory role in the intestinal tissue by influencing cellular proliferation and differentiation.[6] As a result, the GI tract is the largest consumer of glutamine in the body[7]; suboptimal dietary amounts of glutamine can lead to atrophic changes, including ulceration and necrosis of the intestinal tissue.

Immune Function

Similar to the cells of the GI system, certain cells of the immune system utilize glutamine preferentially during times of unusual stress. Even at times of relative physiologic normalcy, lymphocytes and macrophages consume glutamine at high rates.[8] The intricate relationship between skeletal muscle glutamine stores and plasma levels of this amino acid is thought to influence immune function directly. Muscular overuse can lead to reduced levels of glutamine in the plasma and, thereby, may have a negative effect on lymphocyte function. The ''glutamine hypothesis'' suggests that, at times when muscular cells are under intense and prolonged physical stress, the demand for glutamine in the muscle itself and in other organs may leave the lymphoid system in a state of relative glutamine scarcity. This is supported by studies that demonstrate a sharp decline in plasma glutamine concentration following long-term physical stress.[9] Low plasma levels of glutamine are associated with overtraining as well.[10] Given this evidence, however, some studies[11,12] have demonstrated that, even though glutamine supplementation was able to offset postexercise drops in glutamine levels, postexercise immunodeficiency was not significantly altered. Researchers are still not certain if the quantitative decline in plasma glutamine is actually great enough to compromise immune-cell function or if intracellular glutamine concentrations are reduced because of declining plasma levels postexercise.

Because of this uncertainty, some researchers speculate that the glutamine hypothesis explains immune function decline in relation to stressful conditions adequately, but low plasma levels following exercise do not entirely explain postexercise immunodeficiency.[13] Despite these findings, the literature is full of evidence that supports the need for exogenous glutamine supplementation in maintaining immune function in very ill patients and the utility of this amino acid in supporting muscle protein mass. When given to endurance athletes, glutamine was able to reduce the incidence of self-reported illness significantly.[14] Immune function itself is a very broad term and, thus, simply stating that glutamine benefits the immune system is a very nonspecific claim. More research points to neutrophils as possible immune-system beneficiaries specific to glutamine supplementation.[15] The majority of studies using glutamine for immunodeficient conditions used doses ranging from 3 to 6 g per day at a minimum. Other studies have used amounts ranging from 500 mg=kg per day in patients with radiation mucositis[16] to 40 g per day in patients[17] with HIV.

GLYCINE AND DIMETHYLGLYCINE

Glycine is a nonessential amino acid and is derived (in the body) from serine. Typically, a person may consume roughly 2 g of glycine as part of a standard diet (rich in meat, fish,

Table 32–1. Dosing Review for Select Amino Acids

Amino acid	Comments
Glutamine	Gastrointestinal-related conditions: Typical doses are 4 g, swished and swallowed (can be taken several times per day) Immune function: Most studies have shown benefit using doses from 3 to 6 g per day
Glycine	Typical doses start at 4 g per day and are increased by 4 g per day
Dimethylglycine	Typical dose is 125 mg per day, with food
N-acetyl-carnitine	Alzheimer's disease: 1,500–4,000 mg, in divided doses, per day Age-related memory impairment: 1,500–2,000 mg per day Stroke recovery: 1,500 mg per day Age-related depression: 1,500–3,000 mg, in divided doses, per day
Arginine	Typical doses range from 3 to 20 g per day, in divided doses
DL-phenylalanine	150–200 mg per day
Tyrosine	100–150 mg=kg per day

Notes: There are no recommended daily allowances for any of the amino acids in this chart.
See "Conclusions" in the text for information about the importance of vitamin B_6.

legumes, and dairy products). Glycine is transported easily into the brain and acts primarily as an inhibitory neurotransmitter. Brain concentrations of glycine are mainly stable with an adequate diet; however, supplemental intake can bolster central nervous system concentrations.[18]

Glycine binds avidly with receptors in the locus ceruleus, a group of cell bodies located in the pons of the midbrain, and inhibits noradrenergic cell discharge. The locus ceruleus contains mainly norepinephrine neurons and is considered to be a key brain center for anxiety, arousal, fear, and vigilance. Norepinephrine released from the locus ceruleus affects other parts of the brain (namely the nucleus accumbens), which can then lead to more feelings of anxiety and panic as well as an increased sense of energy. The locus ceruleus may be up-regulated in addictive states as well.

Addictions, Stress, Anxiety, and Insomnia

Glycine, because of its effects on this one area of the brain, can be used as an adjunctive treatment in several conditions. In people suffering from drug and alcohol dependency, it is thought that this area of the brain is periodically up-regulated, leading to excessive norepinephrine release. People who become dependent on substances may use drugs or alcohol to satisfy the cravings created by an up-regulated locus ceruleus. Other conditions in which glycine can be useful for down-regulation of the locus ceruleus are panic disorders, nervous tension, anxiety, substance withdrawal, and insomnia (which is marked by awakening with anxiety). Glycine also interacts in an inhibitory action with motor neurons in the spinal cord and can have a calming effect on muscle spasms, muscle twitching, guarding, and rigidity that results from excessive spinal reflex activity. Glycine can inhibit spasms associated with the urinary and reproductive systems as well.[19]

Potentials for Other Amino Acids

The realm of amino acids and their treatments is of course not limited to those included in this chapter. We encourage readers to investigate the many other amino acids available for treating a multitude of other medical conditions. Some of these include:

Alanine—blood-sugar regulation
Branched chain amino acids (leucine, isoleucine, and valine)—postoperative conditions, liver disease
Citrulline—cholesterol and cancer; as a precursor to nitric oxide
Cysteine and glutathione—as detoxification and anti-aging agents
Histidine—for arthritis
Lysine—herpes and osteoporosis
Methionine—cystitis and allergy
Ornithine—as a potential growth-hormone imitator
Phenylalanine—pain relief
Proline and hydroxyproline—telopeptides, collagen, and aging
Serine—psychiatric disorders, mood, and memory
Threonine—immune system function, precursor to phosphatidylserine
Tyrosine—antidepressant
Tryptophan and melatonin—anxiety, depression, and sleep disorders
Taurine—antiseizure.

Schizophrenia

Glycine works as an agonist at another type of receptor site in the central nervous system: the N-methyl-D-aspartate (NMDA) receptor. NMDA receptors are associated with memory and learning[20] and are thought to play a role in both the negative and positive symptoms of schizophrenia.[21] Schizophrenia is thought to be associated with underactivity of glutamatergic receptors, especially the NMDA type. In schizophrenic patients, those who have demonstrated resistance to therapy using singular antipsychotic medications have experienced a decreased amount of schizophrenic symptoms with glycine treatment.[22] Glycine was also shown to reduce depressive and cognitive symptoms in these patients. In the study with the patients who were resistant to singular antipsychotics, the investigators noted that the greatest symptomatic improvements were made in subjects with the lowest baseline serum glycine amounts. However, another investigation revealed that, when used with the atypical neuroleptic drug clozapine, glycine demonstrated no statistically significant change in symptoms or cognitive functioning,[23] while another study showed that patients treated with clozapine without glycine (in comparison to another group treated with both) fared better in terms of symptom reduction.[24] These investigators concluded, based on their findings, that glycine may interfere with atypical neuroleptics such as clozapine.

Dimethylglycine

Dimethylglycine (DMG) is a methylated form of the amino acid glycine. DMG is produced in the body, but exists for only a few seconds before undergoing conversion. (It is formed from

betaine as homocysteine is methylated).[25] Acting as a methyl group donor, DMG has a reputation for benefiting children with autism, who have symptomatic improvement within days of taking the supplement. Other research shows that DMG also has an immune-enhancing effect. Both humoral and cell-mediated immune responses are increased with DMG supplementation.[26] DMG is absorbed in the small intestine and metabolized in the liver to monomethylglycine or ''sarcosine,'' which, in turn, is converted into glycine. DMG has been shown to have anticonvulsant effects in patients with mixed complex partial and grand mal seizures.[27] Some research has investigated DMG for improvement of oxygen utilization, liver function, and athletic performance.[28]

N-ACETYL-CARNITINE

Derived from the amino acid carnitine, N-acetyl-carnitine is an ester form of carnitine; it is sometimes referred to as acetyl-L-carnitine and is structurally similar to the neurotransmitter acetylcholine. Formed in small amounts inside the mitochondria, N-acetyl-carnitine is a precursor to the molecule acetyl coenzyme A (which is, in turn, a structural segment of acetylcholine[29]) and is thought to enhance the activity of the cholinergic nervous system. In addition, N-acetyl-carnitine assists transportation of acetyl groups into the mitochondria and enhances production and release of the neurotransmitter acetylcholine.[30]

Neurologic Function

N-acetyl-carnitine is also thought to have neuroprotective effects, assisting the serotonin neurotransmitter pathways, enhancing transmission of nerve impulses in the brain, and decreasing loss of age-related glucocorticoid receptors in the hippocampus. In conditions of compromised cerebrovascular blood flow, N-acetyl-carnitine may increase blood flow to the brain in patients with cerebrovascular disease.[31] N-acetyl-carnitine is also beneficial for people with vascular dementia and those who are recovering from strokes.[32] This amino acid has improved cerebral blood flow in people with chronic brain ischemia after only one dose.[33] The supplement can improve memory and visual–spatial orientation skills in individuals with cognitive impairment who are recovering from alcohol dependency.[34] Similarly, N-acetyl-carnitine may improve cognitive function and memory in people with age-related cognitive decline and memory impairment.[35] Much research has been done, using this compound, to help people with Alzheimer's disease, which is marked by a significant decrease in acetylcholine and cholinergic neurons.[36]

AIDS, Energy, Fertility

Other uses of this amino acid include impeding the decline of CD4 lymphocytes in patients with acquired immunodeficiency syndrome (AIDS).[37] N-acetyl-carnitine is also used for treating HIV medication–related neuropathy.[38] Similar to carnitine, N-acetyl-carnitine improves energy production and is included in formulas designed for weight loss, as this compound assists in the transport of long-chain fatty acids into the mitochondria, where they are used for energy production.[36] N-acetyl-carnitine is found in the seminal fluid and sperm and is used to improve sperm motility; this compound has been found to be low in infertile and low-motility sperm samples.[39]

ARGININE

Arginine is a conditionally essential amino acid because it can be synthesized from the amino acids glutamine, glutamate, and proline. Despite this, dietary intake remains the preferred means of obtaining this amino acid because the rate of arginine synthesis in the body is not altered in response to depletion or low supplies.[40] Arginine exerts many positive effects in the body, not all of which are covered here. One area where arginine has significant use and effect is on the endocrine system, specifically adrenal and pituitary function. Arginine is well-known for its ability to stimulate catecholamine release, insulin and glucagon, prolactin, and growth hormone.[41] The mechanism of action behind these effects is not well understood at present.

Immune Function

A potent immune system modulator, arginine is useful for treating suboptimal immune responses and can reduce the occurrence of postsurgical infections. Supplemental arginine can decrease the amount of cell-adhesion molecules (useful for preventing viral and bacterial entry) and lowers pro-inflammatory cytokines; arginine's effects on these molecules are thought to alter the balance of cytokines positively. In one study, arginine (30 g per day, for three days) up-regulated natural-killer cell activity, lymphocyte reactivity, and lymphokine activation of natural-killer cells in patients with breast cancer.[42] Conversely, arginine may promote tumor growth by providing a source of nitrogen.[43]

Cardiovascular System

Arginine is best known for its effects on the cardiovascular system. It is a substrate for nitric oxide synthase, which converts arginine into nitric oxide (NO) in the vascular endothelial cells. NO is also known as endothelium-derived relaxation factor that causes vasodilation in the vasculature. Many of arginine's effects are thought to be the result of this effect. NO itself is a vastly important molecule in several vascular-related conditions including maintenance of blood pressure[44] and proper myocardial function.[45]

Angina Pectoris

Arginine has been shown to reduce the symptoms of angina pectoris and increase exercise tolerance and improve quality of life in people with various grades (class II, III, and IV) of the condition.[46] In patients with class IV angina pectoris, who do not benefit from standard antianginal medications, arginine was thought to provide a significant clinical benefit.[47] Not all investigations of arginine and angina pectoris have shown a benefit, however.

Congestive Heart Failure

Patients with congestive heart failure (CHF) experience reduced peripheral blood flow at rest and exercise. NO derived from arginine can assist regulation of blood flow in these patients. In a double-blind trial, investigators demonstrated a significant improvement in blood flow, arterial compliance, and functional status in patients who received doses ranging from 5.6 to 12.6 g of arginine, three times a day, for six weeks, over patients on a placebo.[48] Another study demonstrated positive effects on kidney function (important in CHF) as evidenced by increased

glomerular filtration rate, creatinine clearance, and elimination of sodium and water following saline loading.[49]

Other Uses

Arginine has demonstrated usefulness for addressing several other vascular-related conditions, including erectile dysfunction,[50] peripheral artery disease,[51] and renal transplants.[52] Other conditions include AIDS-related wasting syndrome,[53] interstitial cystitis,[54] necrotizing enterocolitis,[55] and postsurgical recovery.[56]

L-TYROSINE AND L-PHENYLALANINE

Phenylalanine is an essential amino acid metabolized into tyrosine. Tyrosine is the precursor used for the synthesis of norepinephrine, epinephrine, and dopamine. In a double-blind study, DL-phenylalanine at a dosage of 150–200 mg per day or the pharmaceutical imipramine at 150–200 mg per day was administered to a group of depressed patients for 30 days. No statistical difference could be found between these two drug treatment groups, suggesting antidepressant activity of phenylalanine. In an open study, DL-phenylalanine in doses from 75–200 mg per day was administered to 20 depressed patients for 20 days. The results showed that 60% of patients had complete or ''good'' response to treatment.[57] Depletion of brain stores of norepinephrine is associated with stress-induced impairment of performance. Research shows tyrosine supplementation improves stress-associated declines in both neural norepinephrine levels and performance.[58] In addition, individuals under psychosocial and physical stress who were supplemented with tyrosine performed better on memory and tracking tasks.[59] Tyrosine supplementation generally ranges from 100–150 mg=kg.

L-THEANINE

Theanine is an amino acid found in high concentrations in green tea. Theanine can pass through the brain-blood barrier and may play an agonist or an antagonist of some receptors. Research has shown that L-theanine supplementation does provide some relaxing effects possibly by increasing levels of GABA and serotonin.[60] A small study showed that administration of 200 mg of L-theanine increased alpha brain wave activity and induced a sense of relaxation.[61] L-theanine is also known to block the binding of L-glutamic acid to glutamate receptors in the brain. A double-blind placebo-controlled study showed that L-theanine intake resulted in a reduction in the heart rate and salivary immunoglobulin A responses to an acute stress task compared to the placebo group, likely attributable to an attenuation of sympathetic nervous activation suggesting anti-stress activity of theanine.[62] Using animal models, L-theanine has been shown to cause dopamine release from dopaminergic neurons and may inhibit excitatory neurotransmission and cause inhibitory neurotransmission via glycine receptors, suggesting a possible mechanism for its anxiolytic activity.[63]

CONCLUSIONS

When using amino acids for treatment, a highly important dietary consideration should be kept in mind. Vitamin B_6 (pyridoxine) is necessary for the metabolism of amino acids, lipids, and

carbohydrates in the body. Converted into the coenzymes pyridoxal phosphate and pyridoxamine phosphate, vitamin B_6 is involved in the function of approximately 60 enzyme systems including transamination of amino acids, the synthesis of gamma-aminobutyric acid in the brain, and the conversion of tryptophan to niacin. Vitamin B_6 plays a critical role in healthy brain function because of the vitamin's role in producing amino acid–based neurotransmitters (serotonin, dopamine, melatonin, epinephrine, and norepinephrine). Finally, vitamin B_6 is needed for the metabolism of the amino acid homocysteine, which is an independent risk factor for cardiovascular disease. More amino acids than the ones covered in this chapter have potential for addressing a range of conditions either for prevention or treatment (see the box on page 367 entitled "Potentials for Other Amino Acids").

REFERENCES

[1]Griffiths RD. Glutamine: Establishing clinical indications. Curr Opin Clin Nutr Metab Care. 1999;2: 177–182.

[2]Kusumoto I. Industrial production of L-glutamine. J Nutr. 2001;131:255(suppl.):2S–5S.

[3]Anderson PM, Schroeder G, Skubitz KM. Oral glutamine reduces the duration and severity of stomatitis after cytotoxic cancer chemotherapy. Cancer. 1998;83:1433–1439.

[4]Anderson PM, Ramsay NK, Shu XO. Effect of low-dose oral glutamine on painful stomatitis during bone marrow transplantation. Bone Marrow Transpl. 1998;22:339–344.

[5]Yoshida S, Kaibara A, Ishibashi N, et al. Glutamine supplementation in cancer patients. Nutrition. 2001; 17:766–788.

[6]Reeds PJ, Burrin DG. Glutamine and the bowel. J Nutr. 2001;131(suppl.):2505S–2508S.

[7]Miller AL. Therapeutic considerations of L-glutamine: A review of the literature. Altern Med Rev. 1999;4:239–248.

[8]Newsholme EA, Parry Billings M. Properties of glutamine release from muscle and its importance for the immune system. J Parenteral Enteral Nutr. 1990;14(suppl.):63S–67S.

[9]Keast D, Arstein D, Harper W, et al. Depression of plasma glutamine concentration after exercise stress and its possible influence on the immune system. Med J Aust. 1995;162:15–18.

[10]Rowbottom DG, Keast D, Morton AR. The emerging role of glutamine as an indicator of exercise stress and overtraining. Sports Med. 1996;21:80–97.

[11]Rohde T, Asp S, MacLean DA, et al. Competitive sustained exercise in humans, lymphokine activated killer cell activity, and glutamine: An intervention study. Eur J Appl Physiol. 1998;78:448– 453.

[12]Rohde T, MacLean D, Pedersen BK. Effect of glutamine on changes in the immune system induced by repeated exercise. Med Sci Sports Exerc. 1998;30:856–862.

[13]Hiscock N, Pedersen BK. Exercise-induced immunodepression: Plasma glutamine is not the link. J Appl Physiol. 2002;93:813–822.

[14]Castell L. Glutamine supplementation in vitro and in vivo, in exercise and in immunodepression. Sports Med. 2003;33:323–345.

[15]Castell LM. Can glutamine modify the apparent immunodepression observed after prolonged, exhaustive exercise? Nutrition. 2002;18:371–375.

[16]Rubio IT, Cao Y, Hutchins LF. Effect of glutamine on methotrexate efficacy and toxicity. Ann Surg. 1998;227:772–778.

[17]Shabert JK, Winslow C, Lacey JM, et al. Glutamine-antioxidant supplementation increases body cell mass in AIDS patients with weight loss: A randomized, double-blind controlled trial. Nutrition. 1999;15: 860–864.

[18]Heresco-Levy U, Javitt DC, Ermilov M. Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. Arch Gen Psychiatry. 1999;56:29–36.

[19]Mitchell WA. Foundations of Natural Therapeutics: Biochemical Apologetics of Naturopathic Medicine. Tempe: Southwest College Press, 1997.

[20]File SE, Fluck E, Fernandes C. Beneficial effects of glycine (bioglycin) on memory and attention in young and middle-aged adults. J Clin Psychopharmacol. 1999;19:506–512.

[21]Javitt DC, Balla A, Sershen H, et al. A.E. Bennett Research Award: Reversal of phencyclidine-induced effects by glycine and glycine transport inhibitors. Biol Psychiatry. 1999;45:668–679.

[22]Heresco-Levy U, Javitt DC, Ermilov M. Double-blind, placebo-controlled, crossover trial of glycine adjuvant therapy for treatment-resistant schizophrenia. Br J Psychiatry. 1996;169:610–617.

[23]Evins AE, Fitzgerald SM, Wine L. Placebo-controlled trial of glycine added to clozapine in schizophrenia. Am J Psychiatry. 2000;157:826–828.
[24]Potkin SG, Jin Y, Bunney BG, et al. Effect of clozapine and adjunctive high-dose glycine in treatment-resistant schizophrenia. Am J Psychiatry. 1999;156:145–147.
[25]Freed WJ. N,N-dimethylglycine, betaine and seizures [letter]. Arch Neurol. 1984;41:1129–1130.
[26]Reap EA, Lawson JW. Stimulation of the immune response by dimethylglycine, a nontoxic metabolite. J Lab Clin Med. 1990;115:481–486.
[27]Roach ES, Carlin L. N,N dimethylglycine for epilepsy [letter]. N Engl J Med. 1982;307:1081–1082.
[28]Gray ME, Titlow LW. The effect of pangamic acid on maximal treadmill performance. Med Sci Sports Exerc. 1982;14:424–427.
[29]Pettegrew JW, Levine J, McClure RJ. Acetyl-L-carnitine physical–chemical, metabolic, and therapeutic properties: Relevance for its mode of action in Alzheimer's disease and geriatric depression. Mol Psychiatry. 2000;5:616–632.
[30]Mayeux R, Sano M. Treatment of Alzheimer's disease. N Engl J Med. 1999;341:1670–1679.
[31]Micromedex Healthcare Series. Englewood, CO: Micromedex, Inc.
[32]Kidd PM. A review of nutrients and botanicals in the integrative management of cognitive dysfunction. Altern Med Rev. 1999;4:144–161.
[33]Postiglione A, Soricelli A, Cicerano U. Effect of acute administration of L-acetyl carnitine on cerebral blood flow in patients with chronic cerebral infarct. Pharmacol Res. 1991;23:241–246.
[34]Tempesta E, Troncon R, Janiri L. Role of acetyl-L-carnitine in the treatment of cognitive deficit in chronic alcoholism. Int J Clin Pharmacol Res. 1990;10(1–2):101–107.
[35]Cucinotta D, Passeri M, Ventura S. Multicenter clinical placebo-controlled study with acetyl-L-carnitine (ALC) in the treatment of mildly demented elderly patients. Drug Development Res. 1988;14:213–216.
[36]Thal LJ, Carta A, Clarke WR. A 1-year multicenter placebo-controlled study of acetyl-L-carnitine in patients with Alzheimer's disease. Neurology. 1996;47:705–711.
[37]Di Marzio L, Moretti S, D'Alo S. Acetyl-L-carnitine administration increases insulin-like growth factor 1 levels in asymptomatic HIV-1-infected subjects: Correlation with its suppressive effect on lymphocyte apoptosis and ceramide generation. Clin Immunol. 1999;92:103–110.
[38]Famularo G, Moretti S, Marcellini S. Acetyl-carnitine deficiency in AIDS patients with neurotoxicity on treatment with antiretroviral nucleoside analogues. AIDS. 1997;11:185–190.
[39]Golan R, Weissenberg R, Lewin LM. Carnitine and acetyl-carnitine in motile and immotile human spermatozoa. Int J Androl. 1984;7:484–494.
[40]Castillo L, Ajami A, Branch S, et al. Plasma arginine kinetics in adult man: Response to an arginine-free diet. Metabolism. 1994;43:114–122.
[41]Appleton J. Arginine: Clinical potential of a semi-essential amino. Altern Med Rev. 2002;7:512–522.
[42]Brittenden J, Park KGM, Heys SD, et al. L-arginine stimulates host defenses in patients with breast cancer. Surgery. 1994;115:205–212.
[43]Park KG. The immunological and metabolic effects of L-arginine in human cancer. Proc Nutr Soc. 1993; 52:387–401.
[44]Umans JG, Levi R. Nitric oxide in the regulation of blood flow and arterial pressure. Annu Rev Physiol. 1995;57:771–790.
[45]Hare JM, Colucci WS. Role of nitric oxide in the regulation of myocardial function. Prog Cardiovasc Dis. 1995;38:155–166.
[46]Ceremuzynski L, Chamiec T, Herbaczynska-Cedro K. Effect of supplemental oral L-arginine on exercise capacity in patients with stable angina pectoris. Am J Cardiol. 1997;80:331–333.
[47]Blum A, Porat R, Rosenschein U. Clinical and inflammatory effects of dietary L-arginine in patients with intractable angina pectoris. Am J Cardiol. 1999;15:1488–1490.
[48]Rector TS, Bank A, Mullen KA. Randomized, double-blind, placebo controlled study of supplemental oral L-arginine in patients with heart failure. Circulation. 1996;93:2135–2141.
[49]Watanabe G, Tomiyama H, Doba N. Effects of oral administration of L-arginine on renal function in patients with heart failure. J Hypertens. 2000;18:229–234.
[50]Chen J, Wollman Y, Chernichovsky T, et al. 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. 1999;83:269–273.
[51]Boger RH, Bode-Boger SM, Thiele W, et al. 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. 1998;32:1336–1344.
[52]Andres A, Morales JM, Praga M, et al. L-arginine reverses the antinatriuretic effect of cyclosporin in renal transplant patients. Nephrol Dial Transplant. 1997;12:1437–1440.

[53]Clark RH, Feleke G, Din M, et al. Nutritional treatment for acquired immunodeficiency virus-associated wasting using beta-hydroxy betamethylbutyrate, glutamine, and arginine: A randomized, double-blind, placebo-controlled study. J Parenter Enteral Nutr. 2000;24:133–139.

[54]Ehren I, Lundberg JO, Adolfsson J, et al. Effects of L-arginine treatment on symptoms and bladder nitric oxide levels in patients with interstitial cystitis. Urology. 1998;52:1026–1029.

[55]Amin HJ, Zamora SA, McMillan DD, et al. Arginine supplementation prevents necrotizing enterocolitis in the premature infant. J Pediatr. 2002;140:425–431.

[56]Daly JM, Lieberman MD, Goldfine J, et al. Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: Immunologic, metabolic and clinical outcome. Surgery. 1992;112:56–67.

[57]Beckmann H, Strauss MA, Ludolph E. DI-phenylalanine in depressed patients: an open study. J Neural Transm. 1977;41(2–3):123–134.

[58]Salter CA. Dietary tyrosine as an aid to stress resistance among troops. Mil Med. 1989 Mar;154(3): 144–146.

[59]Deijen JB, Wientjes CJ, Vullinghs HF, Cloin PA, Langefeld JJ. Tyrosine improves cognitive performance and reduces blood pressure in cadets after one week of a combat training course. Brain Res Bull. 1999 Jan 15;48(2):203–209.

[60]Lu K, Gray MA, Oliver C, Liley DT, Harrison BJ, Bartholomeusz CF, Phan KL, Nathan PJ. The acute effects of L-theanine in comparison with alprazolam on anticipatory anxiety in humans. Hum Psychopharmacol. 2004 Oct;19(7):457–465.

[61]Anon. L-theanine. Monograph. Altern Med Rev. 2005 Jun;10(2):136–138.

[62]Kimura K, Ozeki M, Juneja LR, Ohira H. L-Theanine reduces psychological and physiological stress responses. Biol Psychol. 2007 Jan;74(1):39–45. Epub 2006 Aug 22.

[63]Yamada T, Terashima T, Okubo T, Juneja LR, Yokogoshi H. Effects of theanine, r-glutamylethylamide, on neurotransmitter release and its relationship with glutamic acid neurotransmission. Nutr Neurosci. 2005 Aug;8(4):219–226.

33

COFFEE—FUNCTIONAL FOOD AND MEDICINAL HERB

Coffee (Coffea arabica) is the second-largest worldwide commodity, overshadowed only by crude oil. Without question, coffee is the most frequently consumed functional food around the globe: In the United States alone there are 108 million coffee consumers who spend $9.2 billion in the retail sector and $8.7 billion in the food service sector each year.[1] And these numbers represent only a fraction of the global population, large numbers of whom incorporate coffee as a staple in their cultural practices.

Coffee also has a rich medical history. The therapeutic benefits of coffee are now supported by a rapidly growing and significant level of scientific validation. The epidemiologic significance of the research in the field of coffee cannot be overstated, considering the prevalence of coffee ingestion among the peoples of the world. Beyond the cultural and medical ramifications of coffee consumption, the fact is that coffee is big business with huge social, environmental, and economic impacts. The National Coffee Association reported that in 2000, 54% of the U.S. adult population drank coffee.[2] The average consumption per capita in the United States is approximately 4.4 kg annually at a cost of $164.71 per individual. Among U.S. coffee drinkers, the average consumption is 3.1 cups of coffee per day.[2] These statistics provide compelling motivation to investigate the consequences of such large-scale consumption of this beverage. What follows is a review of some of the most recent research into the active constituents and potential clinical applications of the functional food that is humbly known as the coffee bean.

Noteworthy is that this discussion focuses on the benefits of coffee from a botanical perspective. The social use of coffee in its modified forms ''latte'' or ''mocha,'' where dairy and sugary flavors are added, are clear sources of empty calories. For diabetics and weight management many a clinician will find in discussion with their patients that indeed an enlarging waistline, reactive hypoglycemia, and increased blood sugars do not implicate coffee, but the chosen delivery of this therapeutic food ''à la empty calories.''

COFFEE BEAN CHEMISTRY

Coffee's bioactive profile contains many of the most important constituents known to exist within functional foods: flavonoids (catechins, anthocyanins), caffeic acid, and ferulic acid.[3] Additional biologically active components found in coffee include nicotinic acid, trigonelline, quinolinic acid, tannic acid, pyrogallic acid, and caffeine.[4] A simple chemical analysis of whole green and roasted coffee beans shows their chemical constituents and the metabolic changes that occur during processing, preparation, and ingestion, all of which warrant further investigation. An illustrative case in point is the significant niacin content that is formed from trigonelline during the roasting process, producing between 2 and 80 mg of niacin per cup of coffee.[5] Thus, although niacin is not abundantly present in the nonroasted bean, processing itself generates spikes in niacin content that depend on bean quality and the roasting and preparation processes. This raises the question of what other changes occur during the roasting process that might further augment the therapeutic benefits of the coffee bean.[6] Beyond its

phytochemical components, this beverage also provides an array of minerals and other nutrients. A single cup of coffee can provide 8% of the daily intake of chromium[7] as well as being a significant source of magnesium.[8] It has also been reported that the coffee brewing process can help remove toxic metals, such as lead, from contaminated water sources.[9] There is little question that over the next decade the field of coffee research will flourish, and yet-to-be-identified biogenic substances and their therapeutic indices will be elucidated.

ANALYZING THE ANALYSIS OF COFFEE

The investigation of the therapeutic effects of coffee has endured the same shortcomings that plague most of the whole-plant research paradigm. The concept that "one size fits all" simply does not apply to botanicals in the same manner that it does to isolated drug therapies. The standard scientific model, in its attempt to apply a reductionistic methodology, has generally failed to consider coffee as a whole plant complex that is not divisible into single chemical isolates. Just as studying the benefits of beta-carotene is not the same as studying the benefits of eating a carrot, studying the benefits (and downfalls) of caffeine is not the same as understanding what it is that makes coffee a useful medicinal plant. Divergent thinking, as opposed to a convergent analysis of medicinal plants, provides the foundation for the discovery of new and synergistic constituent blends that may make an impact on the physiology of human health. This concept is not foreign to the coffee research community, which has had to be introspective as it investigates why, exactly, research findings in the field remain inconsistent and at times lack reproducibility. Conclusions thus far suggest that variations in the concentration of caffeine and other active constituents, as well as the total volume of fluid consumed, have contributed to the variations in the accuracy of clinical findings. Epidemiologic studies reflect these "discrepancy factors."[10] The scientific literature reports that confounding variables lead to conflicting results in the analysis of the impact of coffee on health.[11] In short, removing culture, diet, and lifestyle from the analyses generates data that are not grounded in the traditional applications of coffee within a given populace, thus diminishing the studies' clinical relevance.

