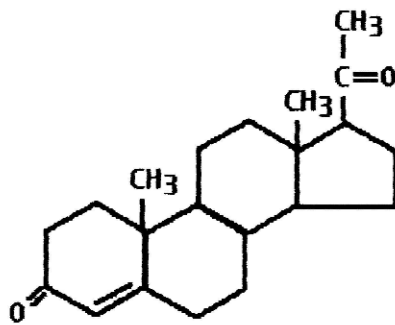


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