In reviewing the diversity of international coffee consumption, factoring in bean roasting, brewing, and preferred methods of ingestion are all essential when seeking to determine the therapeutic effects of the coffee bean.[12] In reviewing eight European and U.S. brewing techniques and roasting methods, wide variations were noted. Brewing techniques alone result in differing levels of active constituents, such as diterpene levels, which consequentially have an impact on therapeutic breadth and efficacy.[13]

This chapter highlights the positive benefits of coffee; yet, as with all herbal products, one size does not fit all. Therefore, those people who have underlying health conditions—such as high blood pressure, fibrocystic breast disease, cardiac arrhythmias, peptic ulcers, anxiety, insomnia, or any other condition that might render one sensitive to the active constituents of coffee—should probably be advised to avoid using coffee as a medicinal food. And, as with all herbal products, people who want to avail themselves of the benefits of coffee should be advised that working closely with one's health care provider is essential.

COFFEE'S ANTIMICROBIAL EFFECTS

Reports of the use of coffee as folk medicine for treating sore throats, colds, and other ailments abound. These empirical observations are now supported by a growing body of scientific

Selected Active Constituents and Classes of Active Constituents in Coffea arabica

Agmatine	Diterpene	Quinolinic acid
Anthocyanins	Ferrulic acid	Serotonin
Caffeic acid	Flavonoids	Soluble fiber
Caffeine	Magnesium	Spermidine
Catechins	Nicotinic acid	Tannic acid
Chlorogenic acid	Polyphenols	Trigonelline
Chromium	Pyrogallic acid	

literature suggesting that antibacterial and antiviral properties may be present in coffee. Namba and Matsuse reported that coffee can lessen the physiologic damage that may arise during viral infections.[14] Antibacterial properties have been reported to arise from caffeic acid, chlorogenic acid, and protocatechnic acid, all of which are present in coffee.[15] Antiadhesive properties have been attributed to roasting-induced molecular changes (e.g., that roasting helps prevent the attachment of bacterial fimbriae to the mucosal membranes). In one study, antiadhesive properties were associated with a specific influence on Streptococcus mutans.[16,17] S. mutans is frequently associated with chronic oral pharyngeal infections, including recurrent tonsillitis. Although clinical studies have yet to be conducted, applying the concept of antiadhesive properties by gargling with coffee to decrease virulence and host burden may hold clinical promise. As a clinical note, when considering the concept of antiadhesive therapeutic interventions, it may be helpful to recall that a prominent mechanism that supports the use of the cranberry in the treatment of bladder infections is the berry's antiadhesive properties. Further research is needed to elucidate the antimicrobial effects of coffee; we would also propose investigation into the effects of naturally occurring tannins in coffee on the resistance of mucous membranes to penetration by infectious microbes.

COFFEE'S ANTIOXIDANT POWER

It is important to note that there is no such thing as a representative cup of coffee with a specific chemical profile. The origin of the bean; the agricultural practices that grew it; the variations between species; and the handling, processing, brewing, and preferred ingestion practices all serve as confounding variables when trying to perform a chemical analysis on a cup of coffee. However, one important control factor regarding the achieve-

Figure 33–1. Coffee (Coffea arabica).

ment of maximum antioxidant levels in coffee has been shown to occur from intermediate roasting techniques.[18,19] Coffee is a rich source of antioxidants, including those derived from the hydroxycinnamic acids family (caffeic, chlorogenic, coumaric, ferulic, and sinapic acids), flavonoids, and polyphenols.[20] Beyond the innate antioxidants found in unprocessed coffee beans, processing by-products have yielded newly formed antioxidants such as the recently discovered "silverskin," which is the innermost skin of the coffee fruit body. Silverskin clings to the dried coffee bean until it is removed by polishing or is liberated during roasting, and represents yet another new, functional ingredient in coffee that contains both soluble fiber and antioxidant activity.[21]

It has been determined that water is the best method for general antioxidant extraction. When four solvents were used—water, methanol, ethanol, and n-hexane—water extracts produced the highest yields of antioxidants and the best lipid-peroxidation protection. The water extract demonstrated a particularly high protective effect against oxidative damage to proteins. The water extract also showed superior free-radical scavenging, generally reducing the ability and capacity to bind ferrous ions, thus, reflecting its dynamic capacity as both a primary and secondary antioxidant. The concentration of flavonoids and polyphenolic compounds—both of which are commonly found in coffee—were 8,400 and 20,400 ppm, respectively.[22]

When evaluating the antioxidant properties of coffee, higher activity levels appear in vivo, after the coffee has been consumed, because colonic microflora metabolize most of the dietary phenols and therefore significantly increase antioxidant activity.[23] When reviewing the coffee literature, additional consideration must be taken into account regarding whether the coffee is consumed filtered or unfiltered. Consumption of unfiltered coffee (as in Italy) has been shown to increase plasma glutathione.[24] As an example of naturally occurring synergy, chlorogenic acid undergoes conjugation with glutathione, increasing the protective mechanism of both of these substances.[25] Revealing more about the unique properties and chemical profile of coffee, research has demonstrated that the melanoidins in coffee produce higher antioxidant activity than the melanoidins present in beer.[26]

This may all be academically interesting but what role might the antioxidant properties of coffee play in maintaining health? It has been concluded by the international scientific community that a Westernized diet is devoid of sufficient antioxidants, in large part the result of inadequate intake of fresh fruits and vegetables. It appears, however, that coffee may help fill this "antioxidant void," serving as a primary source of dietary antioxidants in Germany,[27] Spain,[28] the United States,[29] and probably many other countries.

COFFEE, ASTHMA, AND BRONCHITIS

Asthma and other pulmonary ailments continue to grow in prevalence in the United States. Interestingly, coffee rich in methylxanthines appears to confer a protective effect for maintaining healthy airway function. This is not surprising because another methylxanthine, theophylline, has been used over the years as a prescription asthma medication. Studies have shown that regular consumption of coffee reduces symptoms of asthma and lessens the probability of experiencing bronchial asthma.[30] Further pulmonary applications include using coffee to treat both acute and chronic airflow obstructive disease in smokers.[31] Coffee for treating acute and chronic bronchitis may prove to be a worthy area for further clinical investigation.

COFFEE AND CARDIOVASCULAR DISEASE

In the United States, cardiovascular disease leads to one death every 33 seconds and contributes to 70% of total deaths annually. This makes identifying functional foods as potential modifiers of this disease prevalence an invaluable endeavor. Researchers have investigated whether green coffee bean extract (GCBE), which is rich in chlorogenic acid, may be just such a disease modifier. In one study, two groups were created with 10 people ingesting a green coffee bean extract and 10 ingesting a placebo drink for four months. At the end of the study, the treatment group experienced significant decreases in total plasma homocysteine levels and improvements in vasoreactivity.[32] The ability of GCBE to make an impact on these two independent risk factors for cardiovascular disease progression is significant.

Other studies have shown that regular coffee intake has the potential to decrease the susceptibility of low-density lipoprotein to oxidation and decrease malondialdehyde levels.[33] Further research has examined the ability of caffeine (250 mg two times per day) to lower the incidence of cardiovascular events in patients with type 1 diabetes, demonstrating a positive effect.[34]

COFFEE'S IMPACT ON COGNITION AND MOOD

A popular use of coffee—particularly in vogue among college students—is drinking it to enhance one's ability to assimilate vast amounts of knowledge within finite periods of time. According to recent findings, consuming a few cups of coffee can indeed strengthen information processing and enhance the ability to monitor for erroneous outcomes.[35] The physiologic effects of challenging mental capacity increased catecholamine levels, and coffee drinking increased the concentration of both adrenaline and noradrenaline further, providing "in the moment" clarity. There was also an increased urinary excretion of adrenaline and noradrenaline after the ingestion of a single cup of coffee.[36] Another study tested the effects of spiking coffee with additional caffeine. The findings demonstrated that caffeine augmentation leads to faster encoding and enhanced information acquisition. Ingesting this high-caffeine coffee improved encoding of new information and counteracted the fatigue that developed over the test session.[37] The antifatigue properties of caffeine are well-documented among both bus drivers and airline pilots, and coffee has been documented to improve safety when discontinuing such activities is not an option.[38,39] Beyond improving learning and information-accessing capacities, there is evidence that drinking coffee can help improve mood as well.[40,41] The findings of at least one study pointed to an inverse correlation between caffeine consumption and suicidal ideation, although coffee is not being suggested as a suicide intervention technique.

COFFEE AND DIABETES

As early as the 1970s, research has documented a link between increased coffee consumption and reduced plasma glucose levels.[42] A study conducted in Japan demonstrated an inverse association between coffee drinking and the prevalence of fasting hyperglycemia.[43] More recent studies have shown that coffee consumption protects women from the development of diabetes[44] and further studies have shown that there is a statistically lower risk of developing type 2 diabetes with long-term coffee consumption.[45] Studies conducted in Sweden showed that coffee consumption improved insulin sensitivity in elderly nondiabetic men[46] and reduced the risk of both type 2 diabetes and impaired glucose tolerance in men and women who drank five or more cups per day.[47]

What is especially interesting is the investigation into the role of coffee as a potential modulator of the expression of genetic factors that might impart a tendency toward developing diabetes. Twin studies have shown that, if one twin consumes moderate amounts of coffee while the other twin consumes low levels, the twin consuming more coffee has a higher level of protection against developing diabetes.[48] Maintaining lean body mass is an important clinical factor in helping individuals with diabetes control glucose levels and helping patients with prediabetes gain control over otherwise precarious blood-sugar levels. Coffee, in addition to its other protective properties, has been found to increase metabolic rates in both obese and nonobese individuals, with significant metabolic increases in both groups.[49] A study of lean women demonstrated that coffee consumption increases thermogenesis and lipid oxidation.[50] There is also evidence of increased metabolic rates when coffee is consumed with the first morning meal.[51] Yet another study has identified an increase in skin temperature and caloric expenditure with coffee consumption.[52] When coffee and exercise are combined, there is a higher lipolytic response compared to exercise alone.[53] There is also growing evidence in the literature demonstrating the ability of both caffeine and methylxanthine to make a positive impact on cellular metabolic rates.[54] These findings have been applied broadly in the weight-loss supplement industry and are likely to become applied increasingly as other popular herbal thermogenic substances have been removed from the market.

COFFEE AND GASTROINTESTINAL AND LIVER HEALTH

The effects of coffee on the gastrointestinal (GI) tract, the liver, and the biliary tract are well-documented and have been attributed to the effects of caffeine and chlorogenic and caffeic acids. The effects of coffee as a laxative and digestive aid within the GI tract are triggered either directly or indirectly by the release of gastrin and other GI hormones.[55] Maintaining regular bowel movements is itself protective against GI disease; in addition, specific studies have demonstrated other potential protective effects of coffee for reducing the risk of serious overt disease processes, such as alcohol-induced pancreatitis.[56] Another clinically significant application for coffee appears to arise from its ability to help inhibit both alcoholic and nonalcoholic liver cirrhosis.[57,58]

Several studies have shown that coffee consumption can decrease the incidence or risk of Parkinson's disease.

Because of the unique relationship between caffeine and the hepatic microsomes that metabolize it, it has been proposed that fasting plasma caffeine concentration may serve as a guide to measuring the physiologic impairment arising from chronic liver disease.[59] Caffeine can provide, via hepatic detoxification testing, information on whether an imbalance between phase 1 and phase 2 detoxification pathways are present. The unique physiologic impact of caffeine in the liver has also led to research on the relationship between serum gamma glutamyltransferase—a measure of liver damage—and smoking that suggests coffee may help mitigate some of the damage associated with smoking demonstrated by decreased induction of gamma glutamyltransferase in smokers.[60] What also supports this trend is an observation of an increase in gamma glutamyltransferase in women from Norway who decreased their consumption of boiled coffee.

Finally, gallstone formation may be modified by coffee consumption according to a study of 46,008 men, ages 40 to 75, in which those who consumed two to three cups of coffee per day had a lower risk of forming gallstones.[61] It is noteworthy that all brewing techniques produced a reduction in incidence of stone formation, as long as the coffee had not been decaffeinated. It has also been shown that drinking caffeinated coffee decreases the risk of symptomatic gallstones in women but this has not been demonstrated in men.[62]

COFFEE, PARKINSON'S DISEASE, AND OTHER NEUROLOGIC CONDITIONS

Several studies have shown that coffee consumption can decrease the incidence or risk of Parkinson's disease. Indeed, evidence exists for protection against the incidence of Parkinson's disease in Asian-Americans [63] as well as in the general population in the United States,[64] Italy,[65] and China.[66] Additional studies support findings that coffee consumption lowers the risk of Parkinson's disease.[67] With an ever-increasing number of cases of Alzheimer's disease being diagnosed, interest in ways to mitigate this devastating illness is quite high. It appears that coffee might very well be the beverage of choice in this instance as well, as it has been associated with a reduced risk of Alzheimer's disease.[68,69] However, currently there is a lack of evidence that coffee slows nonspecific, age-related mental decline. There appears to be a synergistic effect between coffee and anticonvulsant therapy, when used together, that results in a reduction of sleep seizures.[70] However, this is not advisable for all patients with seizure disorders, because individual tolerances vary.

COFFEE AND SEXUAL ACTIVITY

A healthy sexual response is achieved when proper neurologic, cardiovascular, hormonal, and mental health is maintained. Common hormonal denominators for both men and women relative to sexual desire and response are total- and free-testosterone levels. It has been reported that total testosterone is positively associated with coffee consumption in men [71] and that drinking at least one cup of coffee per day increases sexual activity in elderly women and higher potency has also been reported in elderly men.

MISCELLANEOUS BIOGENIC AMINES

The variability seen in the chemical profiles of coffee, depending on the amount of roasting and the brewing technique used, cannot be overemphasized. As researchers continue to investigate the bioactive substances in coffee, these investigators have brought to the forefront a series of biogenic amines that become particularly prominent during the roasting process, such as serotonin, spermidine, and agmatine.[12] The efficacies and therapeutic applications of these biogenic amines have not yet been explored thoroughly but may lead to an entirely renewed appreciation of coffee's transcultural appeal to humanity as a whole.

CAFFEINE

No discussion on coffee would be complete without at least a brief review of caffeine. Until recent years, the word coffee was synonymous with caffeine. The scientific literature has attributed to caffeine coffee's ability to enhance mental alertness, reduce fatigue, and enhance wakefulness.[72] This review of the benefits of coffee has not focused on the benefits of caffeine specifically simply because an entire separate treatise would be necessary to do justice to the topic. It is important to realize that because caffeine is a well-known and documented biomarker in coffee research, the frequent large variations in levels of caffeine in prepared coffee serves as a point for consideration. The typical caffeine content in coffee ranges from 58 to 259 mg per dose. In one study, the mean caffeine content for a 16-ounce cup of coffee was 188 mg per dL.[73] There is an equally high variance in caffeine content reflected in a more recent study that shows a caffeine concentration range of 259–564 mg per dose in the same coffee beverage obtained from the same outlet on six consecutive days.[74] Thus, the question must be posed: What other active constituents varied within those same samples? We know that consistent dosing provides a level of clinical predictability, whether this involves standard drug therapies, nutritional interventions, botanicals, or functional foods. If we are to encourage the use of functional foods as tools in overall diet and lifestyle modifications, attempts must be made to provide consistent quality and therapeutic bioactivity.

CONCLUSIONS

Coffee is important for helping to sustain human health. Yet, if we are to prescribe coffee as a therapeutic intervention, it is essential that we understand its dynamic constituent profile better. It is even more important to note that, because current scientific research has yet to determine the best across-the-board method to achieve maximum therapeutic efficacy, coffee remains a food best consumed in its purest, most natural form. The epidemiologic studies that identify the most effective mix of coffee, diet, and lifestyle are providing us—as clinicians—with the most useful information as we seek to modify disease expression in our patients. There is a tremendous movement to help make the production of coffee a sustainable industry, and proposed guidelines for this endeavor seek to encourage the consumption of coffee that is shade-grown, organic, and fairly traded. To use coffee actively as medicine is to adhere to the guidance of Hippocrates, who stated in 400 b.c.: ''May your food be your medicine and your medicine be your food.''

REFERENCES

[1]Specialty Coffee Association of America (SCAA). SCAA 1999 Market Report. California, 1999.
[2]National Coffee Association (NCA). NCA Coffee Drinking Trend Survey. New York, 2000.
[3]Hasler CM. The changing face of functional foods. J Am Coll Nutr. 2000;19(suppl.):499–506.
[4]Minamisawa M, Yoshida S, Takai N. Determination of biologically active substances in roasted coffees using diode-array HPLC system. Anal Sci. 2004;20:325–328.
[5]Casal S, Oliveira MB, Alves MR, Ferreira MA. Discriminate analysis of roasted coffee varieties for trigonelline, nicotinic acid, and caffeine content. J Agric Food Chem. 2000;48:3420–3424.
[6]Adrian J, Frangne R. Synthesis and availability of niacin in roasted coffee. Adv Exp Med Biol. 1991;289:49–59.
[7]Santos EE, Lauria DC, Porto da Silveria CL. Assessment of daily intake of trace elements due to consumption of food stuffs by adult inhabitants of Rio de Janeiro city. Sci Total Env. 2004;327:69–79.

[8]Astier-Dumas M, Gounelle de Pantanel H. Some nutritional aspects of coffee [in French]. Arch Sci Med. 1974;131:18–23.
[9]Impellitteri CA, Allen HE, Lagos G, McLaughlin MJ. Removal of soluble Cu and Pb by the automatic drip coffee brewing process: Application to risk assessment. Hum Ecol Risk Assess. 2000;6:313–322.
[10]Stavric B, Klassen R, Watkinson B, et al. Variability in caffeine consumption from coffee and tea: Possible significance for epidemiological studies. Food Chem Toxicol. 1988;26:111–118.
[11]Kubo Shlonsky A, Klatsky AL, Armstrong MA. Traits of persons who drink decaffeinated coffee. Ann Epidemiol. 2003;13:273–279.
[12]Cirilo MPG, Coelho AFS, Araujo CM, et al. Profile and levels of bioactive amines in green and roasted coffee. Food Chem. 2003;82:397– 402.
[13]Urgert R, de Groot CP. Consumption of unfiltered coffee brews in elderly Europeans. Eur J Clin Nutr. 1996;50:101–104.
[14]Namba T, Matuse T. A historical study of coffee in Japanese and Asian countries: Focusing the medicinal uses in Asian traditional medicines. Yakushigaku Zasshi. 2002;37:65–75.
[15]Dogasaki C, Shindo T, Furuhata K, Fukuyama M. Identification of chemical structure of antibacterial components against Legionella pneumophilia in a coffee beverage. Yakugaku Zasshi. 2002;122:487– 494.
[16]Daglia M, Papetti A, Dacarro C, Gazzani G. Isolation of anti-bacterial components from roasted coffee. J Pharm Biomed Anal. 1998;18: 219–225.
[17]Daglia M, Tarsi R, Papetti A, et al. Antiadhesive effect of green and roasted coffee on Streptococcus mutans adhesive properties on saliva coated hydroxyapatite beads. J Agric Food Chem. 2002;50:1225–1229.
[18]Nicoli MC, Anese M, Parpinel M. Influence of processing on the antioxidant properties of fruits and vegetables. Trends Food Sci Technol. 1999;10:94–100.
[19]Nicoli MC, Anese M, Manzocco L, Lerici CR. Antioxidant properties of coffee brews in relation to the roasting degree. Lebens Wiss Technol. 1997;30:292–297.
[20]Manach C, Scalbert A, Morand C, et al. Polyphenols: Food sources and bioavailability. Am J Clin Nutr. 2004;79:727–747.
[21]Borrelli RC, Esposito F, Napolitano A, et al. Characterization of a new potential functional ingredient: Coffee silverskin. J Agric Food Chem. 2004;52:1338–1343.
[22]Yen WJ, Wang BS, Chang LW, Duh PD. Antioxidant properties of roasted coffee residues. J Agric Food Chem. 2005;53:2658–2663.
[23]Olthof MR, Hollman PCH, Katan MB. Chlorogenic acid and caffeic acid are absorbed in humans. J Nutr. 2001;131:66–71.
[24]Esposito F, Morisco F, Verde V, et al. Moderate coffee consumption increases plasma glutathione but not homocysteine in healthy subjects. Aliment Pharmacol Ther. 2003;17:595–601.
[25]Panzella L, Napolitano A, d'Ishchia M. Oxidative conjugation of chlorogenic acid with glutathione: Structural characterization of addition products and a new nitrite-promoted pathway. Bioorg Med Chem. 2003;11:4797– 4805.
[26]Morales FJ, Jiminex-Perez S. Peroxyl radicals scavenging activity of melanoidins in aqueous systems. Eur Food Res Technol. 2004;218:515–520.
[27]Radtke J, Linseisen J, Wolfram G. Phenolic acid intake of adults in Bavarian subgroup of the national food consumption survey. Z Ernahrungswiss. 1998;37:190–197.
[28]Pulido R, Hernandez-Garcia M, Saura-Calixto F. Contribution of beverages to the intake of lipophilic and hydrophilic antioxidants in the Spanish diet. Eur J Clin Nutr. 2003;57:1275–1282.
[29]Svilaas A, Sakhi AK, Andersen LF, et al. Intakes of antioxidants in coffee, wine, and vegetables are correlated with plasma carotenoids in humans. J Nutr. 2004;134:562–567.
[30]Schwartz J, Weiss ST. Caffeine intake and asthma symptoms. Ann Epidemiol. 1992;2:627–635.
[31]Santos RM, Lima DR. Coffee as a medicinal plant and vitamin source for smokers. Int J Chest Dis. 1989;43:56–58.
[32]Ochiai R, Jokura H, Suzuki A, et al. Green coffee bean extract improves human vasoreactivity. Hypertense Res. 2004;27:731–737.
[33]Yukawa GS, Mune M, Otani H, et al. Effect of coffee consumption on oxidative susceptibility of low-density lipoproteins and serum lipid levels in humans. Biochemistry. 2004;69:70–74.
[34]Richardson T, Rozkovec A, Thomas P, et al. Influence of caffeine on heart rate variability in patients with long standing type I diabetes. Diabetes Care. 2004;27:1127–1131.
[35]Tieges Z, Richard Ridderinkhof K, Snel J, Kok A. Caffeine strengthens action monitoring evidence from error related activity. Brain Res Cogn Brain Res. 2004;21:87–93.
[36]Papadelis C, Kurido-Papadeli C, Vlachogiannis E, et al. Effects of mental work load and caffeine on catecholamines and blood pressure compared to performance variation. Brain Cogn. 2003;51:143–154.
[37]Smith AP, Clark R, Gallagher J. Breakfast cereal and caffeinated coffee: Effects on working memory, attention, mood, and cardiovascular function. Physiol Behav. 1999;67:9–17.

[38]Rey de Castro J, Gallo J, Loureiro H. Tiredness and sleepiness in bus drivers and road accidents in Peru: A quantitative study. Rev Panam Salud Pub. 2004;16:11–18.
[39]Sparco P. Combating fatigue to enhance safety. Aviat Week Space Technol. 1996;145:53–55.
[40]Quinlan P, Lane J, Aspinall L. Effects of hot tea, coffee and water ingestion on physiological responses and mood: The role of caffeine, water and beverage type. Psychopharmacology. 1997;134:164–173.
[41]Kawachi I, Willett WC, Colditz GA, et al. A prospective study of coffee drinking and suicide in women. Arch Intern Med. 1996;156:521–525.
[42]Naismith DJ, Akinyanju PA, Szanto S, Yudkin J. The effect in volunteers of coffee and decaffeinated coffee on load glucose, insulin, plasma lipids and some factors involved in blood clotting. Nutr Metab. 1970;12: 144–151.
[43]Isogawa A, Noda M, Takahashi Y, et al. Coffee consumption and risk of type 2 diabetes mellitus. Lancet. 2003;361:703–704.
[44]Rosengren A, Dotevall A, Wilhelmsen L, et al. Coffee and incidence of diabetes in Swedish women: A prospective 18 year follow-up study. J Intern Med. 2004;255:89–95.
[45]Salazar-Martinez E, Willett WC, Ascherio A, et al. Coffee consumption and risk for type 2 diabetes mellitus. Ann Intern Med. 2004;140:1–8.
[46]Arnlov J, Vessby B, Riserus U. Coffee consumption and insulin sensitivity. JAMA. 2004;291:1199–1201.
[47]Agardh EE, Carlsson S, Ahlbom A, et al. Coffee consumption, type 2 diabetes and impaired glucose tolerance in Swedish men and women. J Intern Med. 2004;255:645–652.
[48]Carlsson S, Hammar N, Grill V, Kaprio J. Coffee consumption and risk of type 2 diabetes in Finnish twins. Int J Epidemiol. 2004;33:1–2.
[49]Acheson KJ, Zahorska-Markiewicz B, Pittet P, et al. Caffeine and coffee: Their influence on metabolic rate and substrate utilization in normal weight and obese individuals. Am J Clin Nutr. 1980;33:989–997.
[50]Bracco D, Ferrarra JM, Arnaud MJ, et al. Effects of caffeine on energy metabolism, heart rate, and methylxanthine metabolism in lean and obese women. Am J Physiol. 1995;269:671–678.
[51]Zahorska-Markiewicz B. The thermic effect of caffeinated and decaffeinated coffee ingested with breakfast. Acta Physiol Pol. 1980;31:17–20.
[52]Tagliabue A, Terracina D, Cena H, et al. Coffee induced thermogenesis and skin temperature. Int J Obes Relat Metab Disord. 1994;18:537–541.
[53]Mougios V, Ring S, Pettidou A, Mikolaidis MG. Duration of coffee and exercise-induced changes in fatty acid profile of human serum. J Appl Physiol. 2003;94:476–484.
[54]Nehlig A, Derby G. Caffeine and sports activity: A review. Int J Sports Med. 1994;15:215–223.
[55]Ckok G. Coffee and health. Z Ernahrungswiss. 1977;16:248–255.
[56]Morton C, Klatshky AL, Udaltsova N. Smoking, coffee and pancreatitis. Am J Gastroenterol. 2004; 99:731–738.
[57]Klatsky AL, Armstrong MA. Alcohol, smoking, coffee and cirrhosis. Am J Epidemiol. 1992;136:1248–1257.
[58]Gallus S, Tavani A, Negri E, La Vecchia C. Does coffee protect against liver cirrhosis? Ann Epidemiol. 2002;12:202–205.
[59]Wahllander A, Renner E, Preisig R. Fasting plasma caffeine concentration: A guide to the severity of chronic liver disease. Scand J Gastroenterol. 1985;20:1133–1141.
[60]Nakanishi N, Nakamura K, Makajima K, et al. Coffee consumption and decreased serum gamma-glutamyltransferase: A study of middle-aged Japanese men. Eur J Epidemiol. 2000;16:419–423.
[61]Leitzmann MF, Willett WC, Rimm EB, et al. A prospective study of coffee consumption and the risk of symptomatic gallstone disease in men. JAMA. 1999;281:2106–2112.
[62]Leitzmann MF, Stampfer MJ, Willett WC, et al. Coffee intake is associated with lower risk of symptomatic gallstone disease in women. Gastroenterology. 2002;123:1823–1830.
[63]Abbott RD, Webster Ross G, White LR, et al. Environmental, lifestyle and physical precursors of clinical Parkinson's disease: Recent findings from Honolulu-Asia Aging Study. J Neurol. 2003;250:30–39.
[64]Ascherio A, Zhang SM, Hernan MA, et al. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. Ann Neurol. 2001;50:56–63.
[65]Ragonese P, Salemi G, Morgante L, et al. A case control study of cigarette, alcohol, and coffee consumption preceding Parkinson's disease. Neuroepidemiology. 2003;22:297–304.
[66]Tan EK, Tan C, Fook-Chong SM, et al. Dose dependent protective effect of coffee, tea and smoking in Parkinson's disease: A study in ethnic Chinese. J Neurol Sci. 2003;216:163–167.
[67]Ross GW, Abbott RD, Petrovich H, et al. Association of coffee and caffeine intake with the risk of Parkinson's disease. JAMA. 2000;283:2674–2679.
[68]Heuser I. Prevention of dementia: State of the art. Stsch Med Wochenschr. 2003;128:421–422.
[69]Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: A prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol. 2002;256:445–453.

[70]Feijoo M, Bilbao J. Seizures of sleep onset: Clinical and therapeutic aspects. Clin Neuropharmacol. 1992;15:50–55.
[71]Svartberg J, Midtby M, Bonaa KH, et al. The associations of age, lifestyle factors and chronic disease with testosterone in men: The Tromso Study. Eur J Endocrinol. 2003;149:145–152.
[72]Harland BF. Caffeine and nutrition. Nutrition. 2000;16:522–526.
[73]Bell LN, Wetzel CR, Grand AN. Caffeine content in coffee as influenced by grinding and brewing technique. Food Res Intern. 1996;29 85–89.
[74]McCusker RR, Goldberger BA, Cone EJ. Caffeine content of specialty coffees. J Anal Toxicol. 2003; 7:520–522.

34

MEDICINAL MUSHROOMS

The Validation of Millennia of Therapeutic Use

Most people, if they think about mushrooms at all, consider them a food with no particular value beyond taste. As a significant source of protein, fiber, several minerals, B vitamins, and ascorbic acid, mushrooms are actually a healthy addition to the diet. They also have uses beyond nutrition, having numerous medicinal qualities. A large body of work details the health benefits of mushrooms. There is even a journal that specializes in mushroom use in medicine, the International Journal of Medicinal Mushrooms.

Recent interest in the medicinal qualities of mushrooms has paralleled the rise in widespread commercial cultivation of these useful fungi. Their production and sales in the year 1999 totaled $18 billion, an amount similar to that of coffee sales worldwide.[1] However, the use of fungi for medicinal purposes predates modern cultivation and scientific interest by thousands of years. In traditional Eastern medicine, mushrooms were used to treat diseases, increase longevity, and cleanse the mind and spirit.[2] Modern investigations into the medicinal effects of mushrooms began in the late 1960s.[3] Science continues to reveal the efficacy of mushrooms, and new uses for them will undoubtedly be discovered. Among the 38,000 species of mushrooms, only a small portion of these have been studied for medicinal properties. Research has shown that mushrooms can be used as antioxidants, vascular support agents, immune-system enhancers, and anti-inflammatory agents.

CORDYCEPS

Cordyceps sinensis has perhaps one of the oddest places of origin of any natural medicine. Sometimes referred to as ''caterpillar fungus,'' cordyceps was originally found on the surface of a caterpillar, Hepialus armoricanus. Considered to be rare, the fungus was found at high elevations in the mountains of Asia and its use was limited to ancient royalty. Traditional uses included enhancing endurance and stamina; boosting energy and fighting fatigue; promoting sexual vitality; supporting the lungs, heart, kidney, and immune system; nourishing the vital essence; and promoting longevity. Cordyceps research has increased markedly, together with research on other popular medicinal mushrooms. Modern investigations on the benefits of cordyceps have supported its ancient use as a tonifying agent.

Several active constituents have been identified, including saccharides (oligosaccharide, polysaccharide, and D-mannitol), sterols (ergosterol, ergosterol peroxide, beta-sitosterol, daucosterol, and campasterol), peptides and polyamines (cadaverine, spermidine, spermine, 1,3-diamino propane, and putresine), fatty and organic acids (nearly 30 identified fatty-acid compounds), vitamins, nucleotides (adenosine, adenine, deoxyuridine, guanosine, thymidine, uracil, and uridine), and inorganic constituents and minerals (numerous macrominerals and trace minerals, including selenium).[4,5]

More than one species of cordyceps and artificially cultured mycelium are all currently used. C. capita, C. ophioglossoides, and C. militaris are in many commercial preparations. The strain

Cs–4, an artificially propagated form of cordyceps, is used most frequently in these preparations.

Research on natural medicine substances almost always includes an investigation into their antioxidative abilities. Cordyceps research is no exception. One study examined the antioxidative abilities of both water and ethanol soluble extracts of C. sinensis and revealed what investigators termed "potent antioxidant activity."[6] While the extracts' ability to scavenge superoxide ions was minimal, the extracts inhibited hydroxyl radical by-products moderately. In addition, when incubated with low-density lipoprotein (LDL) and copper chloride (a prooxidative molecule) in the presence of macrophages, a cordyceps extract strongly inhibited lipid peroxidation in the medium and in the macrophages. The researchers noted that this effect was similar to that of superoxide dismutase (SOD), a powerful cellular weapon against superoxide radicals. SOD is one of the cell's main protectants against oxidative damage. Researchers in another trial showed that SOD activity was increased by 16% while plasma malondialdehyde (a product of hydroxy radicals) and plasma lipoperoxide were decreased by roughly 34% in patients who used cordyceps as a supplement.[7]

Recent studies suggest that cordyceps is beneficial for the vascular system and useful for supporting healthier microcirculation. Cordyceps has demonstrated hypotensive and vasodilating effects[8] and may prevent blood clotting and ischemia.[9] Cordyceps' ability to decrease serum lipid peroxide levels and inhibit LDL oxidation, and thus aortic cholesteryl-ester deposition, may contribute to the fungus' vascular protective ability.[10]

One of the most frequent therapeutic uses of medicinal mushrooms is for immune enhancement. While not the leading mushroom for this purpose, cordyceps nonetheless has some value. Several studies demonstrate the ability of the fungus to affect immune-cell function and populations. In one experiment, cordyceps use led to a significant increase in the number of T-helper leukocytes and increased the ratio of T-helper to T-suppressor cells.[11] Other studies showed that cordyceps could enhance natural-killer (NK) cells as well as certain CD marker designations and their binding abilities on lymphocytes in people with leukemia.[12] Cordyceps was also shown to inhibit the formation of melanoma in laboratory animals treated with a fungal extract; researchers attributed this effect to improved NK cell function.[13]

This mushroom has been studied in other models of cancer as well. In another experiment utilizing laboratory animals, a cordyceps extract was able to stimulate mononuclear blood cells and inhibit human leukemia-cell growth by roughly 80% and to induce other immature immune cells into mature tumor-fighting form.[14] Numerous other immune effects of cordyceps have been identified. These include the ability to increase levels of specific cytokines including interferon-gamma, tumor necrosis factor-alpha (TNF-a) and interleukin-1 (IL-1).[14] Cordyceps has prolonged the survival of lymphocytes[15] and has had direct toxic effects on cancer cells,[16,17] especially against carcinoma of the lung.[18] The use of cordyceps for promoting immune function is relatively well-documented; however, more research is needed for application to human health and to disease prevention.

The use of cordyceps as an anti-inflammatory holds promise as well. In conditions with inflammation, cordyceps may be valuable as an adjunctive agent because of its ability to modulate cytokines and increase levels of corticosterone.[19] Corticosterone is one of the body's primary means of controlling inflammation. It is not yet known if the fungal extract works directly by increasing adrenal gland output or indirectly through the hypothalamus-pituitary axis. An increase in levels of corticosterone may be responsible, in part, for the tonifying effects of this fungus when it is included in adrenal-gland supportive protocols.

MAITAKE

Maitake (Grifola frondosa) is found mainly in temperate mountainous regions of Japan, North America, and Europe. The fruiting body of this mushroom is one of the largest of any mushroom, approaching the size of a basketball. Maitake fruiting bodies grow with a distinctive overlapping pattern, which has been described as looking like dancing butterflies. Maitake is prized for its culinary benefits; its medicinal effects have only recently been emphasized although some of them have been known for many years. The mushroom was used medicinally as a general tonic to promote wellness and vitality, and is now considered to be an adaptogenic medicine. Historically, maitake was also used for lowering high blood pressure and treating cancer; these uses are two foci of current research. This mushroom has been a staple in Asian diets for thousands of years. Once difficult to cultivate, maitake is now grown relatively easily in Japan, increasing the mushroom's availability as a medicine.

Maitake can benefit circulation in a number of ways, one of which is to prevent cardiovascular conditions caused by elevated blood lipids. Maitake changes the metabolism of lipids in the body by inhibiting their accumulation in the liver and in the serum. The exact mechanisms of these actions are not yet fully known.[20] Other actions of maitake include its ability to lower blood glucose, thereby decreasing the insulin burden on the micro– and macrovasculature. Mounting evidence shows a correlation between elevated insulin levels and cardiovascular morbidity.[21] Maitake is thought to lower blood glucose levels by activating insulin receptors.[22,23] Another effect of this mushroom on vascular health may be an ability to lower blood pressure. Two preliminary studies demonstrated that maitake lowered blood pressure in laboratory animals significantly.[24,25]

Other significant health effects of maitake include its immune-enhancing properties. One of the active ingredients of the fungus is beta-glucan. Found in several plants, beta-glucan is a polysaccharide molecule that can support the body's defenses against tumors. Maitake's beta-glucan content may be responsible for its immunostimulatory actions, including regulation of interleukin-1, NK cells, cytotoxic T-cells, and superoxide anions.[26] Several preliminary studies on the effects of maitake on certain cancers were performed in the mid-1990s.[27–29] However, no follow-up studies have yet been done. Promising studies on beta-glucan as an immune stimulant suggest that maitake is a viable choice for treating conditions that involve impaired immunity. Other immunostimulatory principles of this fungus should be examined in future research.

REISHI

Reishi (Ganoderma lucidum) mushrooms are sometimes referred to as Ling Chih or Ling Zhi. The medicinal use of this mushroom is detailed in the Chinese pharmacopoeia of the first century BC.[30] Reishi was highly valued even at this time and had the most medical applications of all medicines in the pharmacopoeia. The very slow growth of reishi, along with its scarcity in the wild, made the mushroom highly prized. Recently, however, it has been cultivated successfully and is now widely available. Reishi's native habitats include decaying logs and plant matter near coastal areas. The mushroom comes in several different colors, with the red one most frequently used in Asia and North America. Traditional Chinese medicine uses of reishi included treating fatigue, weakness, insomnia, asthma, and coughs.[31] Despite a long history of medical use, research on reishi's many health benefits was not able to be conducted

until the mushroom became more available recently. Some of its health benefits include cardiovascular and liver protection, and immune boosting, anti-aging, anti-diabetic, antiviral, antibacterial, and anti-cancer effects.

Several constituents of the reishi mushroom have antioxidant effects. Investigators isolated the active terpene and polysaccharide fractions and investigated their ability to protect cells against oxidative damage.[32] The study looked primarily at the ability of these constituents to protect cells against lipid peroxidation and erythrocyte membrane oxidation. The results showed that the fractions had dose-dependent antioxidant capabilities, with the terpene fraction having the strongest effect.

Reishi contains several components that improve vascular health. Among these are the alkaloid cyclo-octasulfur, which has known cardiotonic effects;[33] the triterpene ganodermadiol, known for its ability to lower blood pressure by blocking the effects of angiotensin converting enzyme;[34] and the ganoderic acids, which also have antihypertensive effects and can inhibit the synthesis of cholesterol. One study showed that reishi can inhibit platelet aggregation. This dose-dependent effect was noted in both healthy subjects and in those with atherosclerotic disease.[35] The exact mechanism of inhibition was not elucidated in the study, however. The reishi mushroom's wide-ranging effects on the vascular system make it an important supportive therapy for prevention or treatment of vascular conditions caused by cholesterol accumulation, platelet aggregation, and high blood pressure.

Reishi contains two constituents that are thought to be responsible for its effectiveness as an immune system modulator. Like maitake, reishi contains the immune-stimulating compound beta-glucan in the form of beta-D-glucan.[36] Beta-D-glucan is well known for its ability to assist one of the body's premier immune cells, the macrophage, to mature. Researchers have also identified a triterpene compound, Ling Zhi–8, which is believed to be a generalized immune-system modulator and to have antiallergy effects.[37] By activating cells of the immune system (macrophages and T-lymphocytes), reishi components enhance cytokine levels, propagating the immune systems' alarm effect further.[38]

CORIOLUS

Yet another traditional medicine in the Chinese medical armamentarium, coriolus (Coriolus versicolor) was harvested and ground to make a powder and tea. Traditional medical applications included improving vitality and strength, enhancing respiratory function, promoting calmness and well-being, restoring energy following intense physical exertion, strengthening tendons and bones, enhancing liver health, and fostering longevity. Coriolus became very popular during the Ming Dynasty, when the mushroom was widely prescribed to enhance vigor and longevity.

As an antioxidant, coriolus has shown great potential. In one study, the fungus demonstrated an approximately 59% inhibitory effect on the oxidative process. The mushroom's free-radical scavenging ability was near 25% when challenged in a laboratory setting.[39] Free-radical scavenging ability can be applied to immune function. NK cells can be damaged easily by reactive oxygen species. Polysaccharide krestin (PSK), which is derived from coriolus, can mimic SOD and restore NK cell function in people who have cancer.[40] Coriolus, like other medicinal mushrooms, is well known for its immune-enhancing effects. One group of researchers noted a wide-ranging enhancement of immune-cell function and the mushroom's ability to inhibit the growth of certain cancers.[41]

Numerous studies have been conducted on coriolus' immune-enhancing properties. These studies have identified the mushroom's active constituents. Among them are the beta-glucan polysaccharides. Coriolus contains several different types: 1–3 beta-glucan, 1–4 beta-glucan, and 1–6 beta-glucan, protein-bound PSK, and polysaccharide peptide (PSP).[42] The target of numerous research investigations, PSK and PSP have anti-tumor effects and are used widely as biologic response modifiers in cancer chemotherapy regimens in Japan.[43,44] In fact, PSP has been used throughout Asia as an adjunctive cancer treatment for the last 30 years. PSK has shown benefit in gastric, esophageal, colorectal, breast, and lung cancer therapies.[45]

Coriolus holds promise as an antiviral as well. Both PSK and PSP have demonstrated inhibitory effects against HIV-1 in laboratory settings.[46,47] Coriolus appears to have wide-ranging immunomodulatory effects, making it a prime therapy in conditions of impaired immunity.

AGARICUS

Agaricus (Agaricus blazei, Agaricus subrufescens) has traditionally been used for the prevention of cancer, diabetes, hyperlipidemia, arteriosclerosis, and chronic hepatitis. It has anti-cancer, antioxidant, anti-diabetes, hepatoprotective, and immune-stimulating activity.

Extracts of beta-glucan from Agaricus blazei murill has show potent anti-cancer activity. One study showed that this extract was cytotoxic to human ovarian cancer cells, suppressed cell proliferation, increased apoptosis, and decreased metastasis in mouse models.[48] The constituent ergosterol, a vitamin D precursor, has been shown to inhibit tumor growth through the inhibition of tumor-induced neovascularization. An additional constituent, sodium pyroglutamate, has shown similar activity as an antiangiogenic substance with potent anti-tumor and antimetastatic actions, as well as immune-modulatory activity, as shown in tumor-bearing mice.[49] In a human study with 100 gynecological cancer patients undergoing chemotherapy, an extract of Agaricus was shown to increase NK cell activity, as well as improve chemotherapy-associated side effects such as alopecia, appetite, emotional stability, and general weakness.[50] In addition to increasing NK cell activity, Agaricus extracts also enhanced the induction of antigen-specific cytotoxic T lymphocytes and interferon-gamma production.[51] Polysaccharide fractions of Agaricus have also been evaluated for antioxidant activity. Research has shown potent antioxidant and free-radical scavenging activity in vitro.[52]

A study using diabetic rats showed that beta-glucans extracted from Agaricus showed antihyperglycemic, antihypertriglyceridemic, antihypercholesterolemic, and antiarteriosclerotic activity indicating overall anti-diabetic activity.[53] A randomized, double-blind, placebo-controlled human trial with diabetic individuals evaluated the efficacy of Agaricus blazei Murill extract. Supplement of Agaricus extract improved insulin resistance in individuals with type 2 diabetes. It was suggested that the increase in adiponectin concentration after taking Agaricus extract for 12 weeks may be the mechanism of action for improving insulin resistance.[54]

SHIITAKE

The shiitake mushroom (Lentinus edodes) has been used historically for anti-cancer and immune-modulating activity. An ethyl acetate fraction from shiitake mushrooms was evaluated in breast cell carcinoma and myeloma cell lines. The results showed an up-regulation of

pro-apoptotic proteins inducing apoptosis and resulting in a 51% anti-proliferative effect in cancer cells treated with the shiitake extract.[55] A study was conducted to examine the anti-cancer effects of four alpha-D-glucans extracted from shiitake mushrooms compared with O-sulfonated alpha-D-glucan derivatives. The results showed that the O-sulfonation of the alpha-D-glucan considerably increased the anti-tumor activities compared to the native alpha-D-glucans.[56] The constituent lentinan was also shown to exhibit anti-cancer activity. Lentinan extract was given orally to mice for seven days prior to inoculation with either murine lymphoma cells or human colon-carcinoma cells. The results showed significant regression in tumor formation in pre-fed mice compared to controls in both cancer cell lines.[57] A polysaccharide containing d-glucopyranose was extracted from shiitake mushrooms and evaluated for immune activity in mice-transplanted sarcoma cells. A significant increase in phagocytosis by macrophages and a significant decrease in tumor formation was observed. The concentration of serum TNF-alpha and IFN-gamma increased significantly in the polysaccharide-treated groups. The polysaccharide also increased NO production and catalase activity in macrophages. Thus, the results indicated that the anti-tumor activity of this polysaccharide was mediated by immune modulation by inducing T-cells and macrophage-dependent immune responses.[58]

Shiitake mushrooms have also demonstrated antibacterial activity. One study showed that a 5% concentration of shiitake juice extract produced a pronounced antimicrobial effect with respect to the pathogenic bacteria Escherichia coli, Staphylococcus aureus, and Enterococcus faecalis, while the beneficial colonic bacteria Bifidobacterium and Lactobacillus exhibited resistance to the action of shiitake juice.[59]

Extracts from shiitake mushrooms have also demonstrated hypoglycemic and cholesterol-lowering action as well. Diabetic rats were treated with an exo-polymer from Lentinus edodes. The results showed a reduction of plasma glucose levels by as much as 21.5% and increased plasma insulin by 22.1% compared to controls. Additionally, total cholesterol levels were reduced by 25.1% and triglyceride levels decreased by 44.5%.[60]

ADDITIONAL MEDICINAL MUSHROOMS

Tremella (Tremella fuciformis, Tremella mesenterica, Tremella aurantia). Tremella species have shown hypoglycemic and immune-modulating activity. Oral supplementation with a polysaccharide extract from T. aurantia showed significantly lowered levels of insulin, total-cholesterol, triglyceride, and lipoperoxide levels in genetically non-insulin-dependent diabetic mice.[61] Oral supplementation with T. aurantia has also been shown to suppress plasma testosterone levels in normal rats.[62] Additionally, constituents isolated from T. fuciformis have been shown to induce human monocytes to produce interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF) in vitro.[63]

Hericium (Hericium erinaceus, Hericium laciniatum). Hericium species have shown anti-tumor, immune-modulating, and lipid-lowering action. One study analyzed polysaccharides from both H. erinaceus and H. laciniatum. The results revealed that both polysaccharides had significant antiartificial pulmonary metastatic tumor effects in mice with the polysaccharide from H. erinaceus showing more effectiveness than that from H. laciniatum. Both of the polysaccharide extracts did demonstrate a significant increase in CD4 T cells and macrophages compared to controls.[64] A study with oral supplementation of H. erinaceus showed dramatic lipid-modulating activity in

hyperlipidemic rats. The results showed a 32.9% decrease in the plasma total cholesterol, a 45.4% decrease in LDL cholesterol, a 34.3% decrease in triglycerides, an 18.9% decrease in phospholipid, 58.7% decreased atherogenic index, 20.2% decreased hepatic HMG-CoA reductase activity, and a 31.1% increase in the plasma HDL cholesterol level compared to the controls.[65]

Auricularia (Auricularia auricular). Auricularia has been shown to exhibit hypoglycemic, anticoagulant, and antioxidant activity. A study with diabetic mice showed that supplementation with a constituent from Auricularia had a significantly lowered plasma glucose, insulin, urinary glucose, and food intake and increased the tolerance to intraperitoneal glucose loading.[66] A polysaccharide extracted from Auricularia has also demonstrated anticoagulant activity and inhibited platelet aggregation in rats.[67] Additional research has shown antioxidant action by Auricularia showing significant inhibition of lipid peroxidation, potent hydroxyl radical scavenging activity, and significantly increased nitric oxide production.[68]

Flammulina (Flammulina velutipes). Flammulina has been shown to have antimicrobial,[69] anti-tumor, and immune-modulating activity.[70] Constituents have been shown to inhibit cancer cell proliferation, and can activate T-cells increasing the production and secretion of INF-gamma.[71]

CONCLUSIONS

Numerous mushrooms have been used as traditional medicines, and modern studies are showing that they have antioxidant, vascular, immune, and anti-inflammatory effects. In addition, we are now learning the mechanisms by which these mushrooms work.

REFERENCES

[1]Chang ST. Global impact of edible and medicinal mushrooms on human welfare in the 21st century: Nongreen revolution. Int J Med Mushrooms. 1999;1:1–8.

[2]Chang ST, Buswell JA. Ganoderma lucidum (Curt.:Fr.) P.Karst. (Aphyllophoromycetideae)—a mushrooming medicinal mushroom. Int J Med Mushrooms. 1999;1:139–148.

[3]Ikekawa T, Uehara N, Maeda Y, Nakanishi M, Fukuoka F. Antitumor activity of aqueous extracts of edible mushrooms. Cancer Res. 1969;29:734–735.

[4]Xu WH. Water-soluble constituents of Cordyceps sinensis (Berk.) Sacc.—the nucleosides [in Chinese]. Zhong Yao Tong Bao. 1988;13:34–36,63.

[5]Xiao YQ. Studies on chemical constituents of Cordyceps sinensis I [in Chinese]. Zhong Yao Tong Bao. 1983;8:32–33.

[6]Yamaguchi Y, Kagota S, Nakamura K, Shinozuka K, Kunitomo M. Antioxidant activity of the extracts from fruiting bodies of cultured Cordyceps sinensis. Phytother Res. 2000;14:647–649.

[7]Jiang J, Gao Y. Summary of treatment of 37 chronic renal dysfunction patients with JinShuiBao. J Admin TCM. 1995;5(suppl.):23–24.

[8]Chiou WF, Chang PC, Chou CJ, Chen CF. Protein constituent contributes to the hypotensive and vasorelaxant activities of Cordyceps sinensis. Life Sci. 2000;66:1369–1376.

[9]Zhao Y. Inhibitory effects of alcoholic extract of Cordyceps sinensis on abdominal aortic thrombus formation in rabbits [Chinese]. Zhonghua Yi Xue Za Zhi. 1991;71:612–615,642.

[10]Yamaguchi Y, Kagota S, Nakamura K, Shinozuka K, Kunitomo M. Inhibitory effects of water extracts from fruiting bodies of cultured Cordyceps sinensis on raised serum lipid peroxide levels and aortic cholesterol deposition in atherosclerotic mice. Phytother Res. 2000;14:650–652.

[11]Chen GZ, Chen GL, Sun T, et al. Effects of Cordyceps sinensis on murine T lymphocyte subsets. Chin Med J (English). 1991;104:4–8.

[12]Liu C, Lu S, Ji MR. Effects of Cordyceps sinensis (CS) on in vitro natural killer cells [in Chinese]. Chung Kuo Chung Hsi I Chieh Ho Tsa Chih. 1992;12:267–269, 259.
[13]Xu RH, Peng XE, Chen GZ, Chen GL. Effects of Cordyceps sinensis on natural killer activity and colony formation of B16 melanoma. Chin Med J (English). 1992;105:97–101.
[14]Chen YJ, Shiao MS, Lee SS, Wang SY. Effect of Cordyceps sinensis on the proliferation and differentiation of human leukemic U937 cells. Life Sci. 1997;60:2349–2359.
[15]Zhu XY, Yu HY. Immunosuppressive effect of cultured Cordyceps sinensis on cellular immune response [in Chinese]. Chung Hsi I Chieh Ho Tsa Chih. 1990;10:485–487,454.
[16]Bok JW, Lermer L, Chilton J, et al. Antitumor sterols from the mycelia of Cordyceps sinensis. Phytochemistry. 1999;51:891–898.
[17]Kuo YC, Lin CY, Tsai WJ, et al. Growth inhibitors against tumor cells in Cordyceps sinensis other than cordycepin and polysaccharides. Cancer Invest. 1994;12:611–615.
[18]Nakamura K, Yamaguchi Y, Kagota S, et al. Inhibitory effect of Cordyceps sinensis on spontaneous liver metastasis of Lewis lung carcinoma and B16 melanoma cells in syngeneic mice. Jpn J Pharmacol. 1999;79: 335–341.
[19]Wang SM, Lee LJ, Lin WW, Chang CM. Effects of a water-soluble extract of Cordyceps sinensis on steroidogenesis and capsular morphology of lipid droplets in cultured rat adrenocortical cells. J Cell Biochem. 1998;69:483–489.
[20]Kubo K, Nanba H. The effect of maitake mushrooms on liver and serum lipids. Alt Ther Health Med. 1996;2:62–66.
[21]Soldatos G, Cooper ME, Jandeleit-Dahm KA. Advanced-glycation end products in insulin-resistant states. Curr Hypertens Rep. 2005;7:96–102.
[22]Konno S, Tortorelis DG, Fullerton SA, et al. A possible hypoglycaemic effect of maitake mushroom on Type 2 diabetic patients. Diabet Med. 2001;18:1010.
[23]Kubo K, Aoki H, Nanba H. Anti-diabetic activity present in the fruit body of Grifola frondosa (Maitake): I. Biol Pharm Bull. 1994;17:1106–1110.
[24]Kabir Y, Kimura S. Dietary mushrooms reduce blood pressure in spontaneously hypertensive rats (SHR). J Nutr Sci Vitaminol (Tokyo). 1989;35:91–94.
[25]Kabir Y, Yamaguchi M, Kimura S. Effect of shiitake (Lentinus edodes) and maitake (Grifola frondosa) mushrooms on blood pressure and plasma lipids of spontaneously hypertensive rats. J Nutr Sci Vitaminol (Tokyo). 1987;33:341–346.
[26]Ross GD, Vetvicka V, Yan J, et al. Therapeutic intervention with complement and beta-glucan in cancer. Immunopharmacology. 1999;42:61–74.
[27]Adachi K, Nanba H, Kuroda H. Potentiation of host-mediated anti-tumor activity in mice by beta-glucan obtained from Grifola frondosa (maitake). Chem Pharm Bull (Tokyo). 1987;35:262–270.
[28]Nanba H. Activity of maitake D-fraction to inhibit carcinogenesis and metastasis. Ann NY Acad Sci. 1995;768:243–245.
[29]Nanba H, Kubo K. Effect of Maitake D-fraction on cancer prevention. Ann NY Acad Sci. 1997;833: 204–207.
[30]Jones K. Reishi: Ancient Herb for Modern Times. Issaquah, WA: Sylvan Press, 1990, 6.
[31]Shu HY. Oriental Materia Medica: A Concise Guide. Palos Verdes: Oriental Healing Arts Press, 1986, 640–641.
[32]Zhu M, Chang Q, Wong LK, Chong FS, Li RC. Triterpene antioxidants from Ganoderma lucidum. Phytother Res. 1999;13:529–531.
[33]LingZhi. In: Chang H-M, But RP-H, eds. Pharmacology and Application of Chinese Materia Medica, vol. 1. Singapore: World Scientific Publishing Co. Ltd. 1986, 642–653.
[34]Morigiwa A, Kitabatake K, Fujimoto Y, Ikekawa N. Angiotension converting enzyme-inhibitory triterpenes from Ganoderma lucidum. Chem Pharmaceutical Bull. 1986;34:3025–3028.
[35]Tao J, Feng KY. Experimental and clinical studies on inhibitory effect of Ganoderma lucidum on platelet aggregation. J Tongji Med Univ. 1990;10:240–243.
[36]Yoshiaki S, et al. Structures and anti-tumor activities of the polysaccharides isolated from fruiting body and the growing culture of mycelium of Ganoderma lucidum. Agric Biol Chem. 1985;49:2641–2653.
[37]Kino K, Yamashita A, Yamaoka K, Watanabe J, Tanaka S, Ko K, Shimizu K, Tsunoo H. Isolation and characterization of a new immunomodulatory protein, Ling Zhi-8 (LZ-8), from Ganoderma lucidum. J Biol Chem. 1989;264:472–478.
[38]Wang SY, et al. The anti-tumor effect of Ganoderma lucidum is mediated by cytokines released from activated macrophage and T lymphocytes. Int J Cancer. 1997;70:699–705.
[39]Mau JL, et al. Antioxidant properties of several medicinal mushrooms. J Agric Food Chem. 2002;50: 6072–6077.

[40]Nakamura K, et al. Susceptibility of natural killer (NK) cells to reactive oxygen species (ROS) and their restoration by the mimics of superoxide dismutase (SOD). Cancer Biother Radiopharm. 1998;13:275–290.
[41]Chu KK, et al. Coriolus versicolor: A medicinal mushroom with promising immunotherapeutic values. J Clin Pharmacol. 2002;42:976–984.
[42]Dong Y, Yang MM, Kwan CY. In vitro inhibition of proliferation of HL-60 cells by tetrandrine and Coriolus versicolor peptide derived from Chinese medicinal herbs. Life Sci. 1997;60:PL135–140.
[43]Suto T, Fukuda S, Moriya N, et al. Clinical study of biological response modifiers as maintenance therapy for hepatocellular carcinoma. Cancer Chemother Pharmacol. 1994;33(suppl.)S145–S148.
[44]Nakazato H, Koike A, Saji S, et al. Efficacy of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer: Study Group of Immunochemotherapy with PSK for Gastric Cancer. Lancet. 1994;343:1122–1126.
[45]Ng TB. A review of research on the protein-bound polysaccharide (polysaccharopeptide, PSP) from the mushroom Coriolus versicolor (Basidiomycetes: Polyporaceae). Gen Pharmacol. 1998;30:1–4.
[46]Collins RA, Ng TB. Polysaccharopeptide from Coriolus versicolor has potential for use against human immunodeficiency virus type 1 infection. Life Sci. 1997;60:PL383–387.
[47]Tochikura TS, Nakashima H, Hirose K, et al. A biological response modifier, PSK, inhibits human immunodeficiency virus infection in vitro. Biochem Biophys Res Commun. 1987;148:726–733.
[48]Kobayashi H, Yoshida R, Kanada Y, Fukuda Y, Yagyu T, Inagaki K, Kondo T, Kurita N, Suzuki M, Kanayama N, Terao T. Suppressing effects of daily oral supplementation of beta-glucan extracted from Agaricus blazei Murill on spontaneous and peritoneal disseminated metastasis in mouse model. J Cancer Res Clin Oncol. 2005 Aug;131(8):527–538. Epub 2005 May 10.
[49]Kimura Y, Kido T, Takaku T, Sumiyoshi M, Baba K. Isolation of an anti-angiogenic substance from Agaricus blazei Murill: Its anti-tumor and antimetastatic actions. Cancer Sci. 2004 Sep;95(9):758–764.
[50]Ahn WS, Kim DJ, Chae GT, Lee JM, Bae SM, Sin JI, Kim YW, Namkoong SE, Lee IP. Natural killer cell activity and quality of life were improved by consumption of a mushroom extract, Agaricus blazei Murill Kyowa, in gynecological cancer patients undergoing chemotherapy. Int J Gynecol Cancer. 2004 Jul–Aug; 14(4):589–594.
[51]Takimoto H, Wakita D, Kawaguchi K, Kumazawa Y. Potentiation of cytotoxic activity in naïve and tumor-bearing mice by oral administration of hot-water extracts from Agaricus brazei fruiting bodies. Biol Pharm Bull. 2004 Mar;27(3):404–406.
[52]Ker YB, Chen KC, Chyau CC, Chen CC, Guo JH, Hsieh CL, Wang HE, Peng CC, Chang CH, Peng RY. Antioxidant capability of polysaccharides fractionated from submerge-cultured Agaricus blazei mycelia. J Agric Food Chem. 2005 Sep 7;53(18):7052–7058.
[53]Kim YW, Kim KH, Choi HJ, Lee DS. Anti-diabetic activity of beta-glucans and their enzymatically hydrolyzed oligosaccharides from Agaricus blazei. Biotechnol Lett. 2005 Apr;27(7):483–487.
[54]Hsu CH, Liao YL, Lin SC, Hwang KC, Chou P. The mushroom Agaricus Blazei Murill in combination with metformin and gliclazide improves insulin resistance in type 2 diabetes: A randomized, double-blinded, and placebo-controlled clinical trial. J Altern Complement Med. 2007 Jan–Feb;13(1):97–102.
[55]Fang N, Li Q, Yu S, Zhang J, He L, Ronis MJ, Badger TM. Inhibition of growth and induction of apoptosis in human cancer cell lines by an ethyl acetate fraction from shiitake mushrooms. J Altern Complement Med. 2006 Mar;12(2):125–132.
[56]Unursaikhan S, Xu X, Zeng F, Zhang L. Antitumor activities of O-sulfonated derivatives of (1ï 3)-alpha-D-glucan from different Lentinus edodes. Biosci Biotechnol Biochem. 2006 Jan;70(1):38–46.
[57]Ng ML, Yap AT. Inhibition of human colon carcinoma development by lentinan from shiitake mushrooms (Lentinus edodes). J Altern Complement Med. 2002 Oct;8(5):581–589.
[58]Zheng R, Jie S, Hanchuan D, Moucheng W. Characterization and immunomodulating activities of polysaccharide from Lentinus edodes. Int Immunopharmacol. 2005 May;5(5):811–820. Epub 2004 Dec 2.
[59]Kuznetsov OIu, Mil'kova EV, Sosnina AE, Sotnikova NIu. [Antimicrobial action of Lentinus edodes juice on human microflora]. Zh Mikrobiol Epidemiol Immunobiol. 2005 Jan–Feb;(1):80–82.
[60]Yang BK, Kim DH, Jeong SC, Das S, Choi YS, Shin JS, Lee SC, Song CH. Hypoglycemic effect of a Lentinus edodes exo-polymer produced from a submerged mycelial culture. Biosci Biotechnol Biochem. 2002 May;66(5):937–942.
[61]Kiho T, Kochi M, Usui S, Hirano K, Aizawa K, Inakuma T. Antidiabetic effect of an acidic polysaccharide (TAP) from Tremella aurantia and its degradation product (TAP-H). Biol Pharm Bull. 2001 Dec; 24(12):1400–1403.
[62]Lo HC, Yang JG, Liu BC, Chen YW, Huang YL, Poon SL, Liu MY, Huang BM. The effects of Tremella aurantia on testosterone and corticosterone productions in normal and diabetic rats. Arch Androl. 2004 Nov–Dec;50(6):395–404.
[63]Gao Q, Killie MK, Chen H, Jiang R, Seljelid R. Characterization and cytokine-stimulating activities of acidic heteroglycans from Tremella fuciformis. Planta Med. 1997 Oct;63(5):457–460.

[64]Wang JC, Hu SH, Su CH, Lee TM. Antitumor and immunoenhancing activities of polysaccharide from culture broth of Hericium spp. Kaohsiung J Med Sci. 2001 Sep;17(9):461–467.

[65]Yang BK, Park JB, Song CH. Hypolipidemic effect of an Exo-biopolymer produced from a submerged mycelial culture of Hericium erinaceus. Biosci Biotechnol Biochem. 2003 Jun;67(6):1292–1298.

[66]Yuan Z, He P, Cui J, Takeuchi H. Hypoglycemic effect of water-soluble polysaccharide from Auricularia auricula-judae Quel. on genetically diabetic KK-Ay mice. Biosci Biotechnol Biochem. 1998 Oct;62(10): 1898–1903.

[67]Yoon SJ, Yu MA, Pyun YR, Hwang JK, Chu DC, Juneja LR, Mourão PA. The nontoxic mushroom Auricularia auricula contains a polysaccharide with anticoagulant activity mediated by antithrombin. Thromb Res. 2003;112(3):151–158.

[68]Acharya K, Samui K, Rai M, Dutta BB, Acharya R. Antioxidant and nitric oxide synthase activation properties of Auricularia auricula. Indian J Exp Biol. 2004 May;42(5):538–540.

[69]Ishikawa NK, Fukushi Y, Yamaji K, Tahara S, Takahashi K. Antimicrobial cuparene-type sesquiterpenes, enokipodins C and D, from a mycelial culture of Flammulina velutipes. J Nat Prod. 2001 Jul;64(7): 932–934.

[70]Leung MY, Fung KP, Choy YM. The isolation and characterization of an immunomodulatory and antitumor polysaccharide preparation from Flammulina velutipes. Immunopharmacology. 1997 Jan;35(3):255–263.

[71]Wang PH, Hsu CI, Tang SC, Huang YL, Lin JY, Ko JL. Fungal immunomodulatory protein from Flammulina velutipes induces interferon-gamma production through p38 mitogen-activated protein kinase signaling pathway. J Agric Food Chem. 2004 May 5;52(9):2721–2725.

35

NITRIC OXIDE, A POWERFUL CLINICAL THERAPY

Nitric oxide (NO) is a gas that has significant effects on many physiologic processes in the body. This gas plays a role in inflammation, the immune response, and neurotransmission in the brain, as well as in the functioning of the cardiovascular system. Dysfunction in the NO pathway is associated with many diseases. Conditions such as atherosclerosis, coronary artery disease (CAD), diabetes, hypertension, erectile dysfunction, and stroke are correlated with NO pathology. Current research suggests that manipulation of NO activity may have profound effects on overall health. Many pharmaceuticals as well as nutrients, supplements, and diet are being investigated and prescribed to modulate NO activity.

THE PHYSIOLOGY OF NO

NO is most notably produced in endothelial cells, macrophages, and neurons. It is a free-radical gas with a half-life of 6–10 seconds, thus providing only localized effects. NO is synthesized by combining L-arginine with oxygen to form L-citrulline and nitric oxide. The enzyme responsible for this conversion is nitric oxide synthase (NOS), which is found in three forms.[1] One form is found in endothelial cells and platelets and is a calcium-calmodulin–dependent enzyme. The second form is a calcium-independent inducible form of the enzyme, and exists in macrophages, neutrophils, cardiac cells, and hepatocytes.[2,3] The third form is found in neural cells. To do its job properly, NOS requires several cofactors, such as tetrahydrobiopterin, heme, flavin mononucleotide (FMN), and flavin adenine dinucleotide (FAD).[4] FAD and FMN are both active forms of riboflavin. Many factors have been shown to modulate NOS activity.

NO has several physiologic functions. One particularly significant role concerns the relaxation of vascular smooth muscle. Endothelium-derived relaxing factor, which is either identical or closely related to NO, is produced by the endothelial cells. Rapid blood flow through the arteries causes induction of the enzyme, increasing NO availability. The presence of NO activates the enzyme guanylate cyclase, causing an increase in cyclic guanosine monophosphate (cGMP). This leads to relaxation of the vascular smooth muscle and, thus, vasodilation. Bradykinin and acetylcholine also can stimulate NO release from the endothelial cells. The ability of NO to decrease platelet aggregation and adhesion is also significant for cardiovascular health.[5] New studies have suggested that NO also plays a role in lipid metabolism regulation.[6]

White blood cells—including macrophages and neutrophils—produce NO. In the immune system, NO functions as a localized bacteriocidal and tumoricidal agent. NO combines with superoxide anions to form highly toxic, bacteriocidal free radicals. Macrophage NOS synthesis is increased in response to lipopolysaccharides from bacteria and cytokines such as interferon-gamma.[7] NO is also formed in the mitochondria. NOS found in the mitochondria is similar to the isoform found in neural cells.[8] NO in the mitochondria regulates the mitochondrial membrane's proton gradient, its membrane potential, and cellular respiration.[9] In the mitochondrial respiratory chain, NO competes with oxygen to inhibit, reversibly, cytochrome c oxidase, which is the terminal electron acceptor.[8] Studies have shown that mitochondrial NOS

activity in the heart increases with increased altitude, indicating that mitochondrial NOS plays a role in elevation adaptation.[10] In addition, NO exhibits activity in the nervous system. NO has been shown to act as a signaling molecule in the brain. Studies have also found that NO plays a role in neurogenesis in both the embryonic and adult brain.[11] NO also operates in the parasympathetic nerve endings in the penis, causing vasodilation and penile erection. NO is important in bone metabolism, and is produced in bone cells in response to the presence of pro-inflammatory cytokines, estrogen, and mechanical loading. Endothelial NOS produces NO that affects normal anabolic osteoblast function. The inducible NOS pathway produces NO that regulates the effects of the pro-inflammatory cytokines interleukin-1 and tumor necrosis factor, both of which stimulate bone resorption.[12] Insulin, insulin-like growth factor, and estrogen have also been shown to modulate NOS synthesis.[13]

WHEN THERE IS NOT ENOUGH NO

NO deficiencies in the body may present as a variety of different health conditions. Most commonly, individuals with low levels of NO will have signs and symptoms of cardiovascular disease such as atherosclerosis, hypertension, CAD, and stroke. In addition, NO deficiency can present as inflammatory conditions or erectile dysfunction. Because NO produced by white blood cells is bacteriocidal and tumoricidal, individuals with deficiencies may present with infections and possibly malignancies.

Because of their physiologic effects on the body, manipulation of NO levels can provide avenues for health modification. Cardiovascular diseases such as atherosclerosis, stroke, hypertension, and CAD can be attenuated by increases in NO synthesis and activity. Anemia, cancer, diabetes, and erectile dysfunction can also be ameliorated by NO manipulation. Both natural therapies and pharmaceuticals can augment NO bioavailability.

NO and Circulation

Atherosclerosis, hypertension, and CAD have all been shown to have a connection to endothelial dysfunction, which often is the result of lowered NO levels. Platelet aggregation and adhesion as well as arterial stiffness are also affected by NO activity. These cardiovascular conditions have been shown to be the result of abnormal NOS expression, decreased NO availability, or resistance to endothelium-dependent vasodilators.[14,15] Studies have indicated that NO, when combined with low oxygen levels as a result of circulatory insufficiency, sensitizes neurons to hypoxia-induced death. Thus, neurons in the brain may be more likely to be damaged from ischemic or hypoxic damage from NO produced as a result of excitotoxicity or inflammation.[16] However, NO combined with normal oxygen levels does not increase neuronal cell death.[17] In addition, NO increases cerebral blood flow, which may actually mean that NO can be protective during an ischemic attack.[18] In short, NO's modulatory effects appear to have a built-in protective effect regardless of oxygen status. With increased NO levels, oxygen delivery is enhanced, thus providing protection from otherwise-ischemic conditions.

NO and Anemia

Individuals with various forms of anemia have been shown to experience endothelial-cell dysfunction. Pulmonary hypertension—the result of such dysfunction—is the leading cause of death in both sickle-cell anemia and thalassemia, both of which have chronic anemia and

intravascular hemolysis as their hallmarks. Chronic intravascular hemolysis is associated with endothelial dysfunction and results in decreased NO availability with a lack of vasodilation.[19]

NO and Diabetes

Individuals with diabetes are more vulnerable to oxidative stress, leading to an increase in superoxide anions and a subsequent decrease in NO bioavailability.[20] Endothelium-dependent vasodilation is impaired in individuals with either type 1 or type 2 diabetes. Many explanations have been suggested for this impairment, including abnormalities in substrate availability or signal transduction, release of endothelium-derived relaxing factors, destruction of endothelium-derived relaxing factors, decreased sensitivity of the vascular smooth muscle to endothelium-derived relaxing factors, and increased release of endothelium-constricting factors.[21] Studies have shown that NO increases basal and insulin-stimulated glucose uptake in skeletal muscle in rats with type 2 diabetes. However, high concentrations of NO inhibit this uptake.[22]

NO and Erectile Dysfunction

Erectile dysfunction is significantly increased in individuals with cardiovascular disease, diabetes, and hypercholesterolemia. Erectile dysfunction is believed to be a condition of vascular origin that may be caused by endothelial damage or dysfunction. Such damage has been correlated with oxidative stress and the resulting decrease in NO.[23] Research has demonstrated that men with erectile dysfunction and without overt cardiovascular disease or diabetes do, in fact, have endothelial dysfunction.[24] Although there are many noncirculatory forms of erectile dysfunction—such as psychogenic, drug-induced, and other types—NO modulation helps patients who experience the condition as a result of circulatory problems.

NO and Neoplasia

The role of NO in neoplastic disease is controversial; research indicates that inducible NOS may have either negative or positive influences on metastasis, malignant transformation, and angiogenesis. NO derived from macrophages has a potentially cytotoxic action on malignant cells.[25] Studies indicate that tumor cells that produce high levels of NO undergo apoptosis. Induction of inducible NOS in sarcoma cells increases NO such that the tumors studied showed complete regression.[26]

Figure 35–1. Artichoke (Cynara scolymus; also called Cynara cardunculus).

NO and Various Other Conditions

Many other diseases have been shown to have a connection to either deficiencies or excesses in NO production. Ocular diseases—from cataracts to glaucoma to diabetic retinopathy—are among such NO-related conditions.[27,28] Other conditions include psoriasis, systemic sclerosis, Parkinson's disease, Alzheimer's disease, and diabetic nephropathy.[29–33] In addition, NO abnormalities may be correlated with diseases such as Huntington's disease, amyotrophic lateral sclerosis, migraine headache, hypertrophic pyloric stenosis, and muscular dystrophy.[34]

> Dysfunction in the nitric acid pathways can cause various disease processes.

''NO''-FRIENDLY NUTRIENTS AND HERBS

L-Arginine

L-Arginine is commonly found in red meat, dairy products, fish, and poultry. As previously mentioned, it is the substrate in the NOS pathway. Many studies have shown that supplementation with L-arginine improves small-vessel coronary endothelial function and promotes vasodilation in individuals with CAD or hypercholesteremia.[35,36] In addition, researchers have found that arginine supplementation improved blood pressure in patients with type 2 diabetes who also had mild hypertension.[37] L-Arginine is commonly taken at 3–9 g per day. Clinically, there remains a concern because of anecdotal evidence that arginine exacerbates herpes

Table 35–1. Natural Therapies for Increasing Nitric Oxide Synthase Levels

Supplement	Dose
L-Arginine	3 g 1–3 times per day
Folic acid	25–100 mg per day
Vitamin B_6	800–3,000 mcg per day
Vitamin B_{12}	500–2,000 mcg per day
Vitamin E	400–800 IU per day
N-acetyl-L-cysteine	1,500–2,000 mg per day
Pycnogenol [a] (French pine bark; Pinus maritima)	100 mg 3 times per day
Garlic (Allium sativum)	600–1200 mg per day
Grape (Vitis vinifera)	75–300 mg per day
American ginseng (Panax quinquefolius)	400 mg per day
Artichoke (Cynara scolymus)	320–640 mg 3 times per day
Dehydroepiandrosterone (DHEA)[b]	25–100 mg per day

[a]Horphag Research, Ltd., Geneva, Switzerland.
[b]DHEA levels should be measured prior to and monitored after beginning this therapy.
IU international unit.

simplex, and thus L-arginine is still commonly avoided in the presence of herpes. Additionally, L-citrulline supplementation increases plasma L-arginine concentration and augments NO-dependent signaling in a dose-dependent manner.[38]

Folic Acid

Several studies have demonstrated that folic acid supplementation can improve endothelium-dependent vasodilation in individuals with CAD.[39,40] Studies have also suggested that folic acid may improve nitrate tolerance in individuals on continuous nitroglycerin as well as improving NOS function, possibly via regenerating tetrahydrobiopterin.[41] Folate inhibits intracellular superoxide production, which increases the half-life of NO, allowing for greater vasodilation. In addition, folic acid decreases homocysteine levels, which are an independent risk factor for cardiovascular disease.[42] Insufficiency of tetrahydrobiopterin results in uncoupling of the arginine-NO pathway, which results in increased superoxide production by NOS and decreased availability of NO. Thus, the regeneration of tetrahydrobiopterin by folate plays a critical role in preventing oxidative stress and enhancing NO synthesis.[43]

Vitamins B_6 and B_{12}

Vitamins B_6 and B_{12}, in addition to folic acid, will decrease homocysteine levels. High levels of homocysteine are suspected of causing endothelial damage, resulting in decreased NO release rates.[44,45]

Vitamin E

Vitamin E is a fat-soluble vitamin, found in grains, fruits, vegetables, and animal products, which has antioxidant and anti-inflammatory actions. Studies performed with mixed

Figure 35–2. Grape (Vinus vitifera) cluster, left, and
Figure 35–3. garlic (Allium sativium), right.

tocopherols have demonstrated that this form of vitamin E supplementation activates endothelial NOS, increases NO release, and decreases platelet aggregation in vivo. While alpha-tocopherol has also been shown to increase NOS activity and NO production, it has a less significant effect.[46]

Figure 35–4. Dandelion (Taraxicum officinale).

N-Acetyl-L-Cysteine

N-acetyl-L-cysteine (NAC) is a thiol derived from the amino acid cysteine. It is the precursor to the potent antioxidant glutathione. NAC has been shown to directly decrease platelet aggregation by increasing the bioavailability of platelet NO.[47]

Pycnogenol

Pycnogenol (Horphag Research, Ltd., Geneva, Switzerland) is an extract from French maritime pine bark (Pinus maritima). This product is commonly used to treat venous insufficiency, asthma, and hypertension. Pycnogenol has anti-inflammatory and antioxidant properties; it also decreases platelet aggregation and prevents oxidation of low-density lipoproteins.[48,49] Pycnogenol has been shown to increase NOS activity in endothelial cells in vitro, resulting in an increase in NO.[50]

Garlic

Garlic (Allium sativum) is frequently used for preventing atherosclerosis, hypertension, and hyperlipidemia, and as an antifungal agent and a cancer preventative.[51–53] Studies have suggested that garlic increases NO production. One study on rats showed that arterial hypertension caused by N-omega-nitro-L-arginine-methylester, which inhibits NOS, is prevented by garlic supplementation. Additionally, NO metabolites were measurably higher in the group treated with garlic, suggesting increased NO production.[54]

Grapes

Vitis vinifera is commonly known as the classic wine grape. Grapes and their juices are high in flavonoids, which are believed to give red wine its cardiovascular protective qualities. Research has shown that grape products, such as grape juice and red wine, increase NO release from platelets, and decrease platelet aggregation and superoxide production.[55] More specifically, research on a constituent of grape skins and seeds known as resveratrol has produced effects on NO. Resveratrol has been demonstrated to have estrogen-like activity and antioxidant, antiplatelet, anti-inflammatory, and anticarcinogenic properties. Studies indicate that resveratrol up-regulates the gene expression of endothelial NOS with a resulting increase in NO levels.[56]

American Ginseng

The root of American ginseng (Panax quinquefolius) is often used as a supplement because of its adaptogenic properties. It is often used for immune modulation and stress resistance, to treat diabetes and hormone imbalances, and as a stimulant. Studies have indicated that ginseng stimulates NO release in vitro.[57]

Artichoke

Cynara scolymus (or Cynara cardunculus) is commonly known as the artichoke. This plant lowers lipids, has antioxidant properties, and calms the digestive system. Luteolin and cynaroside are two flavonoids found in artichoke, which affect NO. These flavonoids increase NOS expression in endothelial cells.[58]

Quercetin

Quercetin is a citrus bioflavonoid used for treating conditions such as atherosclerosis, coronary heart disease, hypercholesterolemia, vascular insufficiency, diabetes, and allergies. Many studies on rats with diabetes have demonstrated that quercetin increases NO availability and induces vasorelaxation via the endothelial NOS pathway.[59,60]

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is an androgen made in the adrenal glands, liver, and testes. This androgen is converted to androstenedione, which is metabolized to other androgens and estrogen. Studies have suggested that DHEA decreases atherosclerosis via a NO-dependent system; researchers have measured increases in NO with DHEA supplementation. This may be partially explained by DHEA's conversion to estrogen.[61]

Melatonin

Melatonin has been shown to decrease mitochondrial NOS induction from bacteria as a result of lipopolysaccharides. It has been suggested that age-related decreases in melatonin may be correlated with the mitochondrial damage that increases with aging. However, this may protect the body from oxidative damage because large amounts of NO are produced in sepsis and shock.[62]

HERBS THAT REDUCE NO LEVELS

A number of botanicals and nutrients have been shown to decrease—rather than increase—NO levels. Generally, these herbs decrease excessive NO. Many of these are herbs known for their anti-inflammatory and antioxidant properties. They include:

- Green tea (Camellia sinensis), which is composed of multiple catechins such as epigallocatechin gallate, is believed to provide much of the physiologic activity of this herb. This particular flavonol has been shown to inhibit inducible NOS activity.[63]

Devil's claw (Harpagophytum procumbens), which is often used to produce anti-inflammatory and analgesic effects. Studies have indicated that this botanical inhibits NOS expression.[64]

Dandelion (Taraxacum officinale), which offers anti-inflammatory, diuretic, and digestive support among its many actions. Research has shown that dandelion inhibits expression of the NOS enzyme as well as cyclooxygenase-2.[65]

Beefsteak plant (Perilla frutescens), which is high in rosmarinic acid as is basil (Ocimum basilicum), mint (Mentha spp.), and sage (Salvia spp.). Rosmarinic acid is an antioxidant that inhibits NO activity and NOS synthesis in macrophages.[66]

PHARMACEUTICALS THAT AFFECT NO LEVELS

While there are clearly a large number of natural therapies that can address NO dysfunctions, there are also pharmaceuticals that are aimed at the problem. Nitroglycerin, sodium nitroprusside, and other nitrates and nitrites increase NO in the endothelium and cause vasodilation of the arteries. These drugs are used to treat hypertensive crisis, angina pectoris, acute myocardial infarction, and heart failure. Tadalafil (Cialis), vardenafil (Levitra), and sildenafil (Viagra) are pharmaceuticals prescribed for erectile dysfunction. They are phosphodiesterase inhibitors that cause vasodilation and hypotension. They are contraindicated for patients who are taking nitrates because NO increases cGMP by activating the enzyme guanyl cyclase and phosphodiesterase metabolizes cGMP. In other words, the enhancement of NO activity by pharmaceuticals may potentiate the effects of the nitrates.[67] It is prudent to use these pharmaceuticals cautiously, especially with patients who have leukemia, sickle-cell anemia, and other underlying health conditions. Some studies have shown that NO may play a significant role in increasing the chemosensitivity of cancer cells. Via the cGMP pathway, NO may be used therapeutically to improve the efficacy of chemotherapeutic agents such as doxorubicin.[68] Statin drugs—or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors—are prescribed to lower cholesterol and decrease the risk of cardiovascular disease and stroke. Studies performed on the statin drug Mevastatin have shown that some of its cardioprotective benefits are the result of this drug's ability to increase endothelial NOS, which has been shown to improve cerebral blood flow in addition to relaxing vascular smooth muscle and inducing vasodilation.[69] Steroid hormones, such as estrogen and DHEA, have also been shown to be cardioprotective and affect NO activity. Studies using 17 beta-estradiol showed an increase in activity of endothelial NOS, which may at least partially explain the antiatherosclerotic effects of estrogen.[70]

MAKING ''NO''-POSITIVE CHANGES IN DIET AND LIFESTYLE

NO levels can be manipulated by dietary intake of specific nutrients such as folic acid, L-arginine, fish oil, and soy foods. The Mediterranean diet—which is high in vegetables, olive oil, red wine, and fish—has been shown to improve endothelial function as well.[71] Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 fatty acids found in the oils of fish such as salmon, cod, and mackerel. These fatty acids compete with arachidonic acid in the lipo-oxygenase and cyclooxygenase pathways, leading to a decrease in inflammatory eicosanoids.[72–74] Fish oils high in DHA and EPA reduce the production of pro-inflammatory

cytokines including interleukin-1, interleukin-2, and tumor necrosis factor.[75–77] Cofactors for NOS such as vitamins B_2 and B_3 and folic acid will improve NO production. In addition, antioxidants such as vitamin C, vitamin E, glutathione, and alpha-lipoic acid improve NO levels by decreasing reactive oxygen species.[78] Vitamins B_6 and B_{12} can decrease cardiovascular risk factors further by decreasing homocysteine. Physical activity has been shown to increase NO activity.[79] Studies have indicated that even low-frequency exercise improves endothelial function as well as decreasing blood pressure (at least in patients with mild hypertension) and raising high-density lipoprotein levels.[80]

CONCLUSIONS

Dysfunction in the NO pathways can cause various disease processes. Natural therapeutics provide many ways to augment NO synthesis and bioavailability and improve overall health. Nutrients, diet, and botanical supplementation are proven methods for modulating NO and addressing health conditions that result from its deficiency. As with all health interventions, of course, treatment should be individualized to each patient.

REFERENCES

[1]Morishita T, Tsutsui M, Shimokawa H, et al. Nephrogenic diabetes insipidus in mice lacking all nitric oxide synthase isoforms. Proc Natl Acad Sci USA. 2005;102:10616–10621.

[2]Champe, PC, Harvey RA. Lippincott's Illustrated Reviews: Biochemistry, 2nd Edition. Philadelphia: Lippincott-Raven Publishers, 1994.

[3]Balligand JL, Cannon PJ. Nitric oxide synthases and cardiac muscle: Autocrine and paracrine influences. Arterioscler Thromb Vasc Biol. 1997;17:1846–1858.

[4]Wyatt AW, Steinert JR, Mann GE. Modulation of the L-arginine=nitric oxide signaling pathway in vascular endothelial cells. Biochem Soc Symp. 2004;71:143–156.

[5]Guyton AC, Hall JE. Textbook of Medical Physiology, 9th Edition. Philadelphia: W.B. Saunders, 1996.

[6]Schild L, Jaroscakova I, Lendeckel U, et al. Neuronal nitric oxide synthase controls enzyme activity pattern of mitochondria and lipid metabolism. FASEB J. 2005;20:145–147.

[7]Cotran RS, Kumar V, Robbins SL. Pathological Basis of Disease, 5th Edition. Philadelphia: W.B. Saunders, 1994.

[8]Persichini T, Mazzone V, Polticelli F, et al. Mitochondrial type I nitric oxide synthase physically interacts with cytochrome c oxidase. Neurosci Lett. 2005;384:254–259.

[9]Schulz R, Rassaf T, Massion PB, et al. Recent advances in the understanding of the role of nitric oxide in cardiovascular homeostasis. Pharmacol Ther. 2005;108:225–256.

[10]Gonzales GF, Chung FA, Miranda S, et al. Heart mitochondrial nitric oxide synthase is upregulated in male rats exposed to high altitude (4,340 m). Am J Physiol Heart Circ Physiol. 2005;288:H2568–H2573.

[11]Moreno-Lopez B, Noval JA, Gonzalez-Bonet LG, Estrada C. Morphological bases for a role of nitric oxide in adult neurogenesis. Brain Res. 2000;869(1–2):244–250.

[12]van't Hof RJ, Macphee J, Libouban H, et al. Regulation of bone mass and bone turnover by neuronal nitric oxide synthase. Endocrinology. 2004;145:5068–5074.

[13]Lane P, Gross SS. The autoinhibitory control element and calmodulin conspire to provide physiological modulation of endothelial and neuronal nitric oxide synthase activity. Acta Physiol Scand. 2000 Jan;168(1): 53–63.

[14]Panza JA, Casino PR, Kilcoyne CM, Quyyumi AA. Role of endothelium-derived nitric oxide in the abnormal endothelium-dependent vascular relaxation of patients with essential hypertension. Circulation. 1993;87:1468–1474.

[15]Cockcroft JR. Exploring vascular benefits of endothelium-derived nitric oxide. Am J Hypertens. 2005; 18(suppl.):177–183.

[16]Mander P, Brown GC. Nitric oxide, hypoxia and brain inflammation. Biochem Soc Trans. 2004;32(pt6): 1068–1069.

[17]Mander P, Borutaite V, Moncada S, Brown GC. Nitric oxide from inflammatory-activated glia synergizes with hypoxia to induce neuronal death. J Neurosci Res. 2005;79(1–2):208–215.
[18]Endres M, Laufs U, Liao JK, Moskowitz MA. Targeting eNOS for stroke protection. Trends Neurosci. 2004;27:283–289.
[19]Gladwin MT, Kato GJ. Cardiopulmonary complications of sickle cell disease: Role of nitric oxide and hemolytic anemia. Hematology [Am Soc Hematol Educ Program]. 2005;51–57.
[20]Nitenberg A. Endothelial dysfunction in patients with diabetes: Identification, pathogenesis and treatment [in French]. Presse Med. 2005; 34:1654–1661.
[21]De Vriese AS, Verbeuren TJ, Van de Voorde J, et al. Endothelial dysfunction in diabetes. Br J Pharmacol. 2000;130:963–974.
[22]McGrowder D, Ragoobirsingh D, Brown P. Acute effects of exogenous nitric oxide on glucose uptake in skeletal muscle of normoglycaemic and diabetic rats. Med Sci Monit. 2005;12:BR28–BR35.
[23]Agarwal A, Nandipati KC, Sharma RK, et al. Role of oxidative stress in pathophysiology of erectile dysfunction. J Androl. 2005;[Epub ahead of print]. Abstract in online document at: www.ncbi.nlm.nih.gov=entrez=query.fcgi?cmd Retrieve&db pubmed&dopt Abstract&list_uids 16339449&query_hl 7&itool pubmed_docsum. Accessed March 9, 2006.
[24]Kaya C, Uslu Z, Karaman I. Is endothelial function impaired in erectile dysfunction patients? Int J Impot Res. 2006;18:55–60.
[25]Lechner M, Lirk P, Rieder J. Inducible nitric oxide synthase (iNOS) in tumor biology: The two sides of the same coin. Semin Cancer Biol. 2005; 15:277–289.
[26]Xie K, Fidler IJ. Therapy of cancer metastasis by activation of the inducible nitric oxide synthase. Cancer Metastasis Rev. 1998;17:55–75.
[27]Ohia SE, Opere CA, Leday AM. Pharmacological consequences of oxidative stress in ocular tissues. Mutat Res. 2005;579(1–2):22–36.
[28]Tsai DC, Chiou SH, Lee FL, et al. Possible involvement of nitric oxide in the progression of diabetic retinopathy. Ophthalmologica. 2003;217:342–346.
[29]Ibba-Manneschi L, Niissalo S, Milia AF, et al. Variations of neuronal nitric oxide synthase in systemic sclerosis skin. Arthritis Rheum. 2005;54:202–213.
[30]Lowes MA, Chamian F, Abello MV, et al. Increase in TNF-a and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction with efalizumab (anti-CD11a). Proc Natl Acad Sci USA. 2005;102:19057–19062.
[31]Prabhakar SS. Pathogenic role of nitric oxide alterations in diabetic nephropathy. Curr Diabetes Rep. 2005;5:449–454.
[32]Thatcher GR, Bennett BM, Reynolds JN. Nitric oxide mimetic molecules as therapeutic agents in Alzheimer's disease. Curr Alzheimer Res. 2005;2:171–182.
[33]Okuno T, Nakatsuji Y, Kumanogoh A, et al. Loss of dopaminergic neurons by the induction of inducible nitric oxide synthase and cyclooxygenase-2 via CD 40: Relevance to Parkinson's disease. J Neurosci Res. 2005;81:874–882.
[34]Bredt DS. Endogenous nitric oxide synthesis: Biological functions and pathophysiology. Free Radic Res. 1999;31:577–596.
[35]Lerman A, Burnett JC Jr, Higano ST, et al. Long-term L-arginine improves small-vessel coronary endothelial function in humans. Circulation. 1998;97:2123–2128.
[36]Creager MA, Gallagher SJ, Girerd XJ, et al. L-Arginine improves endothelium-dependent vasodilation in hypercholesterolemic humans. J Clin Invest. 1992;90:1248–1253.
[37]Huynh NT, Tayek JA. Oral arginine reduces systemic blood pressure in type 2 diabetes: Its potential role in nitric oxide generation. J Am Coll Nutr. 2002;21:422–427.
[38]Schwedhelm E, Maas R, Freese R, Jung D, Lukacs Z, Jambrecina A, Spickler W, Schulze F, Böger RH. Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: impact on nitric oxide metabolism. Br J Clin Pharmacol. 2007 Jul 27;[Epub ahead of print]
[39]Voutilainen S, Rissanen TH, Virtanen J, et al. Low dietary folate intake is associated with an excess incidence of acute coronary events. Circulation. 2001;103:2674–2680.
[40]Thambyrajah J, Landray MJ, Jones HJ, et al. A randomized double-blind placebo-controlled trial of the effect of homocysteine-lowering therapy with folic acid on endothelial function in patients with coronary artery disease. J Am Coll Cardiol. 2001;37:1858–1863.
[41]Gori T, Burstein JM, Ahmed S, et al. Folic acid prevents nitroglycerin-induced nitric oxide synthase dysfunction and nitrate tolerance. Circulation. 2001:104;1119–1123.
[42]Das UN. Folic acid says NO to vascular diseases. Nutrition. 2003; 19(7–8):686–692.
[43]Werner ER, Gorren AC, Heller R, Werner-Felmayer G, Mayer B. Tetrahydrobiopterin and nitric oxide: mechanistic and pharmacological aspects. Exp Biol Med (Maywood). 2003 Dec;228(11):1291–1302.

[44]Mayer EL, Jacobsen DW, Robinson K. Homocysteine and coronary atherosclerosis. J Am Coll Cardiol. 1996;27:517–527.
[45]Holven KB, Holm T, Aukrust P, et al. Effect of folic acid treatment on endothelium-dependent vasodilation and nitric oxide-derived end products in hyperhomocysteinemic subjects. Am J Med. 2001;110: 536–542.
[46]Liu M, Wallmon A, Olsson-Mortlock C, et al. Mixed tocopherols inhibit platelet aggregation in humans: Potential mechanisms. Am J Clin Nutr. 2003;77:700–706.
[47]Anfossi G, Russo I, Massucco P, et al. N-acetyl-L-cysteine exerts direct anti-aggregating effect on human platelets. Eur J Clin Invest. 2001;31:452–461.
[48]Packer L, Midori H, Toshikazu Y, eds. Antioxidant Food Supplements in Human Health. San Diego: Academic Press, 1999.
[49]Rice-Evans CA, Packer L, eds. Flavonoids in Health and Disease. New York: Marcel Dekker, 1998.
[50]Fitzpatrick DF, Bing B, Rohdewald P. Endothelium-dependent vascular effects of Pycnogenol. J Cardiovasc Pharmacol. 1998;32:509–515.
[51]Koscielny J, Klussendorf D, Latza R, et al. The antiatherosclerotic effect of Allium sativum. Atherosclerosis. 1999;144:237–249.
[52]Auer W, Eiber A, Hertkorn E, et al. Hypertension and hyperlipidaemia: Garlic helps in mild cases. Br J Clin Pract Symp Suppl. 1990;69:3–6.
[53]Ledezma E, Lopez JC, Marin P, et al. Ajoene in the topical short-term treatment of tinea cruris and tinea corporis in humans: Randomized comparative study with terbinafine. Arzneimittelforschung. 1999;49:544–547.
[54]Pedraza-Chaverri J, Tapia E, Medina-Campos ON, et al. Garlic prevents hypertension induced by chronic inhibition of nitric oxide synthesis. Life Sci. 1998;62:71–77.
[55]Freedman JE, Parker C, Li L, et al. Select flavonoids and whole juice from purple grapes inhibit platelet function and enhance nitric oxide release. Circulation. 2001;103:2792–2798.
[56]Wallerath T, Deckert G, Ternes T, et al. Resveratrol, a polyphenolic phytoalexin present in red wine, enhances expression and activity of endothelial nitric oxide synthase. Circulation. 2002;106:1652–1658.
[57]Yuan CS, Attele AS, Wu JA, et al. Panax quinquefolium L. inhibits thrombin-induced endothelin release in vitro. Am J Chin Med. 1999;27:331–338.
[58]Li H, Xia N, Brausch I, Yao Y, Forstermann U. Flavonoids from artichoke (Cynara scolymus L.) up-regulate endothelial-type nitric-oxide synthase gene expression in human endothelial cells. J Pharmacol Exp Ther. 2004;310:926–932.
[59]Ajay M, Achike FI, Mustafa AM, Mustafa MR. Effect of quercetin on altered vascular reactivity in aortas isolated from streptozotocin-induced diabetic rats. Diabetes Res Clin Pract. 2005;[Epub ahead of print]. Abstract in online document at: www.ncbi.nlm.nih.gov=entrez=query.fcgi?orig_db PubMed&db PubMed& cmd Search&term Diabetes Res Clin Pract[Jour] AND 2005[pdat] AND Ajay M[author]. Accessed March 8, 2006.
[60]Roghani M, Baluchnejadmojarad T, Vaez-Mahdavi MR, Roghani-Dehkordi F. Mechanisms underlying quercetin-induced vasorelaxation in aorta of subchronic diabetic rats: An in vitro study. Vascul Pharmacol. 2004;42:31–35.
[61]Hayashi T, Teiji Esaki T, Emiko Muto E, et al. Dehydroepiandrosterone retards atherosclerosis formation through its conversion to estrogen: The possible role of nitric oxide. Arterioscler Thromb Vasc Biol. 2000; 20:782–792.
[62]Escames G, Leon J, Macias M, et al. Melatonin counteracts lipopolysaccharide-induced expression and activity of mitochondrial nitric oxide synthase in rats. FASEB J. 2003;17:932–934.
[63]Ahmed S, Rahman A, Hasnain A, et al. Green tea polyphenol epigallocatechin-3-gallate inhibits the IL-1 beta-induced activity and expression of cyclooxygenase-2 and nitric oxide synthase-2 in human chondrocytes. Free Radic Biol Med. 2002;33:1097–1105.
[64]Jang MH, Lim S, Han SM, et al. Harpagophytum procumbens suppresses lipopolysaccharide-stimulated expressions of cyclooxygenase-2 and inducible nitric oxide synthase in fibroblast cell line L929. J Pharmacol Sci. 2003 Nov;93:367–371.
[65]Hu C, Kitts DD. Luteolin and luteolin-7-O-glucoside from dandelion flower suppress iNOS and COX-2 in RAW264.7 cells. Mol Cell Biochem. 2004;265:107–113.
[66]Qiao S, Li W, Tsubouchi R, et al. Rosmarinic acid inhibits the formation of reactive oxygen and nitrogen species in RAW264.7 macrophages. Free Radic Res. 2005;39:995–1003
[67]Medscape. Contraindicated Drug Combination: CGMP Specific PDE Type-5 Inhibitors=Nitrates 1994–2005. Online document at: www.medscape.com=druginfo=monoinfobyid?cid med&monotype druginter& monoid 363&mononame CGMP SPECIFIC PDE TYPE-5 INHIBITORS%2FNITRATES&drugid 7418&drugname Sildenafil Oral&intertype contr. Accessed December 30, 2005.

[68]Muir CP, Adams MA, Graham CH. Nitric oxide attenuates resistance to doxorubicin in three-dimensional aggregates of human breast carcinoma cells. Breast Cancer Res Treat. 2005;[Epub ahead of print]. Abstract in online document at: www.ncbi.nlm.nih.gov=entrez=query.fcgi?orig_db PubMed&db PubMed&cmd Search&term Breast Cancer Res Treat.[Jour] AND 2005[pdat AND Muir CP[author]. Accessed March 8, 2006.

[69]Amin-Hanjani S, Stagliano NE, Yamada M, et al. Mevastatin, an HMG-CoA reductase inhibitor, reduces stroke damage and upregulates endothelial nitric oxide synthase in mice. Stroke. 2001;32:980–986.

[70]Hayashi T, Yamada K, Esaki T, et al. Estrogen increases endothelial nitric oxide by a receptor-mediated system. Biochem Biophys Res Commun. 1995;214:847–855.

[71]Cuevas AM, Germain AM. Diet and endothelial function. Biol Res. 2004;37:225–230.

[72]Leaf A. On the reanalysis of the GISSI-Prevenzione. Circulation. 2002;105:1874–1875.

[73]Connor WE. n-3 Fatty acids from fish and fish oil: Panacea or nostrum? Am J Clin Nutr. 2001;74; 415–416.

[74]Calder PC. N-3 polyunsaturated fatty acids, inflammation and immunity: Pouring oil on troubled waters or another fishy tale? Nutr Res. 2001;21:309–341.

[75]Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration. Letter Regarding Dietary Supplement Health Claim for Omega-3 Fatty Acids and Coronary Heart Disease. Online document at: http:=vm.cfsan.fda.gov=~dms=ds-ltr11.html. Accessed May 10, 2005.

[76]Kelley DS, Rudolph IL. Effect of individual fatty acids of omega-6 and omega-3 type on human immune status and role of eicosanoids. Nutrition. 2000;16:143–145.

[77]Meydani SN, Dinarello CA. Influence of dietary fatty acids on cytokine production and its clinical implications. Nutr Clin Pract. 1993;8:65–72.

[78]Osiecki H. The role of chronic inflammation in cardiovascular disease and its regulation by nutrients. Altern Med Rev. 2004;9:32–53.

[79]Jackson MJ. Reactive oxygen species and redox-regulation of skeletal muscle adaptations to exercise. Philos Trans R Soc Lond B Biol Sci. 2005;29;360:2285–2291.

[80]Moriguchi J, Itoh H, Harada S, et al. Low frequency regular exercise improves flow-mediated dilatation of subjects with mild hypertension. Hypertens Res. 2005;28(4):315–321.

36

SYNERGY IN NUTRIENTS

Natural medicine had its beginnings in the use of whole foods at the outset of human history. Prior to the advent of modern encapsulated natural medicine, our ancestors utilized medicines in their natural states without improvements (other than by increasing supply and storage). A central tenet of natural medicine is that food is medicine. Nature's bounty is shown to be truly amazing when we consider the diverse array of natural medicines (and nearly 35% of pharmacologic medicines) that are derived from mainly plants and minerals. Hippocrates's age-old wisdom stated: ''Let your food be your medicine and let your medicine be your food.'' This adage eloquently highlights this principle. The majority of humans who have ever lived on this planet (and those living today) overwhelmingly utilized natural medicines. The use of modern (conventional) medicines (as defined by substances other than foods) began roughly 150–200 years ago. Advances in medical technology have even led us away from the whole-food approach toward a pharmaceutical mentality, as whole medicines are continually separated into increasingly individualized ''active'' components and placed into pills. Despite these technological advances in the process of identification and isolation of active components, we are seeing that this process does not entirely guarantee the ultimate use of a whole medicine. Humankind never matches the mastery of whole-food medicines in quite the way nature has assembled them for us. Today, close to one-third of Americans use some form of nutritional medicine. This is an optimal situation because processed foods and synthetic drugs take their toll on health. It is both amazing and not surprising that, in order to maintain normal physiologic functioning, we are dependent on whole-food–derived supplements. Because of this, our choices in utilizing and understanding nature's pharmacy dictate how we use this bounty from which humans have benefited throughout time. This chapter is merely intended to demonstrate a few out of the thousand synergistic relationships that the clinician should consider when seeking to maximize nutritional therapeutics.

COENZYME Q10

Found in high concentrations in the heart muscle and other highly metabolic organs (the brain and liver), coenzyme Q10's (CoQ10's) main purpose appears to be to serve as a cofactor in energy-producing pathways. Perhaps the most important function is the synthesis of adenosine triphosphate (ATP), the body's currency of energy during oxidative respiration.[1] CoQ10 is found in increasingly higher concentrations within cells, with the highest amounts found in the mitochondria, where all cellular energy is produced. Other important functions of CoQ10 include antioxidative and cellular membrane stabilization.[2] CoQ10 works in the final step in energy production (ATP synthesis) and can also prevent metabolically induced damage (via antioxidant and membrane stabilization) to the cardiovascular system. Not only useful in the cardiovascular system, CoQ10 can be used to treat diseases of the muscle, connective tissues, and brain, among others.

L-CARNITINE

The amino acid L-carnitine is synthesized from two other amino acids, lysine and methionine, and 98% of L-carnitine is found in heart tissue and skeletal muscles. L-carnitine is vital for heart-tissue health because this amino acid plays an essential role in transporting free fatty acids into the mitochondria, where they undergo beta-oxidation, a source of energy production in the heart.[3] Low levels of L-carnitine have been observed in patients suffering from angina pectoris. Using a supplement with L-carnitine can reduce the number of angina episodes, increase exercise performance, and reduce ST segment depression (a marker of cardiac-muscle oxygen starvation on an electrocardiogram).[4] Levels of L-carnitine are reduced in up to 50% in diseased hearts,[5] and use of this supplement can reduce symptoms of congestive heart failure and increase survival.[6] Heart diseases, such as ischemic cardiomyopathy, heart failure, hypertrophy, and dilated cardiomyopathy, all have a similar problem in energy metabolism: ATP synthesis is decreased because inadequate fatty-acid fuels are delivered to the mitochondria. L-carnitine has been indicated as a key nutrient that is depleted in these diseases.[7] Similar to CoQ10, L-carnitine is a key nutrient in heart-muscle metabolism and energy production.

COQ10 AND L-CARNITINE

CoQ10 and L-carnitine assist mitochondrial energy production and prevent oxidative damage in the heart.[8] Taken together, these nutrients assist the heart muscle by increasing transport of crude energy sources (fatty acids) into the mitochondria whereupon beta-oxidation yields energy for the working tissue. When the breakdown of fatty acids is complete, ATP, the body's self-created energy source, is produced. CoQ10 is needed in this process for final synthesis of energy for the heart. The protective effects of these nutrients, when used in combination, have been demonstrated in laboratory animals that were subjected to reperfusion injuries.[9] Investigators demonstrated that, when used in association with each other, these compounds were more effective for preventing oxidative damage and metabolic abnormalities (hemodynamic parameters) than when used individually.

In addition to their role in cardiovascular health, CoQ10 and L-carnitine, with the previously mentioned mitochondrial energy production and antioxidative capabilities, may play a role in the prevention and treatment of Parkinson's disease.[10] Strong evidence suggests that mitochondrial dysfunction and concomitant oxidative damage are integral in the pathogenesis of this disease, and further study of the protective effects of these nutrients are needed. Evidence from animal studies suggests that these nutrients may indeed be helpful. Another condition in mitochondrial dysfunction that plays a role is age-related macular degeneration (ARMD). Researchers who observed the utility of nutritional compounds for improving mitochondrial functions (mitotropic compounds) tested L-carnitine and CoQ10 among others (polyunsaturated fatty acids and vitamin E).[11] Patients with ARMD were treated with a mixture of mitotropic compounds. Measures of macular acuity (recovery time following photostress, foveal sensitivity, and mean visual-field defects) were measured and compared in subjects who took the mixture to these parameters in patients who were given only vitamin E. Follow-ups over the next 3, 6, 9, 12, and 24 months revealed improved visual functions in all areas, and improvements remained stationary throughout the follow-up period while the patients in the control group experienced worsened symptoms. The literature describes several other instances of synergistic benefits from using these nutrients together.

CHOLINE

Recently, it has been discovered that choline, long considered to be a B vitamin, is produced in very small amounts in the human body. Although produced endogenously, the amount of choline is quite minimal and, when it is taken in supplemental doses, has several beneficial effects in the body. Produced in the liver, choline is used to synthesize cellular membranes[12] and works as a methyl donor to create new compounds in the body. This process is important in the creation of DNA and in the conversion of homocysteine (an amino acid with negative effects on the cardiovascular system) to methionine. Choline, in the form of phosphatidylcholine, can increase the solubility of cholesterol in the body, lower cholesterol levels, and inhibit platelet aggregation.[13] In a study, 32 patients with elevated cholesterol and triglycerides were treated with 3.5 g of phosphatidylcholine three times per day before meals. Among the subjects, cholesterol levels decreased by 33%, triglycerides by 33%, and high-density lipoprotein cholesterol increased by 46% after 30 days of treatment.[14] In supplemental form, choline is useful for accelerating the metabolism of cholesterol and in energy production.

CHOLINE AND L-CARNITINE

When supplemented with L-carnitine, choline decreases urinary excretion and renal clearance of L-carnitine. In one study, subjects treated with choline had decreased urinary L-carnitine clearance by up to 84%.[15] In another study, young adult women who took choline at 20 mg per kg of body weight had a 75% lower urinary L-carnitine excretion than a control group, and plasma L-carnitine levels were not significantly altered.[16] A combination of both nutrients can be beneficial for retaining L-carnitine, allowing for greater metabolic utilization of this nutrient. In a small, placebo-controlled study, 19 women were supplemented with choline and=or L-carnitine orally for 21 days. The results showed oxidative stress measured by thiobarbituric acid reactive substances was significantly lower in the groups supplemented with choline, carnitine, or both and mild exercise (walking) did not decrease this effect. In addition, serum concentrations of vitamins A and E were higher in the supplemented groups even though the consumption of these nutrients was not different among the groups, suggesting that choline and carnitine supplementation lowers lipid peroxidation, and promotes conservation of retinol and alpha-tocopherol as well.[17]

L-CARNITINE AND VITAMIN C

Vitamin C, or ascorbate, acts as a cofactor in the synthesis of L-carnitine, specifically in two alpha-ketoglutarate–requiring dioxygenase reactions in the pathway of L-carnitine biosynthesis.[18] Investigations have revealed that higher supplemental amounts of ascorbate will enhance L-carnitine synthesis.[19] Results from a study of ascorbate and L-carnitine biosynthesis showed that increased concentrations of supplemental ascorbate resulted in enhanced ketogenesis and decreased triglyceride accumulation, suggesting that L-carnitine synthesis is dependent on ascorbate.[20] As mentioned earlier, L-carnitine can play a role in addressing reperfusion injury when used with CoQ10. Additional evidence cites the importance of vitamin C and L-carnitine for treating reperfusion injury.[21] In laboratory animals, ischemic changes were seen less frequently in tissue samples treated with both vitamin C and L-carnitine compared to

tissue samples obtained from control and placebo groups. The researchers concluded that these nutrients are effective for reducing reperfusion injury in skeletal muscle.

Another example of the synergistic uses of L-carnitine and ascorbic acid lies in their relative amounts in the body. In order to determine if L-carnitine metabolism is a useful parameter for determining vitamin C requirements, researchers investigated whether a diet with controlled amounts of vitamin C would affect L-carnitine levels.[22] Plasma levels of free L-carnitine (and histamine, another study parameter) were inversely related to vitamin C status. This indicates that L-carnitine levels are altered in subjects with subnormal, but nonscorbutic vitamin C status, indicating that metabolic changes other than collagen metabolism dysfunction occur before scurvy becomes manifested. Therefore, researchers suggest that using the appearance of scurvy as an end point in determining vitamin C requirements may not be useful in establishing reference amounts of vitamin C for optimal health status. Because of the necessity of vitamin C in the synthesis of L-carnitine, and the energy producing effects of L-carnitine, vitamin C should be supplemented with this amino acid to ensure proper function and optimal energy production.

L-carnitine can play a role in addressing reperfusion injury when used with CoQ10.

FLAVONOIDS

Flavonoids are a large grouping of plant pigments responsible for the darker coloring of various fruits, vegetables, and other plants. These molecules are well-known for their affinity for the vascular system and the supportive role they play in decreasing capillary fragility, preventing breakdown of venous support structures, and increasing the tone of the muscles surrounding certain parts of the vasculature.[23] Flavonoids have been well-studied in relation to vasculature disease. Research has shown decreased postinfarct tissue damage, decreased incidence of ventricular fibrillation, decreased free radicals in heart muscle fluids, improved post-myocardial-infarct ventricular function, and reduced amounts of foam cells (an early manifestation of atherosclerosis) all following supplementation with flavonoids.[24] Flavonoid supplementation can also decrease the amount of oxidized low-density lipoprotein (LDL) in patients with elevated blood cholesterol, as demonstrated in the previously mentioned studies. Flavonoids derived from grape (Vitis vinifera) seed extract decrease the activity of proteolytic enzymes that are responsible for the breakdown of connective tissues, thereby preventing premature destruction of venous structures.[25] Flavonoids derived from bilberry (Vaccinium myrtillus) strengthen and stabilize collagen synthesis,[26] as well as decrease vascular permeability and fragility, thereby preventing capillary leakage and swelling.[27] When used to treat cholesterol-induced atheroma, bilberry flavonoids decreased pathologic proliferation in blood vessel linings, lipid deposition, and calcium deposition in the lesions.[28]

FLAVONOIDS AND VITAMIN C

When combined with vitamin C, flavonoids will enhance the vitamin's function by improving its absorption and protecting it from oxidation in the body. One study revealed that, when

administered in combination with a flavonoid-rich citrus extract, ascorbate was absorbed by an increased 35% over ascorbate that was administered alone.[29] Another investigation demonstrated the antioxidative abilities of soy (Glycine soja) and alfalfa (Medicago sativa) extracts, both of which have flavonoids as main active ingredients.[30] The two extracts had notable antioxidant capability as expressed by decreased LDL oxidation; however, when acerola cherry (Malpighia glabra) extract (which is rich in ascorbic acid) was added, the antioxidative effect was enhanced further. The investigators concluded that ascorbate could enhance the activity of flavonoid-rich antioxidants. It was suggested that this synergistic activity was the result of the ''peroxidolitic'' action of ascorbic acid complemented by flavonoid-induced stabilization of the LDL in this particular study and the suppression of free-radical species propagation. This research team also noted that the combination decreased the amounts of phytoestrogens needed to achieve significant antioxidative activity. These studies demonstrate the protective mechanism by which bioflavonoids help to stabilize and strengthen the vasculature as well as preventing cardiovascular disease processes.

MAGNESIUM

Inadequate intake of magnesium is associated with the development of cardiovascular diseases, including hypertension, cardiomyopathy, atherosclerosis, and strokes.[31] In addition, suboptimal tissue stores are implicated in increased heart arrhythmia and cardiovascular-disease complications.[32] Population studies associate higher circulating blood levels of magnesium with decreased risks of coronary heart disease;[33] imbalances of intracellular levels of minerals such as magnesium are associated with cardiovascular disease.[34] Adequate magnesium intake is consistently associated with healthier heart statistics, most probably the result of this mineral's effect on lowering blood pressure. Keeping blood pressure low is an integral part of heart-disease prevention because hypertension is often a reliable predictor of heart disease in later life.

Magnesium, in addition to its use in preventing heart diseases, is necessary for absorption of vitamin B_6.

MAGNESIUM AND B VITAMINS

Magnesium, in addition to its use in preventing heart diseases, is necessary for absorption of vitamin B_6. Investigators have revealed that a deficiency of magnesium will impair vitamin B_6 status via a decreased ability of intracellular magnesium to stimulate alkaline phosphatase, an enzyme that is required for uptake of pyridoxal phosphate in tissues.[35] One study demonstrated the ability of high serum homocysteine levels to deplete magnesium levels in cerebral vascular smooth-muscle cells (VSMCs).[36] Depletion of magnesium was not prevented by incubating the VSMCs with vitamin B_6, folic acid, or vitamin B_{12} alone. When investigators combined all three vitamins however, the loss of magnesium was completely inhibited. These findings are further evidence to support the hypothesis that elevated homocysteine serum levels lead to abnormal metabolism of magnesium in cerebral VSMCs, thereby priming the cells for homocysteine-induced atherogenesis, vasospasms, and stroke. This study demonstrated a need

for all three vitamins in addition to adequate magnesium (to achieve physiologic levels) to prevent cerebral vascular diseases that are induced by homocysteinemia.

CONCLUSIONS

This is a reminder of how amazingly and efficiently the human body responds to the addition of relatively simple nutritional strategies as well as these effects on the physical and mental realms. Despite our many medical technological advances, medicine is far from achieving the ability to mimic natural medicines in their native states. Remembering (and continually discovering) the many ways in which simple nutritional factors work in the body, and that, rarely, does one nutrient achieve what many working in combination will, positive improvements can be made in the direction of true healing. Remembering that nature's wisdom is responsible for the synergism of its bounty, practitioners of natural medicine must realize how powerful the sum of these nutrients is when using nutritionally based medicines.

REFERENCES

[1]Greenberg S, Fishman WH. Coenzyme Q10: A new drug for cardiovascular disease. J Clin Pharmacol. 1990;30:596–608.
[2]Pizzorno JE Jr, Murray M. Textbook of Natural Medicine, 2nd Edition. New York: Churchill Livingstone, 1999.
[3]Evans A, Fornasini G. Pharmacokinetics of L-carnitine. Clin Pharmacokinet. 2003;42:941–967.
[4]Cacciatore L, Cerio R, Ciarimboli M, et al. The therapeutic effect of L-carnitine in patients with exercise-induced stable angina: A controlled study. Drugs Exp Clin Res. 1991;17:225–235.
[5]Sole MJ, Jeejeebhoy KN. Conditioned nutritional requirements and the pathogenesis and treatment of myocardial failure. Curr Opin Clin Nutr Metab Care. 2000;3:417–424.
[6]Rizos I. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. Am Heart J. 2000;139 (2pt3):S120–S123.
[7]Carvajal K, Moreno-Sanchez R. Heart metabolic disturbances in cardiovascular diseases. Arch Med Res. 2003;34:89–99.
[8]Bertelli A, Ronca G. Carnitine and coenzyme Q10: Biochemical properties and functions, synergism and complementary action. Int J Tissue React. 1990;12:183–186.
[9]Bertelli A, Ronca F, Ronca G, Palmieri L, Zucchi R. L-Carnitine and coenzyme Q10 protective action against ischaemia and reperfusion of working rat heart. Drugs Exp Clin Res. 1992;18:431–436.
[10]Beal MF. Bioenergetic approaches for neuroprotection in Parkinson's disease. Ann Neurol. 2003;53 (suppl.3)S39–S47;discussion S47–S48.
[11]Feher J, Papale A, Mannino G, Gualdi L, Balacco Gabrieli C. Mitotropic compounds for the treatment of age-related macular degeneration: The metabolic approach and a pilot study. Ophthalmologica. 2003;217: 351–357.
[12]Zeisel SH. Choline: Needed for normal development of memory. J Am Coll Nutr. 2000;19(5 suppl.):528S–531S.
[13]Brook JG, Linn S, Aviram M. Dietary soya lecithin decreases plasma triglyceride levels and inhibits collagen- and ADP- induced platelet aggregation. Biochem Med Metabol Biol. 1986;35;31–39.
[14]Wojcicki J. Clinical evaluation of lecithin as a lipid-lowering agent. Phytotherapy Res. 1995;9:597–599.
[15]Dodson WL, Sachan DS. Choline supplementation reduces urinary carnitine excretion in humans. Am J Clin Nutr. 1996;63:904–910.
[16]Daily JW 3rd, Sachan DS. Choline supplementation alters carnitine homeostasis in humans and guinea pigs. J Nutr. 1995;125:1938–1944.
[17]Sachan DS, Hongu N, Johnsen M. Decreasing oxidative stress with choline and carnitine in women. J Am Coll Nutr. 2005 Jun;24(3):172–176.
[18]Rebouche CJ. Ascorbic acid and carnitine biosynthesis. Am J Clin Nutr. 1991;54(6 suppl.):1147S–1152S.
[19]Otsuka M, Matsuzawa M, Ha TY, Arakawa N. Contribution of a high dose of L-ascorbic acid to carnitine synthesis in guinea pigs fed high-fat diets. J Nutr Sci Vitaminol (Tokyo). 1999;45:163–171.

[20]Ha TY, Otsuka M, Arakawa N. Ascorbate indirectly stimulates fatty acid utilization in primary cultured guinea pig hepatocytes by enhancing carnitine synthesis. J Nutr. 1994;124:732–737.
[21]Akar H, Sarac A, Konuralp C, Yildiz L, Kolbakir F. Comparison of histopathologic effects of carnitine and ascorbic acid on reperfusion injury. Eur J Cardiothorac Surg. 2001;19:500–506.
[22]Johnston CS, Solomon RE, Corte C. Vitamin C depletion is associated with alterations in blood histamine and plasma free carnitine in adults. J Am Coll Nutr. 1996;15:586–591.
[23]Henriet JP. Veno-lymphatic insufficiency: 4,729 patients undergoing hormonal and procyanidol oligomer therapy Phlebologie. 1993;46:313–325.
[24]Bagchi D, Sen CK, Ray SD, Das DK, Bagchi M, Preuss HG, Vinson JA. Molecular mechanisms of cardioprotection by a novel grape seed proanthocyanidin extract. Mutat Res. 2003;523–524:87–97.
[25]Peirce A. The American Pharmaceutical Association Practical Guide to Natural Medicines. New York: William Morrow and Co., 1999.
[26]Harvsteen B. Flavonoids, a class of natural products of high pharmacological potency. Biochem Pharmacol. 1983;32:1141–1148.
[27]Bottecchia D, et al. Preliminary reports on the inhibitory effect of Vaccinium myrtillus anthocyanosides on platelet aggregation and clot retraction. Fitoterapia. 1987;48:3–8.
[28]Kadar A, Robert L, Miskulin M, Tixier JM, Brechemier D, Robert AM. Influence of anthocyanoside treatment on the cholesterol-induced atherosclerosis in the rabbit. Paroi Arterielle. 1979;5:187–205.
[29]Vinson JA, Bose P. Comparative bioavailability to humans of ascorbic acid alone or in a citrus extract. Am J Clin Nutr. 1988;48:601–604.
[30]Hwang J, Hodis HN, Sevanian A. Soy and alfalfa phytoestrogen extracts become potent low-density lipoprotein antioxidants in the presence of acerola cherry extract. J Agric Food Chem. 2001;49:308–314.
[31]Appel LJ. Nonpharmacologic therapies that reduce blood pressure: A fresh perspective. Clin Cardiol. 1999;22:1111–1115.
[32]Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride. Washington, DC: National Academy Press, 1999.
[33]Ford ES. Serum magnesium and ischaemic heart disease: Findings from a national sample of U.S. adults. Intl J Epidemiol. 1999;28:645–651.
[34]Resnick LM. Cellular ions in hypertension, insulin resistance, obesity, and diabetes: A unifying theme. J Am Soc Nephrol. 1992;3(4 suppl.):S78–S85.
[35]Planells E, Lerma A, Sanchez-Morito N, Aranda P, Llopis J. Effect of magnesium deficiency on vitamin B_2 and B_6 status in the rat. J Am Coll Nutr. 1997;16:352–356.
[36]Li W, Zheng T, Wang J, Altura BT, Altura BM. Extracellular magnesium regulates effects of vitamin B_6, B_{12} and folate on homocysteinemia-induced depletion of intracellular free magnesium ions in canine cerebral vascular smooth muscle cells: Possible relationship to [Ca2]i, atherogenesis and stroke. Neurosci Lett. 1999;274:83–86.

37

THERAPEUTIC ENZYMES

Using the Body's Helpers as Healers

Enzyme therapies are becoming more prevalent in medicine today, with many manufacturers targeting their advantages in disease treatment. In the last 100 years, enzymes have been increasingly used to treat various diseases. Early observations of Bacillus pyocyaneus revealed that its secretions could destroy anthrax bacilli and protect mice from inoculation with this deadly bacterium. Scientists deduced that the secretions were able to destroy anthrax by chewing apart its nucleic acids, via enzymatic degradation. This early observation paved the way for the use of enzymes in medicine. Today, enzymes are used as oncolytics, anticoagulants, thrombolytics, anti-inflammatories, fibrinolytics, mucolytics, antimicrobials, and digestive aids. Enzymes are found throughout the natural world; the number of uses for them in various fields of industry in addition to medicine is staggering. Enzymes are found in animal and plant sources.

Enzymes can be thought of as protein molecules with a specific mission—to initiate and regulate countless biologic reactions in living organisms. Enzymes are used for metabolic and digestive processes. Metabolic enzymes greatly increase the speed at which chemical processes take place within the body; without enzymes, cells could not perform their multiple functions. Every aspect of life depends on the energetic stimulus that enzymes provide. Perhaps therapeutic enzymes are used most often for enhancing digestive function. Enzymes help food break down into its smallest components. Enzymes secreted by humans include pepsin and protease for breakdown of proteins, lipase for fats, and amylase for carbohydrates. Cellulase, which helps with digestion of plant cells, is not produced by humans but is extracted from plant tissues as they are mechanically broken down. Plant-based foods are often cooked, but heat destroys enzymes; a plant food in its raw, fresh state produces considerably more enzyme activity than one that has been cooked.

MECHANISMS OF ACTION

Enzymes, like their application in medicine, exert their effects in a multitude of ways. One primary focus of enzymatic action is on the protein fibrin. Fibrin is an insoluble protein involved in blood clotting. In the many steps of the clotting cascade, fibrin is the final product. It is derived from its soluble protein precursor, fibrinogen. Fibrin is laid down inside blood vessels that have been compromised by disease or injury. Fibrin forms minuscule strands that eventually dry and harden, which captures the blood vessel components effectively. Certainly, fibrin occupies a vital role in health and healing; however, fibrin may also be responsible for an overzealous propensity to form inappropriate clots in the body. Inappropriate clotting, of course, is a major risk factor for myocardial infarctions and strokes.[1] When correctly balanced, deposition and removal of fibrin maintains an avoidance of blood loss and adverse viscosity in the vascular system. A balance tipped in favor of fibrin overproduction leads to dangerous clotting.

NATTOKINASE: PREVENTION AND TREATMENT OF HEART CONDITIONS

In the interest of preventive medicine, proteolytic enzymes can be used as interventional medicines that serve to inhibit overactivity of fibrin. One particular enzyme, known as nattokinase, has demonstrable fibrinolytic activity.[2] Nattokinase is derived from a Japanese food known as natto, a preparation of soybeans that has undergone fermentation with a bacterium known as Bacillus subtilis natto.[3] Hiroyuki Sumi, M.D., University of Chicago, is credited with the discovery of nattokinase. Thought to be produced specifically from this process of fermentation, nattokinase is not derived directly from other soy-based foods. Nattokinase causes mild enhancement of fibrinolysis in plasma, as evidenced by its effect on fibrinolytic parameters and production of tissue plasminogen activator, a potent thrombolytic agent that causes fibrinolysis at the site of a blood clot.[4] Nattokinase is thought to work by inhibiting plasminogen activator inhibitor-1 (PAI-1).[5] That is, nattokinase works by preventing the inhibition of plasminogen activator by PAI-1, thus potentiating clot dissolution. The fibrinolytic activity of nattokinase is fourfold that of plasmin, a main fibrinolytic enzyme found in the body.[6]

In animal studies, nattokinase can reduce markedly the thickening of blood vessel walls that normally occurs following an injury to the endothelium. In addition, nattokinase leads to dissolution of clots that build inside vessel walls as responses to injuries.[7] These actions suggest that nattokinase can be used to treat and prevent atherosclerosis because of its fibrinolytic activity at the blood-vessel wall. When taken orally in humans, nattokinase retains its activity (thereby escaping degradation during the digestive process) and has been shown to raise the level of fibrinolytic activity significantly for several hours after dosing.[4] Other applications of nattokinase include treating cardiovascular diseases, such as stroke, angina, deep-vein thrombosis, atherosclerosis, venous stasis, peripheral vascular disease, and claudication. Arteriosclerosis, excessive clotting, and inflammation are routine in developing arterial plaques. Enzyme therapy digests the fibrin and reverses the inflammation, which decreases the size of the artery-obstructing plaques. We have noted that symptoms of angina, impaired blood flow to the brain, and poor circulation to the legs often disappear with enzymatic treatment for cardiovascular conditions. The gentle, yet effective use of nattokinase for preventing cardiovascular diseases makes this an optimal choice from preventive and treatment perspectives. Combination with other anticoagulative therapies or drugs should be approached with great caution, however. Nattokinase is widely available today; one particular version of this enzyme is marketed as a preventive treatment for deep-vein thrombosis on long flights.[8]

OTHER CONDITIONS TREATED BY PROTEOLYTIC ENZYMES

Use of enzymes in controlling fibrin can be applied in several other disease models. One interesting aspect of fibrin control is the use of fibrinolytic enzymes in multiple sclerosis (MS). Researchers at the University of California, San Diego, School of Medicine found that, when fibrin was removed from the body (in animal models of MS), tissue damage resulting from MS was decreased and the life spans of animals were lengthened. These animals had decreased inflammatory measures and expression of major histocompatibility complex class I antigens, and reduced demyelination.[9] Fibrin is, however, better known for its role in blood clotting.

Fibrinolysis via proteolytic enzymes may also affect some conditions that have historically been resistant to treatment. Conditions, such as Peyronie's disease, Dupuytren's contracture,

Other Applications for Serrapeptase

Carpal tunnel syndrome—10 mg of serrapeptase, twice daily for six weeks, led to significant clinical improvement in 65% of patients treated. Improvements were confirmed using electrophysiologic measurements (nerve-conduction studies), and no side effects were noted during or following the treatment period.[a]

Breast engorgement—70 patients with breast engorgement were treated with an unspecified dose of serrapeptase, resulting in an 85% reduction in symptoms. Serrapeptase in this study was superior to a placebo for resolving symptoms of breast pain, breast swelling, and induration. As in previous studies, no side effects were noted in the study period.[b]

Inflammatory venous disease—A comparison study between two different forms of serrapeptase was conducted on patients with venous inflammatory disease. Efficacy of the two forms of enzyme therapy was determined to be 65% and 85%, with only one case of adverse reaction (diarrhea). This side effect was halted by a temporary reduction in dosage. Patients in this study were shown to benefit from serrapeptase enzyme therapy.[c]

[a]Malshe PC. A preliminary trial of serratiopeptidase in patients with carpal tunnel syndrome. J Assoc Physicians India. 1999;47:1170–1172. [b]Kee WH, Tan SL, Lee V, Salmon YM. The treatment of breast engorgement with serrapeptase (Danzen): A randomised double-blind controlled trial. Singapore Med J. 1989;30:48–54. [c]Bracale G, Selvetella L. Clinical study of the efficacy of and tolerance to seaprose S in inflammatory venous disease. Controlled study versus serratio-peptidase. Minerva Cardioangiol. 1996;44:515–524.

and Ledderhose's disease, are all marked by loss of elasticity and possible tearing of tissue, leading to bleeding and clot formation. This formation of localized clots is marked by fibrin deposition as well. Over time, continuous treatment with fibrinolytic enzymes may lead to resolution of scar tissue that has formed at sites of repeated trauma and bleeding. Several disease processes in humans are marked by their inflammatory components and scarring; one classic example of this is asthma. Over time, the continual inflammatory state of asthma can lead to scarring of the alveoli. Prophylactic therapy with enzymes is a therapeutic option for treating such conditions. Well-known for their role in the digestive process, enzymes can be used effectively in maintaining health by breaking up circulating immune complexes and controlling the amount of fibrin deposited in wounds, fractures, and joints. Enzymes digest necrotic debris and excess fibrin in the bloodstream as well. Neoplastic (cancerous) cells are often found surrounded by a coating of fibrin.[10] This has been speculated to be a protective element devised by cancer cells, allowing them to escape destruction by the cells of the immune system. Appropriate dosing with proteolytic enzymes has been utilized as an adjunctive cancer treatment.

Enzyme therapy for musculoskeletal trauma is an excellent first-line therapy. Proteolysis can block the production of pain-inducing chemicals from inflamed tissue. In patients with osteoarthritis (OA), treatment with a combination enzyme product (Phlogenzym,™ MUCOS Pharma GmbH & Co., Geretsreid, Germany) produced similar results for relieving pain and improving knee function compared to a popular OA drug, diclofenac.[11] Early and aggressive use of enzymes following musculoskeletal trauma can promote inflammation control and enhanced recovery. In a study examining the use of enzymes in wound healing, topical ap-

plication of enzymes helped to clean the wound area of necrotic tissue and sped the tissue recovery process.[12]

SERRAPEPTASE FOR INFLAMMATION

Also known as serratiopeptidase, serrapeptase is used in Japanese medicine. Serrapeptase is isolated from the microorganism Serratia E15, which dwells in the intestine of the silkworm. The true purpose of this organism is to help silkworms dissolve their own cocoons. Serrapeptase is adept at dissolving necrotic tissue, blood clots, arterial plaques, and inflammatory factors.

Used clinically in Europe and Asia for nearly a quarter century, serrapeptase is utilized for its anti-inflammatory actions to treat conditions such as chronic sinusitis, thinning of bronchopulmonary secretions, sprains and strains, edema, and even postoperative inflammatory states. New research on this novel enzyme demonstrates its efficacy for treating several disease states. Studies on serrapeptase have focused on its use for treating chronic lung disease; ear, nose, and throat disorders; carpal tunnel syndrome; and edema following injury and surgery.

In patients with chronic airway disease (in which mucus production and removal are problematic), treatment with 30 mg per day of serrapeptase for four weeks resulted in changes in sputum. Weight, viscosity, elasticity, and neutrophil content were all decreased. Coughing and expectoration frequency were significantly decreased.[13] Using serrapeptase for treating chronic lung conditions in which sputum production is a problem (for example, cystic fibrosis) leads to improved lifestyle parameters. In a separate investigation, serrapeptase was studied in conjunction with chronic sinusitis in adults. Again, a dose of 30 mg a day, for four weeks, led to significant decreases in viscosity but not elasticity of nasal mucus in this study, providing a better quality of life for these patients.[14] Researchers did not speculate about the contribution that enzyme therapy could make in cases of chronic sinusitis in which mucus removal is enhanced, thereby leading to quicker resolution of the condition.

Serrapeptase has also been used to treat several chronic conditions with ear, nose, and throat pathology in which inflammatory processes are a component.[15] This study on chronic conditions was performed at several treatment centers and 193 subjects were involved. Treatment lasted for seven to eight days and was compared to a placebo. The serrapeptase-treated group experienced significant reduction of symptoms beginning after three days of treatment. The researchers noted a more rapid response to serrapeptase compared to the placebo. The treatment group tolerated the enzyme therapy well. The investigators concluded that serrapeptase produced anti-inflammatory, antiedemic, and fibrinolytic activity and produced more rapid action than the placebo. Similarly, serrapeptase was used to treat swelling of the buccal membrane following a specified surgical procedure (Caldwell-Luc antrotomy) for chronic empyema in that area.[16] A total of 174 patients underwent the procedure, 80 of whom received treatment with the enzyme. The dose of serrapeptase was 30 mg per day, in divided doses, on the day before the procedure, the day it was performed, and five days postprocedure. Patients treated with serrapeptase had significantly less buccal membrane swelling compared to patients who received a placebo at each point of observation following the operation. The point of maximal swelling in these patients never approached that of the patients treated with the placebo. Subjects receiving treatment reported no side effects from the enzyme therapy.

In another surgical study using serrapeptase, the amount of postoperative swelling in ankle joints was studied.[17] This study examined swelling intensity following surgery for acute

Dosage Recommendations for Two Enzymes*

Nattokinase—72–200 mg (higher doses as clinically indicated)
Serrapeptase—10–30 mg (higher doses as clinically indicated)

*WARNING: Tell patients not to use these products if they have blood coagulation disorders. Close professional supervision and laboratory monitoring should occur before patients take these products if patients are taking any drugs that affect blood coagulation, such as prescription vitamin K, heparin, or warfarin (coumadin), or if patients are pregnant or breast-feeding. In addition, these products should be used with caution if active gastrointestinal irritation or ulceration is present.

rupture of lateral ankle ligaments. Patients who received serrapeptase after surgery experienced a 50% decrease in swelling by the third day following surgery. Patients treated with conventional postsurgical measures (leg elevation, bed rest, ice) had no reductions in swelling. Degrees of pain abatement also correlated well with reductions in swelling. The investigators concluded that serrapeptase is a viable treatment for postsurgical swelling; the enzyme produced results far better than those of standard conservative measures. For additional applications of serrapeptase, see the box on page 416 entitled ''Other Applications for Serrapeptase.''

BROMELAIN

Bromelain includes a grouping of sulfhydryl proteolytic enzymes obtained from the pineapple plant (Ananas comosus). Bromelain is typically derived from either the fruit or stem of the plant, with most commercial sources being derived from the stem. In addition to a proteolytic portion, bromelain contains peroxidase, acid phosphatase, and protease inhibitors. It is interesting to note that the purified proteolytic fraction has been shown to be physiologically inactive whereas whole bromelain extract inhibits platelet aggregation and exhibits fibrinolytic activity, anti-inflammatory activity, and cytokine modulation as well as producing mucolytic effects and cardiovascular and circulatory improvements.[17] The fibrinolytic activity of bromelain is thought to be the result of the conversion of plasminogen to plasmin, limiting the coagulation cascade by degrading fibrin.[18] Bromelain acts as a more efficient fibrinolytic in vitro compared to in vivo, possibly because of the antiprotease compounds found in plasma.[17] Bromelain produces a dose-dependent decrease in serum fibrinogen, and at higher concentrations, prothrombin and activated partial thromboplastin time are prolonged.[19]

Bromelain supplementation has shown efficacy in several conditions. A study examined the effect of bromelain supplementation in 116 children under the age of 11 years diagnosed with acute sinusitis. The group taking bromelain showed a statistically significant faster recovery from symptoms compared to a placebo and combination therapy with standard treatment.[18] In a randomized, double-blind, parallel group trial, an enzyme-rutosid combination containing rutosid and the enzymes bromelain and trypsin, was compared to the NSAID diclofenac in 103 patients with osteoarthritis of the knee for six weeks. Both treatments resulted in clear improvements, with the global judgment of efficacy by physician resulting in at least good ratings for 51.4% of the oral enzyme supplementation group and for 37.2% of the diclofenac patients.[19] Additionally, one study investigated the effects of bromelain supplementation in 59 patients with blunt injuries to the musculoskeletal system. Treatment with bromelain resulted in a clear reduction in swelling, pain at rest and during movement, and tenderness. Both

swelling and the symptoms of pain had improved appreciably at all evaluation time points as compared with baseline.[20]

CONCLUSIONS

Natural medicines, such as enzymes, provide a safe, nontoxic therapy for addressing several conditions. One is reminded of the incredible bounty that nature provides when we are able to use a secretion produced by a microorganism found dwelling in the innards of another creature! Enzymes are not only useful in promoting chemical reactions within the body to ensure its smooth function. These versatile chemicals can also be used to help prevent and treat a number of conditions. It is important, however, that patients are informed of possible side effects and contraindications. When used properly, enzymes can be helpful for patients with heart conditions and various types of inflammation.

REFERENCES

[1]Nesheim M. Myocardial infarction and the balance between fibrin deposition and removal. Ital Heart J. 2001;2:641–645.

[2]Fujita M, Nomura K, Hong K, Ito Y, Asada A, Nishimuro S. Purification and characterization of a strong fibrinolytic enzyme (nattokinase) in the vegetable cheese natto, a popular soybean fermented food in Japan. Biochem Biophys Res Commun. 1993;197:1340–1347.

[3]Sumi H, Hamada H, Tsushima H, et al. A novel fibrinolytic enzyme (nattokinase) in the vegetable cheese natto; a typical and popular soybean food in the Japanese diet. Experientia. 1987;43:1110–1111.

[4]Sumi H, Hamada H, Nakanishi K, Hiratani H. Enhancement of the fibrinolytic activity in plasma by oral administration of nattokinase. Acta Haematol. 1990;84:139–143.

[5]Suzuki Y, Kondo K, Matsumoto Y, et al. Dietary supplementation of fermented soybean, natto, suppresses intimal thickening and modulates the lysis of mural thrombi after endothelial injury in rat femoral artery. Life Sci. 2003;73:1289–1298.

[6]Fujita M, Hong K, Ito Y, et al. Thrombolytic effect of nattokinase on a chemically induced thrombosis model in rat. Biol Pharm Bull. 1995;18:1387–1391.

[7]Suzuki Y, Kondo K, Ichise H, et al. Dietary supplementation with fermented soybeans suppresses intimal thickening. Nutrition. 2003;19:261–264.

[8]Cesarone MR, Belcaro G, Nicolaides AN, et al. Prevention of venous thrombosis in long-haul flights with Flite Tabs: The LONFLIT-FLITE randomized, controlled trial. Angiology. 2003;54:531–539.

[9]Akassoglou K, Adams RA, Bauer J, Mercado P, Tseveleki V, Lassmann H, Probert L, Strickland S. Fibrin depletion decreases inflammation and delays the onset of demyelination in a tumor necrosis factor transgenic mouse model for multiple sclerosis. Proc Natl Acad Sci USA. 2004;101:6698–6703; Epub 2004 April 19.

[10]Bardos H, Molnar P, Csecsei G, Adany R. Fibrin deposition in primary and metastatic human brain tumours. Blood Coagul Fibrinolysis. 1996;7:536–548.

[11]Klein G, Kullich W. Short-term treatment of painful osteoarthritis of the knee with oral enzymes. Clin Drug Invest. 2000;19:15–23.

[12]Latha B, Ramakrishnan M, Jayaraman V, Babu M. Serum enzymatic changes modulated using trypsin: Chymotrypsin preparation during burn wounds in humans. Burns. 1997;23:560–564.

[13]Nakamura S, Hashimoto Y, Mikami M, Yamanaka E, Soma T, Hino M, Azuma A, Kudoh S. Effect of the proteolytic enzyme serrapeptase in patients with chronic airway disease. Respirology. 2003;8:316–320.

[14]Majima Y, Inagaki M, Hirata K, Takeuchi K, Morishita A, Sakakura Y. The effect of an orally administered proteolytic enzyme on the elasticity and viscosity of nasal mucus. Arch Otorhinolaryngol. 1988; 244:355–359.

[15]Mazzone A, Catalani M, Costanzo M, Drusian A, Mandoli A, Russo S, Guarini E, Vesperini G. Evaluation of Serratia peptidase in acute or chronic inflammation of otorhinolaryngology pathology: A multicentre, double-blind, randomized trial versus placebo. J Int Med Res. 1990;18:379–388.

[16]Tachibana M, Mizukoshi O, Harada Y, Kawamoto K, Nakai Y. A multi-centre, double-blind study of serrapeptase versus placebo in postantrotomy buccal swelling. Pharmatherapeutica. 1984;3:526–530.

[17]Esch PM, Gerngross H, Fabian A. Reduction of postoperative swelling: Objective measurement of swelling of the upper ankle joint in treatment with serrapeptase—a prospective study. Fortschr Med. 1989;107: 67–68, 71–72.

[18]Braun JM, Schneider B, Beuth HJ. Therapeutic use, efficiency and safety of the proteolytic pineapple enzyme Bromelain-POS in children with acute sinusitis in Germany. In Vivo. 2005 Mar–Apr;19(2):417–421.

[19]Akhtar NM, Naseer R, Farooqi AZ, Aziz W, Nazir M. Oral enzyme combination versus diclofenac in the treatment of osteoarthritis of the knee—a double-blind prospective randomized study. Clin Rheumatol. 2004 Oct;23(5):410–415. Epub 2004 Jul 24.

[20]Masson M. [Bromelain in blunt injuries of the locomotor system. A study of observed applications in general practice]. Fortschr Med. 1995 Jul 10;113(19):303–306.

38

COMMON NUTRIENT DEPLETIONS CAUSED BY PHARMACEUTICALS

Pharmaceutical and nutrient interactions have been moderately studied yet often ignored by health care professionals. Many extensively prescribed drugs can lead to decreased absorption or increased excretion of many necessary vitamins, minerals, and amino acids. These drugs may also alter biochemical pathways necessary for proper utilization of nutrients. According to the Centers for Disease Control and Prevention (CDC), the number of adults ages 55 to 64 taking at least one pharmaceutical in the previous month rose from 62% in 1988 to 1994 to 73% in 1999 to 2002.[1] The large number of individuals taking pharmaceuticals suggests that the potential for drug-nutrient interactions is substantial and growing. Owing to the vast number of pharmaceuticals on the market, this chapter is limited to a select group of commonly prescribed medications.

COMMON PHARMACEUTICALS THAT DEPLETE NUTRIENTS

Estrogen and Progestins

Hormone replacement therapy (HRT) is a common prescription for menopausal women. These estrogen=progestin combinations are used to decrease symptoms associated with menopause, such as hot flashes, vaginal dryness, sleep disturbances, and fatigue. In the United States, from 1999 to 2002, approximately 15 million women were on HRT, accounting for 90 million prescriptions per year.[2] The Women's Health Initiative study was widely publicized in 2002; this study demonstrated that HRT increases the risk of coronary heart disease, breast cancer, and strokes.[3] Following the publication of the study, HRT prescriptions decreased by approximately 32% in 2003.[4] Oral contraceptive pills (OCPs) also contain estrogen=progestin combinations. OCPs have been shown to increase the risk of cardiovascular events as well as breast, cervical, and liver cancer.[5,6]

Estrogen=progestin hormones have been shown to deplete many nutrients. Research suggests that estrogens deplete several B vitamins significantly. Oral estradiol decreases pyridoxine (vitamin B_6) and albumin in postmenopausal women.[7] This vitamin B_6 deficiency is believed to be associated with a disruption in tryptophan metabolism.[8] Other research indicates that oral contraceptives deplete riboflavin (vitamin B_2), folic acid, cobalamin (vitamin B_{12}), ascorbic acid (vitamin C), and zinc.[9] Other research indicates a decrease by 40% of both folic acid and serum B_{12} levels with oral contraceptive use.[10] Clinically, lower folic-acid levels appear to correlate with increased prevalence of abnormal Papanicolaou (Pap) smear results. In addition, studies have shown that estrogen supplementation increases magnesium uptake into bone and soft tissue, causing lowered blood magnesium levels. With low magnesium intake, this alters the calcium:magnesium ratio. This change in ratio can cause an increase in coagulation, which may lead to an increased risk of thrombosis that occurs with estrogen supplementation.[11]

Acid Blockers

Proton-pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2 blockers) are commonly prescribed for treating ulcers and gastroesophageal reflux disease (GERD). Lansoprazole, or Prevacid, is a PPI that ranked third in top pharmaceutical sales in the United States in 2004.[12] Many studies indicate that these classes of drugs cause several nutrient deficiencies. Research indicates that treatment with both PPI and H_2 blockers increases the risk of vitamin B_{12} deficiency significantly in elderly patients.[13] Studies have shown that H_2 blockers decrease protein-bound (as opposed to unbound) vitamin B_{12} absorption, owing to decreasing gastric acid and pepsin secretion and a resultant inability to cleave cobalamin. One small study showed a 53% decrease in protein-bound B_{12} absorption in individuals taking an H_2 blocker.[14] In addition, decreased protein-bound B_{12} absorption would not be detected on the standard Schilling test, as it measures unbound cobalamin only.[15]

Research also indicates that folic-acid absorption is decreased with supplementation of H_2 blockers and other antacids.[16] Studies have linked H_2 blockers, which decrease gastric acid secretion, with decreased absorption of iron and zinc.[17,18] One study showed a direct correlation between increasing dosage of cimetidine, an H_2 blocker, and decreasing dietary nonheme iron absorption ranging from 28%–65%.[19]

Animal studies have demonstrated that cimetidine significantly decreases intestinal calcium transport.[20] Cimetidine also alters vitamin D metabolism by altering the enzyme vitamin D 25-hydroxylase activity, suppressing the seasonal increase in the level of 25-hydroxyvitamin D. The levels of 25-hydroxyvitamin D rose significantly after withdrawal of the drug.[21] A small study performed with the PPI omeprazole demonstrated that serum levels of beta-carotene were decreased with increased gastric pH.[22] These findings raise the question of the long-term potential consequence for increased risk of osteoporosis, other vitamin D–linked disease states, such as various cancers and multiple sclerosis, and altered RNA and DNA production as a consequence of lowered B_{12} and folate.

Corticosteroids

Corticosteroids are often prescribed to produce anti-inflammatory and immunosuppressant activity. Prednisone and hydrocortisone are glucocorticoids frequently prescribed to help mitigate symptoms associated with various medical conditions, including autoimmune diseases and inflammatory processes. This class of drugs affects the absorption and excretion of several nutrients. Corticosteroid treatment has been associated with increased loss of bone-mineral density. Studies show that these drugs decrease calcium absorption and increase calcium excretion.[23] In addition, a study with individuals with chronic airway obstruction showed that long-term oral steroid therapy is associated with decreased serum magnesium levels.[24] Steroid medication has also been associated with hypokalemia in both animal and human studies.[25] Research also indicates that prednisone increases urinary excretion of potassium.[26] Studies with individuals with rheumatoid arthritis (RA) show that serum levels of zinc and copper are also decreased with corticosteroid treatment, and urinary excretion of zinc and copper is elevated.[27] Additional studies on patients with RA who received corticosteroid therapy also demonstrated a decrease in plasma selenium levels.[28] Although the evidence appears to be incomplete or conflicting, some studies suggest that vitamin C uptake is inhibited and vitamin D should be supplemented to avoid bone loss caused by corticosteroid therapy.[29,30]

Aspirin

Aspirin is used to produce antipyretic, analgesic, and anti-inflammatory activity. Recent promotion of aspirin (e.g., Bayer Aspirin) as a prophylactic treatment to decrease platelet aggregation to prevent transient ischemic attacks, strokes, and thromboembolisms has increased the use of this over-the-counter medication.[31]

Treatment with aspirin, or acetyl salicylic acid, affects several nutrients. Many studies have shown that aspirin therapy decreases vitamin C absorption.[32] Some studies also indicate that increasing aspirin dosage directly correlates to increasing ascorbic acid excretion in the urine.[33] Research also suggests that aspirin therapy causes an increase in gastric blood loss leading to a decrease in total body iron.[34] Evidence also shows that aspirin significantly decreases both total and bound serum folate, and increases folic-acid excretion slightly.[35]

Antidiabetes Drugs

According to the American Diabetes Association 2005 statistics, approximately 7% of the U.S. population have type 1 or type 2 diabetes. The organization estimates that 57% of adults who have diabetes take oral medication only and an additional 12% take insulin plus oral medication to manage the condition.[36]

Biguanides and sulfonylureas are oral medications used to treat diabetes and affect select nutrient levels adversely. Metformin, a frequently prescribed biguanide, has been shown to deplete vitamin B_{12} and folic acid. Studies indicate that long-term metformin therapy decreases serum vitamin B_{12} levels significantly. Additional studies suggest that short-term treatment with metformin increases homocysteine levels, and that B vitamins (e.g., folic acid) can moderate this response.[37] More specifically, serum folic-acid levels have been shown to decrease by 7%, and vitamin B_{12} levels to decrease by 14%, with metformin therapy in individuals who have type 2 diabetes.[38] Although limited, some research also suggests that treatment with sulfonylureas increases the risk of coenzyme Q10 (CoQ10) deficiency.[39]

Statins

Statin drugs are widely used to decrease elevated cholesterol levels and prevent atherosclerosis and coronary artery disease. The statin drug Lipitor is one of the top-selling pharmaceuticals worldwide and brought in an estimated $12.2 billion in sales to Pfizer in 2005.[40] Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase, which decreases cholesterol synthesis by inhibiting the conversion of acetyl CoA to mevalonate. Mevalonate is also necessary for the production of ubiquinone, or CoQ10. Numerous studies have demonstrated that statin drug therapy significantly decreases plasma levels of CoQ10.[41] CoQ10 is necessary for mitochondrial energy production, and CoQ10 has potent antioxidant activity.[42] Some researchers suggest that the depletion of CoQ10 could account for some side effects associated with statin drugs, such as myotoxicity and hepatotoxicity.[43,44] It has also been hypothesized that the relatively common side effects of fatigue and rhabdomyolysis may be associated to some degree with CoQ10 status.

Antihypertensives

Common antihypertensive medications include beta-adrenergic blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, diuretics, and vasodilators.

According to the American Heart Association, an estimated 65 million Americans, almost one in three adults, has high blood pressure.[45] Vasodilators such as hydralazine deplete vitamin B_6.[46] Captopril, an ACE inhibitor, has been shown to cause hyponatremia by increasing sodium excretion and may cause hyperkalemia.[47,48] In addition, studies with the beta blocker propranolol have shown that the drug inhibits the CoQ10 enzymes in the myocardium.[49] Clinically, it is imperative to control for potential overt and subclinical deficiency states that may otherwise spur the progression of the disease state being treated, or that may manifest with new adverse biochemical imbalances that may otherwise ripple through the 50-trillion-plus cells that comprise the human frame.

Diuretics

Diuretics are known for altering certain nutrient levels such as potassium; however, many other nutrients are affected. Thiazide diuretics have been shown to deplete magnesium, sodium, potassium, and zinc. One study found hyponatremia in 13.7% of individuals treated with thiazide diuretics and hypokalemia in 8.5% of these individuals.[50] Thiazide diuretics also decrease magnesium in approximately 20% of patients.[51] In addition, research indicates that thiazide diuretics cause significantly decreased serum zinc levels.[52]

Loop diuretics have been shown to deplete potassium, magnesium, calcium, zinc, pyridoxine, thiamine, and ascorbic acid. One study showed that thiamine deficiency was found in 98% of patients with congestive heart failure who took 80 mg of furosemide daily and in 57% of such patients who took 40 mg daily.[53] Ascorbic acid and pyridoxine excretion are also increased with furosemide treatment.[54]

In addition, several studies demonstrate that loop diuretics increase the excretion of sodium, potassium, calcium, magnesium, and chloride.[55] Although there is a lack of evidence for other nutrient depletions relative to diuretics, the astute clinician will be watchful for one or more

Table 38–1. Pharmaceuticals and Nutrient Depletion

Pharmaceuticals	Nutrients Depleted
Estrogen=progestins	Riboflavin, pyridoxine, cobalamin, folic acid, ascorbic acid, zinc, magnesium
Statins	CoQ10
Acid blockers	CoQ10, cobalamin, folic acid, iron, vitamin D, beta-carotene, zinc
Corticosteroids	Calcium, magnesium
Aspirin	Ascorbic acid, iron, folic acid
Antidiabetes drugs	Cobalamin, folic acid, CoQ10
Anticonvulsants	Biotin, thiamine, cobalamin, folic acid, CoQ10, vitamin D, vitamin K, calcium, L-carnitine
Antihypertensives	Pyridoxine, sodium, CoQ10
Diuretics	Thiamine, pyridoxine, ascorbic acid, potassium, magnesium, calcium, zinc, sodium
Antibiotics	B vitamins, vitamin K, magnesium, calcium potassium, zinc, iron

CoQ10 coenzyme Q10.

water-soluble vitamin, mineral, and accessory nutrient depletions, including other members of the B vitamin family and substances such as L-carnitine.

Anticonvulsants

According to the CDC, epilepsy affects 2.7 million Americans.[56] Anticonvulsants are commonly used to treat seizure disorders but are also occasionally prescribed for patients who have anxiety, chronic pain, or migraine headaches.[57,58] Several classes of anticonvulsants have been shown to affect nutrient metabolism. Barbiturates have been well-documented to interact adversely with several nutrients and cause osteomalacia. Hypocalcemia and decreased serum 25-hydroxy-vitamin D has been documented in patients treated with phenytoin and phenobarbitone. This study showed that approximately 11% of these individuals were deficient in vitamin D, and supraphysiologic doses of vitamin D were required to restore their calcium levels to normal.[59] One study showed that 29% of patients treated with phenobarbital or phenytoin were hypocalcemic.[60] In addition, studies indicate that these drugs do not affect absorption of folic acid, yet all of the patients who were taking anticonvulsants had reduced serum folate.[61] However, research has also shown that folate supplementation in large doses for patients with epilepsy who are on anticonvulsant therapy can induce seizure activity, thus, caution is advised.[62]

Several anticonvulsants, such as carbamazepine, phenytoin, and phenobarbital, have been reported to decrease biotin in long-term therapy, possibly by increasing biotin catabolism and excretion.[63] Thiamine has been found to be low in both the cerebrospinal fluid and blood in patients with epilepsy who take phenytoin.[64] Research results are conflicting regarding vitamin K and anticonvulsant therapy, yet some researchers and animal studies suggest that phenytoin and phenobarbital do alter vitamin K metabolism.[65,66] Several studies have shown that valproate, more commonly known as Depakote, causes a decrease in serum-free L-carnitine. One study showed that 76.5% of adult patients treated with valproate were deficient in serum-free L-carnitine and 21.5% of individuals treated with other anticonvulsants were also deficient in L-carnitine.[67] In the case of valproate therapy, many physicians are now routinely prescribing L-carnitine proactively to lessen the side-effect profile in these patients.

Antibiotics

Several classes of antibiotics have been shown to affect vitamin and mineral levels. Aminoglycosides are prescribed to 3.2 million patients in the United States annually.[68] Aminoglycosides, such as gentamicin, have been shown to cause imbalances of magnesium, calcium, and potassium.[69] One study showed that gentamicin causes increased excretion of calcium by 5% and magnesium by 8.4%.[70] Tetracycline has been shown to bind with multivalent cations, such as aluminum, calcium, magnesium, zinc, and iron, in the gastrointestinal (GI) tract. This binding forms complexes that are absorbed poorly or are insoluble.[71,72]

Broad-spectrum antibiotics disrupt the normal and beneficial intestinal flora.[73] These bacteria are necessary for the synthesis of both B vitamins and vitamin K along with other nutrients, although there are no current studies determining the effects of antibiotics on these vitamin levels.[74] This interaction could potentially affect these nutrient levels. Strangely enough, though the medical literature abounds with evidence on the use of probiotics such as Lactobacillus GG and others to avert antibiotic diarrhea and secondary GI infections, the practice of supplementation on a routine basis is not yet a standard of practice.

Table 38–2. Symptoms of Nutrient Deficiency

Nutrients	Symptoms
Thiamine	Beriberi, depression, memory loss, numbness, fatigue
Riboflavin	Cheilosis, glossitis, dermatitis, visual disturbance
Niacin	Pellagra, dermatitis, confusion, diarrhea
Pantothenic acid	Fatigue, numbness and pain in the feet
Pyridoxine	Depression, fatigue, dermatitis, anemia, glucose intolerance
Cobalamin	Anemia, fatigue, poor nerve function, diarrhea
Folate	Anemia, fatigue, cervical dysplasia, diarrhea, gingivitis, depression, irritability, insomnia
Biotin	Alopecia, depression, dermatitis, nausea, anorexia
Vitamin C	Scurvy, decreased immunity, poor wound healing
Calcium	Rickets, osteoporosis, osteomalacia, muscle spasms
Magnesium	Fatigue, irritability, weakness, muscle cramps, insomnia, anorexia, poor nerve conduction
Potassium	Fatigue, irregular heartbeat, irritability, confusion, poor nerve conduction
Iron	Anemia, weakness, fatigue, poor immune function
Zinc	Slow wound healing, decreased immunity, loss of taste and smell, alopecia, skin disorders
Selenium	Keshan disease, poor immune function
CoQ10	Hypertension, fatigue, cardiovascular diseases
L-carnitine	Muscle weakness, poor lipid metabolism, failure to thrive in children

From ref. 75.
CoQ10 coenzyme Q10.

COMMON NUTRIENTS DEPLETED BY PHARMACEUTICALS

The potential biochemical consequences and resulting imbalances that could otherwise be preemptively guarded against are described briefly in the sections that follow.

Thiamine

Thiamine (vitamin B_1) is a coenzyme essential for energy metabolism, particularly for carbohydrate metabolism in the brain. The vitamin is also required for synthesis of the neurotransmitter acetylcholine.[75] Anticonvulsants and diuretics may deplete thiamine.[76]

Riboflavin

Riboflavin (vitamin B_2) is incorporated into the coenzymes FNM and FAD, which are required for cellular energy production. The vitamin is also involved with pyridoxine activation, conversion of folate to coenzymes and tryptophan to niacin, and glucose metabolism.[77] Drugs associated with depletion of riboflavin include thiazide diuretics, tetracycline, sulfonamides, birth control pills, antimalarials, and probenecid.[75,77] Tricyclic antidepressants and the antipsychotic drug chlorpromazine also may cause a deficiency.[76]

Niacin

Niacin (vitamin B_3) is integrated into the coenzymes, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are necessary for amino acid, fat, carbohydrate metabolism, and producing cellular energy. Niacin supplementation is often used to address hypercholesterolemia and as an anxiolytic.[77] Isoniazid for treating tuberculosis has been shown to inhibit the conversion of tryptophan to niacin and may cause pellagra.[78]

Pyridoxine

Pyridoxine (vitamin B_6) is an enzymatic cofactor required for synthesis of tryptophan, serotonin, gamma aminobutyric acid (GABA), acetylcholine, histamine, and norepinephrine. The vitamin is also important in the metabolism of homocysteine. In addition, pyridoxine is involved in hemoglobin synthesis and energy production. Drugs that affect pyridoxine levels adversely include isoniazid, birth control pills and other oral estrogens, penicillamine, hydralazine, and levodopa.[76] Loop diuretics also deplete pyridoxine.[54]

Cobalamin

Cobalamin (vitamin B_{12}) is a methyl donor and is required for proper DNA synthesis. This vitamin is involved with carbohydrate metabolism and is required for myelin synthesis. Cobalamin also is necessary to convert homocysteine to methionine. Drugs that interfere with cobalamin include oral contraceptives, H_2 blockers, PPIs, antibiotics such as tetracycline and neomycin, bile-acid sequestrants such as cholestyramine, and biguanides, such as phenformin and metformin.[37,76]

Folate

Folic acid is required for DNA synthesis and cellular division. It is also necessary for neural development and cancer prevention. Folic-acid deficiency in pregnancy is linked to multiple birth defects such as neural-tube defects. Folate is also required to convert homocysteine to methionine, thus making this nutrient important in cardiovascular disease prevention. Numerous drugs affect folate levels and metabolism. Some of these drugs include estrogens, anticonvulsants, barbiturates, sulfasalazine, and methotrexate.[75] Acid blockers, aspirin, cholestyramine, corticosteroids, and the antibiotic trimethoprim also may decrease folic acid.[76]

Biotin

Biotin is a cofactor for several enzymes involved in carbohydrate, amino acid, and fat metabolism. This nutrient is also involved with glucose utilization. Biotin is produced by normal intestinal flora; therefore, antibiotics may decrease biotin levels.[75] Anticonvulsants, such as phenytoin, phenobarbital, and carbamazepine deplete biotin.[63]

Ascorbic Acid

Ascorbic acid (vitamin C) is required for numerous physiologic functions. It is required for collagen synthesis and proper immune function and acts as a potent antioxidant and antihistamine. Vitamin C is a cofactor for the enzyme that converts tyrosine to norepinephrine and

increases absorption of iron from the small intestines when taken concurrently.[77] Ascorbic acid may be depleted by corticosteroids, diuretics, aspirin, and estrogens.[9,54,76]

Vitamin D

Vitamin D is vital for proper calcium metabolism and cancer prevention. Drugs that may affect vitamin D include acid blockers, corticosteroids, and anticonvulsants.[76]

Vitamin K

Vitamin K is required for synthesizing clotting factors. It also is important for activating osteocalcin, a protein in bone that maintains calcium in the bone. Vitamin K_2, or menaquinone, is made by intestinal flora and may be disrupted by antibiotic use.[74] Anticonvulsants may also affect vitamin K levels adversely.[76]

Calcium

Calcium is necessary for numerous physiologic functions. It is important for bone and teeth integrity and for blood clotting, muscle contraction, and neurotransmitter regulation. Drugs that interfere with calcium include corticosteroids, anticonvulsants, antibiotics such as tetracycline and aminoglycosides, loop diuretics, methotrexate, and isoniazid.[76]

Magnesium

Magnesium is essential for normal heart contractility and relaxes smooth muscle. This mineral also is required for proper calcium balance and bone and teeth integrity. Magnesium also acts as a calcium-channel blocker, possibly decreasing blood pressure and improving cardiac function. Drugs that affect magnesium include diuretics, corticosteroids, antibiotics, cyclosporine, and chemotherapeutic drugs.[77]

Potassium

Potassium is required for intracellular water balance as well as acid-base balance. This mineral converts glucose into glycogen for storage and is required for nerve conduction and muscle contraction. Potassium is depleted by diuretics, tetracycline, aminoglycoside antibiotics, and aspirin.[76]

Iron

Iron is a component of heme, which comprises hemoglobin and myoglobin. These are necessary for oxygen transport. Pharmaceuticals that may induce iron deficiency include aspirin, acid blockers, thyroxine, and quinolone antibiotics.[76]

Zinc

Zinc is required for numerous physiologic functions. It is involved with proper immune function, hormone production, taste perception, wound healing, prostate function, and vision. Zinc may be depleted by acid blockers, birth control pills, zidovudine (AZT), and diuretics.[9,76]

Selenium

Selenium is important for detoxification reactions and for converting thyroxine to the more active form triiodothyronine. Corticosteroids have been shown to deplete selenium.[28]

Coenzyme Q10

CoQ10 is a potent antioxidant protecting against lipid peroxidation as well as being necessary for energy production in the mitochondria. Statin drugs inhibit synthesis of CoQ10 by inhibiting the enzyme HMG CoA reductase. Beta blockers, tricyclic antidepressants, and phenothiazine may also alter CoQ10 function.[75]

L-Carnitine

L-carnitine is a nonessential amino acid synthesized from lysine and methionine. It regulates energy production in muscle tissue and is particularly important for cardiac function. Carnitine is also involved with fat metabolism as well as using amino acids for energy. Anticonvulsants, such as valproate, have been shown to deplete carnitine significantly.[79] AZT also depletes carnitine.[80]

CONCLUSIONS

Pharmaceutical-induced nutrient deficiency may be more common than most health care providers currently acknowledge. Patients who are most at risk for drug-induced deficiencies may be individuals who have borderline nutritional status or poor dietary intake of nutrients. It is hoped that new support of vitamin and mineral supplementation on the part of clinicians will encourage patients to optimize their nutritional status and decrease the risk of nutrient deficiencies.

REFERENCES

[1]Centers for Disease Control and Prevention. Health United States 2005. Online document at: www.cdc.gov=nchs=data=hus=hus05.pdf#095. Accessed January 18, 2007.

[2]Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: Annual trends and response to recent evidence. JAMA. 2004;291:47–53.

[3]Rossouw JE, Anderson GL, Prentice RL, et al., Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321–333.

[4]Majumdar SR, Almasi EA, Stafford RS. Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. JAMA. 2004;292:1983–1988.

[5]La Vecchia C. Oral contraceptives and cancer. Minerva Ginecol. 2006;58:209–214.

[6]Wu O, Robertson L, Langhorne P, et al. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: A systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. Thromb Haemost. 2005;94:17–25.

[7]Smolders RG, de Meer K, Kenemans P, et al. Oral estradiol decreases plasma homocysteine, vitamin B6, and albumin in postmenopausal women but does not change the whole-body homocysteine remethylation and transmethylation flux. J Clin Endocrinol Metab. 2005;90:2218–2224.

[8]Haspels AA, Bennink HJ, Schreurs WH. Disturbance of tryptophan metabolism and its correction during oestrogen treatment in postmenopausal women. Maturitas. 1978;1:15–20.

[9]Webb JL. Nutritional effects of oral contraceptive use: A review. J Reprod Med. 1980;25:150–156.

[10]Bielenberg J. Folic acid and vitamin deficiency caused by oral contraceptives [in German]. Med Monatsschr Pharm. 1991;14:244–247.
[11]Seelig MS. Interrelationship of magnesium and estrogen in cardiovascular and bone disorders, eclampsia, migraine and premenstrual syndrome. J Am Coll Nutr. 1993;12:442–458.
[12]Anonymous. The Top 2000 Prescriptions for 2004 by U.S. Sales ($billions). NDC Health. Online document at: www.rxlist.com=top200_sales_2004.htm. Accessed July 8, 2006.
[13]Valuck RJ, Ruscin JM. A case-control study on adverse effects: H_2 blocker or proton pump inhibitor use and risk of vitamin B_{12} deficiency in older adults. J Clin Epidemiol. 2004;57:422–428.
[14]Salom IL, Silvis SE, Doscherholmen A. Effect of cimetidine on the absorption of vitamin B_{12}. Scand J Gastroenterol. 1982;17:129–131.
[15]Steinberg WM, King CE, Toskes PP. Malabsorption of protein-bound cobalamin but not unbound cobalamin during cimetidine administration. Dig Dis Sci. 1980 Mar;25:188–191.
[16]Russell RM, Golner BB, Krasinski SD. Effect of antacid and H2 receptor antagonists on the intestinal absorption of folic acid. J Lab Clin Med. 1988;112:458–463.
[17]Sturniolo GC, Montino MC, Rossetto L, et al. Inhibition of gastric acid secretion reduces zinc absorption in man. J Am Coll Nutr. 1991;10:372–375.
[18]Aymard JP, Aymard B, Netter P, et al. Haematological adverse effects of histamine H_2-receptor antagonists. Med Toxicol Adverse Drug Exp. 1988;3:430–448.
[19]Skikne BS, Lynch SR, Cook JD. Role of gastric acid in food iron absorption. Gastroenterology 1981; 81:1068–1671.
[20]Ghishan FK, Walker F, Meneely R, et al. Intestinal calcium transport: Effect of cimetidine. J Nutr. 1981; 111:2157–2161.
[21]Odes HS, Fraser GM, Krugliak P, et al. Effect of cimetidine on hepatic vitamin D metabolism in humans. Digestion. 1990;46:61–64.
[22]Tang G, Serfaty-Lacrosniere C, Camilo ME, Russell RM. Gastric acidity influences the blood response to a beta-carotene dose in humans. Am J Clin Nutr. 1996;64:622–626.
[23]Lems WF, Van Veen GJ, Gerrits MI, et al. Effect of low-dose prednisone (with calcium and calcitriol supplementation) on calcium and bone metabolism in healthy volunteers. Br J Rheumatol. 1998;37: 27–33.
[24]Rolla G, Bucca C, Bugiani M, et al. Hypomagnesemia in chronic obstructive lung disease: Effect of therapy. Magnes Trace Elem. 1990;9:132–136.
[25]Widmer P, Maibach R, Kunzi UP, et al. Diuretic-related hypokalaemia: The role of diuretics, potassium supplements, glucocorticoids and beta 2-adrenoceptor agonists. Results from the Comprehensive Hospital Drug Monitoring programme, Berne (CHDM). Eur J Clin Pharmacol. 1995;49(1–2):31–36.
[26]Shenfield GM, Knowles GK, Thomas N, Paterson JW. Potassium supplements in patients treated with corticosteroids. Br J Dis Chest. 1975;69:171–176.
[27]Peretz A, Neve J, Famaey JP. Effects of chronic and acute corticosteroid therapy on zinc and copper status in rheumatoid arthritis patients. J Trace Elem Electrolytes Health Dis. 1989;3:103–108.
[28]Peretz A, Neve J, Vertongen F, et al. Selenium status in relation to clinical variables and corticosteroid treatment in rheumatoid arthritis. J Rheumatol. 1987;14:1104–1107.
[29]Levine MA, Pollard HB. Hydrocortisone inhibition of ascorbic acid transport by chromaffin cells. FEBS Lett. 1983;158:134–138.
[30]Anonymous. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Arthritis Rheum. 2001;44:1496–1503.
[31]Anonymous. Bayer Health Care. Online document at: www.bayeraspirin.com=asp_hd.htm. Accessed July 8, 2006.
[32]Basu TK. Vitamin C–aspirin interactions. Int J Vitam Nutr Res Suppl. 1982;23:83–90.
[33]Das N, Nebioglu S. Vitamin C aspirin interactions in laboratory animals. J Clin Pharm Ther. 1992;17: 343–346.
[34]Palme G, Koeppe P. Comparative experimental studies in animals and humans on gastrointestinal blood loss following antirheumatic pharmacotherapy. Arzneimittelforschung. 1978;28:426–428.
[35]Lawrence VA, Loewenstein JE, Eichner ER. Aspirin and folate binding: In vivo and in vitro studies of serum binding and urinary excretion of endogenous folate. J Lab Clin Med. 1984;103:944–948.
[36]National Diabetes Fact Sheet, 2005 American Diabetes Association. Online document at: www.diabetes.org=uedocuments=NationalDiabetesFactSheetRev.pdf. Accessed January 18, 2007.
[37]Kilicdag EB, Bagis T, Tarim E, et al. Administration of B-group vitamins reduces circulating homocysteine in polycystic ovarian syndrome patients treated with metformin: A randomized trial. Hum Reprod. 2005;20:1521–1528.

[38]Wulffele MG, Kooy A, Lehert P, et al. Effects of short-term treatment with metformin on serum concentrations of homocysteine, folate and vitamin B_{12} in type 2 diabetes mellitus: A randomized, placebo-controlled trial. J Intern Med. 2003;254:455–463.
[39]Kishi T, Kishi H, Watanabe T, Folkers K. Bioenergetics in clinical medicine: XI. Studies on coenzyme Q and diabetes mellitus. J Med. 1976;7(3–4):307–321.
[40]Pfizer. Pfizer Annual Review. Online document at: www.pfizer.com=pfizer=annualreport=2005=annual=p2005ar20.jsp. Accessed July 8, 2006.
[41]Langsjoen PH, Langsjoen AM. The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10: A review of animal and human publications. Biofactors. 2003;18(1–4):101–111.
[42]Crane FL. Biochemical functions of coenzyme Q10. J Am Coll Nutr. 2001;20:591–598.
[43]Folkers K, Langsjoen P, Willis R, et al. Lovastatin decreases coenzyme Q levels in humans. Proc Natl Acad Sci USA. 1990;87:8931–8934.
[44]Hargreaves IP, Duncan AJ, Heales SJ, Land JM. The effect of HMGCoA reductase inhibitors on coenzyme Q10: Possible biochemical=clinical implications. Drug Saf. 2005;28:659–676.
[45]High Blood Pressure Statistics. American Heart Association. Online document at: www.americanheart.org=presenter.jhtml?identifier 2139. Accessed January 18, 2007.
[46]Vidrio H. Interaction with pyridoxal as a possible mechanism of hydralazine hypotension. J Cardiovasc Pharmacol. 1990;15:150–156.
[47]Pierpont GL, Francis GS, Cohn JN. Effect of captopril on renal function in patients with congestive heart failure. Br Heart J. 1981;46:522–527.
[48]Schilling H, Scheler F. Angiotensin-converting enzyme inhibition: Side effects and risks. Z Kardiol. 1988;77(suppl.3):47–54.
[49]Kishi T, Watanabe T, Folkers K. Bioenergetics in clinical medicine XV: Inhibition of coenzyme Q10-enzymes by clinically used adrenergic blockers of beta-receptors. Res Commun Chem Pathol Pharmacol. 1977;17:157–164.
[50]Clayton JA, Rodgers S, Blakey J. Thiazide diuretic prescription and electrolyte abnormalities in primary care. Br J Clin Pharmacol. 2006 Jan;61:87–95.
[51]Pak CY. Correction of thiazide-induced hypomagnesemia by potassium-magnesium citrate from review of prior trials. Clin Nephrol. 2000;54:271–275.
[52]Khedun SM, Naicker T, Maharaj B. Zinc, hydrochlorothiazide and sexual dysfunction. Cent Afr J Med. 1995;41:312–315.
[53]Zenuk C, Healey J, Donnelly J, et al. Thiamine deficiency in congestive heart failure patients receiving long term furosemide therapy. Can J Clin Pharmacol. 2003;10:184–188.
[54]Mydlik M, Derzsiova K, Zemberova E. Influence of water and sodium diuresis and furosemide on urinary excretion of vitamin B6, oxalic acid and vitamin C in chronic renal failure. Miner Electrolyte Metab. 1999;25(4–6):352–356.
[55]Lameire N, Dodion L. Acute and chronic effects of torasemide in healthy volunteers. Arzneimittelforschung. 1988;38(1A):167–171.
[56]One of the Nation's Most Common Disabling Neurological Conditions. Centers for Disease Control and Prevention. Online document at: www.cdc.gov=Epilepsy. Accessed January 18, 2007.
[57]Modi S, Lowder DM. Medications for migraine prophylaxis. Am Fam Physician. 2006;73:72–78.
[58]Skidmore-Roth L. Mosby's Nursing Drug Reference. St Louis: Mosby, Inc., 2002.
[59]Davie MW, Emberson CE, Lawson DE, et al. Low plasma 25-hydroxyvitamin D and serum calcium levels in institutionalized epileptic subjects: Associated risk factors, consequences and response to treatment with vitamin D. Q J Med. 1983;52:79–91.
[60]Schmitt BP, Nordlund DJ, Rodgers LA. Prevalence of hypocalcemia and elevated serum alkaline phosphatase in patients receiving chronic anticonvulsant therapy. J Fam Pract. 1984;18:873–877.
[61]Shafer RB, Nuttall FQ. Calcium and folic acid absorption in patients taking anticonvulsant drugs. J Clin Endocrinol Metab. 1975;41:1125–1129.
[62]Ch'ien LT, Krumdieck CL, Scott CW Jr, Butterworth CE Jr. Harmful effect of megadoses of vitamins: Electroencephalogram abnormalities and seizures induced by intravenous folate in drug-treated epileptics. Am J Clin Nutr. 1975;28:51–58.
[63]Mock DM, Mock NI, Nelson RP, Lombard KA. Disturbances in biotin metabolism in children undergoing long-term anticonvulsant therapy. J Pediatr Gastroenterol Nutr. 1998;26:245–250.
[64]Botez MI, Joyal C, Maag U, Bachevalier J. Cerebrospinal fluid and blood thiamine concentrations in phenytoin-treated epileptics. Can J Neurol Sci. 1982;9:37–39.
[65]Keith DA, Gundberg CM, Japour A, et al. Vitamin K-dependent proteins and anticonvulsant medication. Clin Pharmacol Ther. 1983;34:529–532.

[66]Onodera K, Takahashi A, Wakabayashi H, et al. Effects of menatetrenone on the bone and serum levels of vitamin K_2 (menaquinone derivatives) in osteopenia induced by phenytoin in growing rats. Nutrition. 2003;19:446–450.
[67]Rodriguez-Segade S, de la Pena CA, Tutor JC, et al. Carnitine deficiency associated with anticonvulsant therapy. Clin Chim Acta. 1989;181:175–181.
[68]Kumin GD. Clinical nephrotoxicity of tobramycin and gentamicin: A prospective study. JAMA. 1980; 244:1808–1810.
[69]Landau D, Kher KK. Gentamicin-induced Bartter-like syndrome. Pediatr Nephrol. 1997;11:737–740.
[70]Elliott C, Newman N, Madan A. Gentamicin effects on urinary electrolyte excretion in healthy subjects. Clin Pharmacol Ther. 2000;67:16–21.
[71]Neuvonen PJ. Interactions with the absorption of tetracyclines. Drugs. 1976;11:45–54.
[72]Mapp RK, McCarthy TJ. The effect of zinc sulphate and of bicitropeptide on tetracycline absorption. S Afr Med J. 1976;50:1829–1230.
[73]Madden JA, Plummer SF, Tang J, et al. Effect of probiotics on preventing disruption of the intestinal microflora following antibiotic therapy: A double-blind, placebo-controlled pilot study. Int Immunopharmacol. 2005;5:1091–1097.
[74]Cummings JH, Macfarlane GT. Role of intestinal bacteria in nutrient metabolism. J Parenter Enteral Nutr. 1997;21:357–365.
[75]Murray MT. Encyclopedia of Nutritional Supplements: The Essential Guide for Improving Your Health Naturally. Roseville: Prima Publishing, 1996.
[76]Meletis C, Jacobs T. Interactions Between Drugs and Natural Medicines: A Simple Guide to a Complex Subject, 2nd Edition. Sandy, OR: Eclectic Medical Publications, 2005.
[77]Marz RB. Medical Nutrition from Marz, 2nd Edition. Portland: Omni-Press, 1999.
[78]Ishii N, Nishihara Y. Pellagra encephalopathy among tuberculous patients: Its relation to isoniazid therapy. J Neurol Neurosurg Psychiatry. 1985;48:628–634.
[79]Coppola G, Epifanio G, Auricchio G, et al. Plasma free carnitine in epilepsy [sic] children, adolescents and young adults treated with old and new antiepileptic drugs with or without ketogenic diet. Brain Dev. 2006;28:358–365.
[80]Semino-Mora MC, Leon-Monzon ME, Dalakas MC. The effect of L-carnitine on the AZT-induced destruction of human myotubes: Part II. Treatment with L-carnitine improves the AZT-induced changes and prevents further destruction. Lab Invest. 1994;71:773–781.

39

SOME NATURAL MEDICINES MAY ALTER LABORATORY TEST RESULTS

Practitioners who use natural medicine will freely admit that " just because it's natural doesn't make it safe." It is logical that, because 25%–33% of conventional prescription medicines originated from natural sources, certain extracts may also have side effects. Philosophically, some people might argue that there is a difference between an isolated substance used in the form of a drug and using a botanical extract. However, this line of argument for many products has become weakened with the advent and abundant use of standardized products that concentrate isolated active chemicals from plants to create "quasi-drugs." Indeed, the same trends that originally resulted in the creation of pharmaceuticals are beginning to reshape the traditional use of botanical medicines. If an isolated substance in a drug derived from a plant is made into a prescription medicine and can cause side effects, then, of course, herbal medicines that are dissected and modified to create quasi-drugs increase the likelihood of interactions and side effects. This is especially true when quasi-drugs are not used with sufficient knowledge of nature's intended balance.

Drug–drug interactions occur, and it follows quite logically that drug–natural medicine interactions also happen. These potentials for side effects and interactions, however, are not limited to botanical medicines, supplemental forms of vitamins, minerals, and other nutrients when they are taken at doses and durations that do not occur naturally. We have moved beyond the concept of "food as the best medicine" into an arena of actively, and sometimes aggressively, manipulating and changing the biochemical balance of these substances in a broad and global fashion that increases the likelihood of both altered physiologic and chemical functioning, producing both positive and, at times, negative effects. Because integrative medicine practitioners combine natural therapies with conventional ones, it is vital to have a sophisticated understanding of these medicines, particularly how they interact with conventional drugs. This is a topic that is now receiving more attention in the literature. Another area of vital importance—one that demands substantial exploration and investigation—is how natural medicines can affect the results of laboratory tests. This chapter presents a select sampling of these interactions.

NUTRACEUTICAL–LABORATORY TEST INTERACTIONS

At this point in time, fewer than 1 of 10 nutraceuticals appear to have interactions with laboratory tests. This is probably largely because these supplements are generally safe but also because there is no required screening process for all nutraceuticals prior to making them available to consumers. Yet, when an interaction does arise, the result can take the form of an actual alteration of laboratory values resulting from changes in biochemical metabolism in vivo or false laboratory values caused by interference with a given laboratory technique. The tendency for certain nutraceuticals to be used for addressing specific conditions can guide a health provider in determining the potential presence of a culprit that may alter laboratory values. This chapter covers only a select group of common nutraceuticals and botanicals.

Table 39–1. Natural Medicine–Laboratory Test Interaction Summary

Natural Medicine	Common Names	Reasons for Use	Possible Effects on Laboratory Values
Alpha-lipoic acid	a-lipoic acid, ALA, lipoic acid, thioctacid, thioctan	Antioxidant; prevent diabetes, retinopathy, cataracts, or glaucoma; support patients with HIV, Wilson's disease, or lactic acidosis resulting from altered metabolism	Blood glucose: may lower serum glucose levels in patients with type 2 diabetes by reducing insulin resistance and enhanced glucose utilization Glycosylated hemoglobin: may decrease T-helper= T-suppressor ratio: improves ratio of T-helper cells relative to T-suppressor cells
Androstene-dione	Andro, androstene	Replace low endogenous levels or lowered androgen levels; increase athletic performance; enhance exercise endurance; decrease recuperative time; support sexual function	HDL: lowers HDL levels Estrone, estradiol, testosterone, dihydrotestosterone; elevates estrone, free testosterone, dihydrotestosterone, and estradiol levels Nandrolone: urine tests positive for nandrolone marker because of contamination with 19-norandrostenedione Testosterone: free and total testosterone levels may become elevated initially but may then normalize
Beta-glucan	b-glucan, beta-glycan, gifolan, schizophyllan	Support patients with high cholesterol, cancer, HIV, diabetes, allergies, and other conditions	WBC counts: WBC counts may be elevated
Boron	Borate, boric acid, sodium borate	Promote bone health; treat OA; enhance mental functioning; increase muscle mass, (illustrates benefits of using trace minerals therapeutically)	Estrogen: theoretically, may elevate estrogen levels Bone-mineral density: increases in female athletes Phosphorus: decreases serum phosphorus
Glucosamine sulfate	D-Glucosamine, glucosamine sulphate (British spelling)	Support patients with OA and other joint conditions, including TMJ disease	Glucose: may elevate blood glucose Insulin: potential ability to increase insulin level

(continued)

Table 39–1. (Continued)

Natural Medicine	Common Names	Reasons for Use	Possible Effects on Laboratory Values
N-acetyl-cysteine	NAC	Anti-inflammatory; mucolytic; increases levels of glutathione	Prothrombin time: decrease in prothrombin time. Blood pressure: NAC=nitroglycerin combination can lower blood pressure and reduce blood pressure readings Salicylate: falsely low serum salicylate test results Chloride: false-positive serum chloride test results Creatinine: falsely low serum creatinine test results Free cysteine: increases free cysteine plasma concentrations Ketones: on urinary dipstick tests, NAC can cause false-positive urine ketones Lipoprotein A: might reduce serum lipoprotein A concentrations Lithium: very high serum NAC concentrations might cause falsely low serum lithium test results ALT= AST: increases AST and ALT concentrations
Vitamin C		Antioxidant; maintaining normal immune function for infections, cancer, and allergies; a cofactor for several biochemical pathways	Acetominophen: false-negative urine results AST: false increase in results of serum tests Bilirubin: false increase in serum test Theophylline: false decrease in serum assay Carbamazepine (Tegretol): falsely increased serum assay results LDH: false decrease in test results Creatinine: false increase in serum creatinine or urine test results Calcium=sodium: increase in urinary calcium and a decrease in urinary sodium Glucose: false increases in urine test results Uric acid: decrease in serum uric acid concentrations HDL-2: lowers HDL-2 levels Iron: increase measures of iron status, such as serum iron and ferritin Vitamin B_{12}: false decrease in vitamin B_{12} levels Occult stool: false-negative guaiac results
Calcium		Bone mineral density	Bone mineral density: may increase Plasma 11-hydroxycorticosteroid: may increase Urinary 17-hydroxycorticosteroid: may decrease Gastrin: may increase Glucose: may decrease Uptake of I-131: may decrease Insulin: may increase plasma insulin Lipase: may falsely decrease test results Magnesium: may falsely decrease test results

Alpha-Lipoic Acid

Alpha-lipoic acid is generally considered to be a fairly targeted nutrient that is used to achieve specific health goals.

Glucose level—A study, conducted by the Department of Internal Medicine, in Frankfurt, Germany, examined the effect of alpha-lipoic acid, a cofactor of the pyruvate dehydrogenase complex, on insulin sensitivity and glucose effectiveness. The subjects included 10 lean and 10 obese patients with type 2 diabetes and 10 lean and 10 obese healthy controls. Insulin sensitivity and glucose effectiveness were measured after oral glucose loading. A modified, frequently sampled, intravenous (IV) glucose tolerance test was performed after oral treatment with 600 mg of alpha-lipoic acid, twice per day, for four weeks. alpha-lipoic acid was associated with increased glucose effectiveness in both groups of patients with diabetes. Higher insulin sensitivity and lower fasting glucose levels were noted in only the lean patients with diabetes. In addition, lactate and pyruvate, before and after glucose loading, were approximately 45% lower in both the lean and obese patients with diabetes.[1]

Glycosylated hemoglobin level—No effect has been observed, although daily glucose levels may be lower on average in patients who take this supplement.[2,3] A seven-month, multicenter, randomized controlled trial examined the effects of alpha-lipoic acid on polyneuropathy in patients with diabetes. The study involved 509 outpatients who were assigned randomly for six months to sequential treatment with 600 mg of alpha-lipoic acid per day, IV, for three weeks, followed by 600 mg of alpha-lipoic acid three times per day for six months. A placebo group received 600 mg of alpha-lipoic acid for three weeks, followed by a placebo, three per day for six months. There was no overt effect on glycosylated hemoglobin. The researchers concluded that there was a favorable effect on reducing diabetic neuropathy without adverse reactions.[3]

T-helper cell=T-suppressor cell ratio—Alpha-lipoic acid may improve the T-helper=T-suppressor ratio in patients who are infected with human immunodeficiency virus (HIV).[4]

Triiodothyronine (T3)—In experimental models, when alpha-lipoic acid was added to T4 supplementation, there was a decrease of T3 production by 22%–56%.[5]

Androstenedione

Whenever a hormonal intervention is utilized to produce altered physiologic activity or to alter biochemical processes, a myriad of potential effects can arise. All too often, patients will take over-the-counter hormones, not realizing that they are supplements that should be listed on patient intake forms as such or not telling providers about such use. Although this supplement is taken by many patients to enhance wellness, androstenedione can actually alter important cardiovascular indices.

High-density lipoprotein—Androstenedione may suppress high-density lipoprotein (HDL) levels.[6] Young men who consumed 100 mg of androstenedione three times per day for 28 days experienced a 10% decrease in HDL level.[7]

Estrone and estradiol—Because androstenedione is a precursor of estrone, androstenedione supplements may cause elevations of estrone and estradiol levels.[6,7] The

previously described 12-week study of the adverse effects of androstenedione on cholesterol produced a significant increase in the aromatization by-products estrone and estradiol.[6] In a double-blind, randomized, 28-day study of 55 men, 28 subjects were given 100 mg of androstenedione, three times per day, and 27 were given a placebo. Results of serum readings reflected an increase of androstenedione (300%), free testosterone (45%), dihydrotestosterone (83%), and estradiol (68%).[7]

Nandrolone—Patients' urine may test positive for the presence of nandrolone as a result of trace contamination of androstenedione with 19-norandrostenedione.[8] Nandrolone is an anabolic steroid that resembles testosterone in chemical structure and biologic activity. It is the subject of concern for athletic oversight committees, which test for illicit use by measuring the urine levels of its metabolite, 19-norandrostenedione. Trace contamination of androstenedione with 19-norandrostenedione could result in the unjust accusation that an athlete has used steroids illicitly. As noted in an insightful paper in the Journal of the American Medical Association,[8] it is important that consumers be advised to buy supplements from reputable manufacturers who provide certificates of analysis.

The study discussed in this paper involved 41 healthy men, ages 20–44 who took either 100 mg or 300 mg per day of androstenedione for seven days. All subjects were treated with androstenedione containing 19-norandrostenedione. The authors proved that, if androstenedione that was sold over the counter (OTC) contained 19-norandrostenedione, the nandrolone marker was found in the subjects' urine. This led the researchers to test seven OTC products randomly for the presence of 19-norandrostenedione. Of seven brands tested, one contained no androstenedione, one contained 10 mg of testosterone, and four more contained 90% or less of the amount stated on the product labels. The authors concluded that trace contamination of androstenedione with 19-norandrostenedione is sufficient to cause positive urine results for the presence of 19-androstenedione.

Patients' urine may test positive for the presence of nandrolone as a result of trace contamination of androstenedione with 19-norandrostenedione.

Testosterone—Free and total testosterone levels can become elevated, particularly in the first two months of use, although testosterone levels may begin to normalize over the course of time for many patients. This effect is the result of the precursor nature of androstenedione for testosterone production.[6]

Beta-Glucan

Use of beta-glucan may elevate white-blood-cell (WBC) counts (leukocytosis). A phase-II, multicenter, double-blind, randomized, placebo-controlled study of three dosages of beta-glucan was conducted in a population of surgical patients. Doses of 0.1 mg=kg, 0.5 mg=kg, or 1.0 or 2.0 mg=kg of the supplement were administered to 67 patients who were at a high risk for developing postsurgical infections after thoracic or abdominal surgery. Serious infections developed in 4 patients who received the placebo, in 3 patients who took the lowest dose of 0.1 mg=kg, and in only 1 patient who received one of the higher doses. Generalized leukocytosis

was observed; however, the researchers concluded that beta-glucan was safe, well-tolerated, and may decrease postoperative infection rates.[9] The elevated WBC counts seen in these patients may have resulted because the body's defenses are rallied by beta-glucan. This demonstrates the supplement's therapeutic efficacy. However, if use of beta-glucan or other immune-stimulating substances are not reported to clinicians, elevated WBC counts in patients who take the supplement might cause their health providers to believe that such patients have infections or other immunity problems that are actually nonexistent.

Boron

Present in many supplement regimes for the treatment for osteoporosis, this trace mineral can have substantial effects that can serve as an adjunctive therapy to optimize bone-mineral density. The mineral can also affect estrogen and phosphorus levels.

Estrogen—Boron has been shown to increase estrogen levels, thus concomitant use with estrogenic drugs may increase serum estrogen levels even higher.[10] Current knowledge of this potential interaction is based predominantly on the theoretical synergy that could arise from boron's ability to enhance estrogenic effects within the body. Thus, boron should be used cautiously, if at all, for patients with estrogen-dependent disease processes or who have risks for such conditions because of this potential to affect estrogenic properties physiologically.

Bone mineral density—Boron may increase bone-mineral density measurements in female athletes.[11] In a clinical trial, 17 female athletes had a slight increase in bone-mineral density over the period of the year-long study, whereas the sedentary control subjects actually demonstrated a slight decrease.

Phosphorus—Boron may also decrease serum phosphorus concentrations in some patients.[11] Female college students who took the mineral in a study had lowered serum phosphorus levels. Subjects in the study's boron-treated group also had lower magnesium levels, which apparently correlated with participating in exercise.[11]

Glucosamine Sulfate

One of the most popular nutrients on the market for relieving the discomfort and debilitating effects of degenerative arthritis, glucosamine sulfate, is generally considered to be safe. However, there is some preliminary evidence that, in some susceptible patients, glucose levels may become elevated. Thus it is important to ask patients with recalcitrant glucose-control problems or arthritis if this supplement is being used.

Blood glucose—It has been posited that glucosamine may elevate blood glucose levels by increasing insulin resistance or diminishing insulin production.[12,13] Rats who were infused with glucosamine had impaired early activation of phosphoinositide (PI) 3-kinase by insulin in skeletal muscle. Prolonged insulin infusion produced a blunting of the PI 3-kinase response to insulin.[13]

Insulin—According to the results of one study, glucosamine may cause impairment in glucose-induced insulin secretion.[14] This finding was discovered in a research model that used glucosamine infusion, and the study researchers concluded that glucosamine causes severe impairment in glucose-induced insulin secretion. They also concluded

that glucosamine-induced beta-cell secretory dysfunction extends to nonglycemic stimuli such as arginine. This pattern of insulin secretion dysfunction mirrors that seen in patients with noninsulin-dependent diabetes mellitus (NIDDM). Thus, the data indicated that glucosamine may contribute to potential pathogenesis of glucose toxicity at the level of the beta cell in NIDDM.

Although these potential side effects are yet to be broadly proven and have, in part, been based on glucosamine infusion or animal-model projections, clinically we have noted that occasionally, a patient will experience similar effects with oral intake of glucosamine sulfate. Yet, in another study, it was found that glucosamine sulfate, taken at 1,500 mg per day, for 12 weeks, increased blood insulin levels in a group of patients. It should be noted, however, that the vast majority of human studies have not found that glucosamine causes adverse effects on blood sugar or insulin resistance.

N-Acetyl-Cysteine (NAC)

NAC is the acetylated derivative of L-cysteine. It is a potent antioxidant, free-radical scavenger, has anti-inflammatory and mucolytic activity, and increases levels of glutathione. It is used in conventional medicine for acetaminophen hepatotoxicity.

Prothrombin time—Intravenous NAC in healthy individuals causes a significant and rapid decrease in prothrombin time. Coagulation factors II, VII, and X, the three components of prothrombin time, decreased significantly to different degrees in one study.[15]

Blood pressure—In a randomized double-blind study in 46 patients with severe unstable angina pectoris unresponsive to standard treatment, the effects of intravenous nitroglycerin were compared to those of intravenous (IV) nitroglycerin plus IV NAC. Concomitant administration of intravenous NAC and nitroglycerin had a significantly lower incidence of acute myocardial infarction than the nitroglycerin=placebo group and symptomatic hypotension occurred frequently in the combination group, thus the NAC=nitroglycerin combination can lower blood pressure and reduce blood pressure readings.[16]

Salicylate—intravenous NAC administration resulting in serum NAC concentrations of 50 mg=dL can cause falsely low serum salicylate test results when measured with Kodak Ektachem systems.[17]

Chloride—NAC can cause false-positive serum chloride test results measured with the Beckman Synchron CX3 analyzer.[17]

Creatinine—NAC can cause falsely low serum creatinine test results when measured by the single-slide method on Kodak Ektachem systems.[17]

Free cysteine—NAC can increase free cysteine plasma concentrations.[17]

Ketones—On urinary dipstick tests, NAC can cause false-positive urine ketones when measured with Chemstrips (Boehringer Mannheim) or Multistix (Miles).[17]

Lipoprotein(a)—NAC may reduce serum lipoprotein(a) concentrations and test results.[17]

Lithium—High serum NAC concentrations might cause falsely low serum lithium test results when measured with Kodak Ektachem systems. [17]

Liver function tests, alanine aminotransferase (ALT)= aspartate aminotransferase (AST)—NAC may increase AST and ALT concentrations. According to case reports,

liver function tests were significantly elevated on two occasions in a child with cystic fibrosis after receiving large NAC doses.[18]

Calcium

Calcium is an important mineral for various physiological functions including maintaining bone density, nerve transmission, muscle contraction vasodilation, cell membrane permeability, enzyme reactions, and blood coagulation.

Bone Mineral Density (BMD)—In a randomized placebo-controlled trial, 60 older postmenopausal women without osteoporosis were supplemented with calcium via 1,000 mg calcium carbonate or dietary milk. The women who averaged total calcium intake of 1,633 mg per day suffered no bone loss from the greater trochanter and showed a significant increase in spinal and femoral neck BMD. The placebo group consumed a mean of 683 mg per day of calcium and lost 3.0% of their greater trochanteric bone mineral density over the two-year evaluation. The women supplemented with milk averaged a calcium intake of 1,028 mg per day and sustained minimal loss from their greater trochanter.[19]

11- and 17-Hydroxycorticosteroids—According to a case report, calcium gluconate given intravenously may increase plasma 11-hydroxycorticosteroid concentrations and reduce urinary 17-hydroxycorticosteroid concentrations.[17]

Gastrin—Calcium carbonate may increase serum gastrin concentrations within 30–75 minutes after ingestion of calcium carbonate.[17]

Glucose—Calcium gluconate may decrease serum glucose concentrations as reported in newborns.[17]

I-131 uptake—Calcium gluconate may decrease serum uptake of I-131.[17]

Insulin—Calcium gluconate may increase plasma insulin concentrations as reported in newborns.[17]

Lipase—Calcium ions may falsely decrease test results when measuring serum lipase concentrations greater than 5 mmol=L using the method of Teitz.[17]

Magnesium—Calcium gluconate can falsely decrease test results for serum magnesium measured by titan-yellow.[17]

Vitamin C

Vitamin C (ascorbic acid) is a water-soluble vitamin used for many health conditions. It is important as an antioxidant and free-radical scavenger, maintaining normal immune function for infections, cancer, and allergies, and is a cofactor for several biochemical pathways. Due to the wide range of uses, vitamin C is frequently consumed in high doses potentially interacting with many laboratory tests.

Acetominophen—Vitamin C can cause false-negative urine results with methods based on hydrolysis and formation of an indophenol blue chromogen.[17]

Asparate aminotransferase (AST)—Ascorbic acid can cause a false increase in results of serum tests relying on color reactions (Redox reactions) and Technicon SMA 12=60.[17]

Bilirubin—Vitamin C can cause a false increase in serum test results measured by Technicon SMA 12=60 or colorimetric methods.[17]

Theophylline—Large amounts of vitamin C can cause a false decrease in serum assay results when measured by the ARIS system or Ames Seralyzer photometer.[17]
Carbamazepine (Tegretol)—Vitamin C can cause falsely increased serum assay results measured by the Ames ARIS method.[17]
Lactic dehydrogenase (LDH)—Vitamin C can cause a false decrease in test results measured by the Technicon SMA 12=60 and Abbott 100 methods. [17]
Creatinine—Vitamin C can cause a false increase in serum creatinine or urine test results.[17]
Calcium=Sodium—Vitamin C may cause an increase in urinary calcium, and a decrease in urinary sodium.[18]
Glucose—Vitamin C can cause false increases in urine test results measured by copper reduction methods (e.g., Clinitest), and false decreases in results measured by glucose oxidase methods (e.g., Clinistix, Tes-Tape).[18]
Uric acid—Large amounts of vitamin C can cause a decrease in serum uric acid concentrations measured by enzymatic method assays.[18]
High-density lipoprotein-2 (HDL-2)—In a three-year, double-blind trial, 160 patients with coronary disease, low HDL cholesterol levels, and normal LDL cholesterol levels were treated with various combinations of antioxidants and simvastatin plus niacin. Vitamin C in combination with beta-carotene, selenium, and vitamin E seems to lower HDL-2 levels by 15% in people with heart disease.[20]
Iron—Vitamin C can increase the absorption of iron and measures of iron status, such as serum iron and ferritin.[21]
Vitamin B_{12}—Large amounts of vitamin C can interfere with vitamin B_{12} assay, resulting in false decrease in vitamin B_{12} levels.[22]
Occult stool—Vitamin C can cause false-negative guaiac results.[23]

BOTANICAL–LABORATORY TEST INTERACTIONS

Botanical medicines can have many potential interactions with pharmaceuticals. The complex, and frequently abundant, active chemical constituents that produce therapeutic benefits can alter the accuracy of laboratory results and=or effect true changes in the body's biochemical pathways, either positively or negatively.

Goldenseal

Goldenseal (Hydrastis canadensis) has become best known for its antibacterial properties. It also can affect bilirubin levels. Goldenseal may increase bilirubin levels. Although this has been shown with berberine isolates, it has not been proven conclusively when whole goldenseal has been used. Actual increases in total and unbound bilirubin levels can become elevated with berberine use because bilirubin is displaced from albumin. This effect was confirmed in a study of rats that produced the potential physiologic effects. Using a peroxidase kinetic method, protein binding of bilirubin was studied. Berberine was found, in vitro, to have a tenfold superior displacing effect compared to phenylbutazone, a known potent bilirubin displacer. In the same study, berberine was also approximately 100-fold more effective for displacing bilirubin than papaverine, a berberine-like alkaloid.[24] The researchers said that neonates who suffer from kernicterus should not be given berberine-containing preparations. These also include Oregon grape (Berberis vulgaris) and other botanicals.

Table 39–2. Botanical and Lab Value Interaction

Natural Medicine	Common Names	Reasons for Use	Possible Effects on Laboratory Values
Goldenseal (Hydrastis canadensis)	Goldenroot, hydrastis, Indian turmeric, yellow root	Antibacterial; treat nasal congestion, flatulence, and URIs	Increases bilirubin level
Grapefruit	Grapefruit, pomelo, toronja	Weight loss, anticancer agent; cholesterol reduction; potassium, vitamin C, and fiber source	Increases serum levels of numerous drugs, including amlodipine, nifedipine, nisoldipine, felodipine, nimodipine, nicardipine, diltiazem, verapamil, buspirone, midazolam, triazolam, diazepam, carbamazepine, cisapride, cyclosporin, estradiol, lovastatin, saquinavir, simvastatin, atorvastatin, terfenadine, losartan
Botanical component-glucosinolates	Indole-3-carbinol, 3-indolyl-carbinol, I3C, (common sources include broccoli, cauliflower, other cruciferous vegetables, and several botanicals)	Prevent breast or colon cancer, support patients with SLE; liver detoxification	Rarely increases levels of ALT=SGPT
Hypericum perforatum	St. John's Wort	Depression	Affects metabolism of numerous drugs PT=INR: reports suggest that St. John's Wort may decrease PT=INR results in patients treated with warfarin (Coumadin) TSH: may elevate TSH levels
Olea europaea	Olive leaf	Hypertension: antibacterial	Blood Pressure: may decrease Glucose: may decrease Calcium: may decrease

Note: These possible laboratory interactions represent a select sampling of available literature. Additional data becomes available continuously and keeping up to date is important.

HIV human immunodeficiency virus, OA osteoarthritis, TMJ tempormandibular joint, URI upper respiratory infection, SLE systemic lupus erythematosus, HDL high-density lipoprotein,
WBC white blood cells, ALT alanine aminotransferase, SGPT serum glutamic pyruvic transaminase.

Concomitant intake of grapefruit juice increases the concentration of many drugs in humans.

Grapefruit

Grapefruit became quite famous because of the acclaimed Hollywood grapefruit diet; yet, this fruit can cause dramatic increases in blood levels of many substances, including a number of pharmaceuticals. Levels of numerous pharmaceuticals may be increased and will affect serum= plasma measurements. Among the drugs for which levels may become elevated are amlodipine, nifedipine, nisoldipine, felodipine, nimodipine, nicardipine, diltiazem, verapamil, buspirone, midazolam, triazolam, diazepam, carbamazepine, cisapride, cyclosporin, estradiol, lovastatin, saquinavir, simvastatin, atorvastatin, terfenadine, and losartan.[4] Concomitant intake of grapefruit juice increases the concentration of many drugs in humans.[25] The predominant effect seems to be mediated mainly by suppression of the cytochrome P450 enzyme, CYP3A4, and the P-glycoprotein pump, in the small intestine and, to a degree, the liver. This results in a decreased first-pass metabolism with enhanced bioavailability and increased maximal plasma concentrations. The drugs that are most affected by this phenomenon are those with a typical high first-pass degradation. Among these are felodipine, nitrendipine, nisoldipine, and saquinavir. In these cases, the interaction was most marked with median increases of area under the curve and=or the peak plasma drug concentration after a single dose (Cmax), values exceeding 70% of respective controls. Increases for nifedipine, nimodipine, verapamil, cyclosporin, midazolam, triazolam, and terfenadine are less pronounced but are still probably clinically relevant. The grapefruit juice components that are most likely to be the cause of these interactions are psoralen derivatives, more precisely known as furanocoumarins, and the flavonoid naringenin. Recent research indicates that the furanocoumarins epoxybergamottin and dihydroxybergamottin are the main inhibitory agents in grapefruit, with relatively minor contributions from naringenin and its glycoside naringin. Because the effect is so pronounced when patients drink grapefruit juice with some drugs, the researcher who conducted the study on grapefruit's effects concluded that patients should refrain from drinking grapefruit juice if they take drugs that are extensively metabolized by the CYP3A4 pathway.[25] Another study demonstrated that consumption of 250 mL of grapefruit juice caused a Cmax of 115% for a single oral dose of 5 mg of amlodipine taken with the juice.[26] Yet, another trial indicated that the mean felodipine bioavailability with grapefruit juice was 284% (range 164%–469%) of that with water.[27] The effects of the juice on buspirone were tested in a randomized, phase-2 crossover study. For this study, 10 healthy volunteers took either 200 mL of double-strength grapefruit juice or water, three times per day, for two days. On the third day, each subject was given 10 mg of buspirone with either 200 mL of grapefruit juice or water and an additional 200 mL was ingested 0.5 hour and 1.5 hours after the buspirone was administered. The mean increase resulting from the grapefruit juice consumption was 4.3-fold (range 2- to 15.6-fold).[27]

Glucosinolates: A Botanical Component

Scientific validation has now demonstrated that broccoli, cauliflower, and their relatives can prevent serious disease states. When taken in supplement form though, they too can alter laboratory values because of their glucosinolate content. Some patients who take glucosinolates

therapeutically may experience a slight increase in alanine aminotransferase (ALT).[28] In a study of 60 women who were at an increased risk for developing breast cancer, subjects were given either 50, 100, 200, 300, or 400 mg doses of indole-3-carbinol. The minimum effective dose per day as a possible chemopreventive agent against breast cancer was 300 mg. Although this study needs to be replicated on a much larger basis, it demonstrated that indole-3-carbinol can be used safely. However, a small minority of patients may experience a slight increase of ALT, but the reason for this is not yet known.

St. John's Wort

St. John's Wort (Hypericum perforatum) is a frequently utilized botanical medicine for the treatment of depression and mood disorders. The primary constituents attributed to the significant antidepressant activity include hypericin, hyperforin, and adhyperforin. St. John's Wort is thought to induce the cytochrome P450 1A2 (CYP1A2), 2C9 (CYP2C9), and 3A4 (CYP3A4) enzymes. It is well established that St. John's Wort interacts with the metabolism of an extensive list of pharmaceuticals. A few of these include estrogen=progestin contraceptives, warfarin (Coumadin), SSRI antidepressants, alprazolam (Xanax), barbiturates, amitriptyline, nortriptyline, Nefazodone (Serzone) Digoxin (Lanoxin), Clopidogrel (Plavix), cyclosporine, H_2 antagonists, antifungals, protease inhibitors, calcium channel blockers, corticosteroids, erythromycin, cisapride (Propulsid), fexofenadine (Allegra), cyclosporine, loperamide (Imodium), quinidine, meperidine (Demerol), Irinotecan (Camptosar), and Imatinib (Gleevec).[4] Current data does not suggest that it has similar wide-ranging interactions with laboratory values.

> Prothrombin Time (PT)= International Normalized Ratio (INR)—Reports suggest that St. John's Wort may decrease PT=INR results in patients treated with warfarin (Coumadin),[29] although more recent studies did not find evidence of decreased INR.[30]
> Thyroid Stimulating Hormone (TSH)—According to some preliminary data, St. John's Wort may elevate TSH levels. A phone survey correlated increased TSH with exposure to St. John's Wort supplementation three to six months prior to the lab evaluation.[31]

Olive Leaf

Both the oil and the leaf of olive (Olea europaea) are used medicinally. The primary constituent in the leaf is oleuropein which has antioxidant and bacteriostatic activity. Olive leaf is used for the treatment of hypertension as well as numerous types of viral and bacterial infections, such as influenza, pneumonia, Epstein-Barr virus, and hepatitis. A small study showed that Olea europaea L. leaf aqueous extract supplementation for three months' duration showed a statistically significant decrease of blood pressure, blood glucose, and calcium.[32]

CONCLUSIONS

Natural medicines sustained our ancestors for the millennia required for our very existence. But as Socrates could attest if asked today, not all natural substances are safe and sometimes there is a fine line between helpful and hurtful agents. With the advances in technology and growing interest in natural medicines, there is a trend toward utilizing natural medicines by general

consumers who may not realize that they are consuming medicines, even though they are natural in origin. This situation can result in interactions that alter laboratory values, even though the clinical effects of these medicines are sometimes positive and sometimes negative. It is hoped that information provided on these interactions will be used to produce vital literature to guide physicians and consumers on the safest and most prudent ways to use these medicines.

REFERENCES

[1]Konrad T, Vinci P, Kusterer K. Alpha-lipoic acid treatment decreases serum lactate and pyruvate concentrations and improves glucose effectiveness in lean and obese patients with type 2 diabetes. Diabetes. 1999;22:280–287.

[2]Ziegler D, Hanefeld M, Ruhnau K. Treatment of symptomatic diabetic polyneuropathy with the antioxidant thiotic acid (a-lipoic acid): A 2 year, multicenter, randomized, double blind, placebo controlled trial (ALADIN II). Free Radic Res. 1999;13:171–177.

[3]Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: A 7-month multicenter randomized controlled trial (ALADIN III Study): ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. Diabetologia. 1995;38:1425–3143.

[4]Jellin JM. Natural Medicine Comprehensive Database. Stockton, CA: Therapeutic Research Faculty, 2002.

[5]Segermann J, Hotze A, Ulrich H, Rao GS. Effect of alpha-lipoic acid on the peripheral conversion of thyroxine to triiodothyronine and on serum lipid-, protein- and glucose levels. Arzneimittelforschung. 1991 Dec;41(12):1294–1298.

[6]Broeder CE, Quindry J, Brittingham K. The Andro Project: Physiological and hormonal influences of androstenedione supplementation in men 35 to 65 years old participating in a high intensity resistance training program. Arch Intern Med. 2000;160:3093–3104.

[7]Brown GA, Vukovich MD, Martini ER, Kohut ML, Franke WD. Endocrine responses to chronic androstenedione intake in 30- to 56-year old men. J Clin Endocrinol Metab. 2000;85(11):4074–4080.

[8]Catlin DH, Leder BZ, Ahrens B. Trace contamination of over the counter androstenedione and positive urine tests results for a nandrolone metabolite. JAMA. 2000;284:2618–2621.

[9]Babineau TJ, Hackford A, Kenler A. A phase II multicenter, double blind randomized, placebo controlled study of three dosages of an immunomodulator (PGG-glucan) in high risk surgical patients. Arch Surg. 1994;129(11):1204–1210.

[10]Shils M, Olson A, Shike M. Modern Nutrition in Health and Disease, 8th Edition. Philadelphia: Lea and Febiger, 1994.

[11]Meacham SL, Taper LJ, Volpe SL. Effects of boron supplementation on bone mineral density and dietary, blood, and urinary calcium, phophorus, magnesium, and boron in female athletes. Environ Health Perspect. 1994;102(suppl.7):79–82.

[12]Adams ME. Hype about glucosamine. Lancet. 1999;354(9176):353.

[13]Holmang A, Nilsson C, Nikasson M. Induction of insulin resistance by glucosamine reduces blood but not interstitial levels of either glucose or insulin. Diabetes. 1999;48:106–111.

[14]Shanker RR, Zhu JS, Baron AD. Glucosamine infusion in rats mimic the beta-cell dysfunction of non–insulin-dependent diabetes mellitus. Metabolism. 1998;47(5):573–577.

[15]Jepsen S, Hansen AB. The influence of N-acetylcysteine on the measurement of prothrombin time and activated partial thromboplastin time in healthy subjects. Scand J Clin Lab Invest. 1994 Nov;54(7):543–547.

[16]Horowitz JD, Henry CA, Syrjanen ML, Louis WJ, Fish RD, Antman EM, Smith TW. Nitroglycerine= N-acetylcysteine in the management of unstable angina pectoris. Eur Heart J. 1988 Jan;9(suppl. A):95–100.

[17]Young DS. Effects of Drugs on Clinical Laboratory Tests, 4th Edition. Washington: AACC Press, 1995.

[18]McKevoy GK, ed. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists, 1998.

[19]Storm D, Eslin R, Porter ES, Musgrave K, Vereault D, Patton C, Kessenich C, Mohan S, Chen T, Holick MF, Rosen CJ. Calcium supplementation prevents seasonal bone loss and changes in biochemical markers of bone turnover in elderly New England women: A randomized placebo-controlled trial. J Clin Endocrinol Metab. 1998 Nov;83(11):3817–3825.

[20]Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, Frohlich J, Albers JJ. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med. 2001 Nov 29;345(22):1583–1592.

[21]Fishman SM, Christian P, West KP. The role of vitamins in the prevention and control of anaemia. Public Health Nutr. 2000 Jun;3(2):125–150.

[22]Vilter RW. Nutritional aspects of ascorbic acid: Uses and abuses. West J Med. 1980;133:485–492.

[23]Gogel HK, Tandberg D, Strickland RG. Substances that interfere with guaiac card tests: implications for gastric aspirate testing. Am J Emerg Med. 1989 Sep;7(5):474–480.

[24]Chan E. Displacement of bilirubin from albumin by berberine. Biol Neonate. 1993;63(4):201–208.

[25]Fuhr U. Drug interactions with grapefruit juice: Extent, probable mechanism and clinical relevance. Drug Saf. 1998;18(4):251–272.

[26]Josefson M, Zackrisson AL, Ahlner J. Effect of grapefruit juice on the pharmacokinetics of amlopidine in healthy volunteers. Eur J Clin Pharmacol. 1996;51(2):189–193.

[27]Bailey DG, Spence JD, Munoz C, Arnold JM. Interactions of citrus juices with felopidine and nifedipine. Lancet. 1991;337(8736):268–269.

[28]Wong GY, Bradlow L, Sepkovic D. Dose-ranging study of indole-3-carbinol for breast cancer prevention. J Cell Biochem. 1997;28(suppl.):111–116.

[29]Yue QY, Bergquist C, Gerden B. Safety of St. John's Wort (Hypericum perforatum). Lancet. 2000;355: 576–577.

[30]Jiang X, Williams KM, Liauw WS, Ammit AJ, Roufogalis BD, Duke CC, Day RO, McLachlan AJ. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol. 2004 May;57(5):592–599.

[31]Ferko N, Levine MA. Evaluation of the association between St. John's wort and elevated thyroid-stimulating hormone. Pharmacotherapy. 2001 Dec;21(12):1574–1578.

[32]Cherif S, Rahal N, Haouala M, Hizaoui B, Dargouth F, Gueddiche M, Kallel Z, Balansard G, Boukef K. [A clinical trial of a titrated Olea extract in the treatment of essential arterial hypertension]. J Pharm Belg. 1996 Mar–Apr;51(2):69–71.

Index

Note: Page numbers followed by i or t indicate illustrations and tables, respectively.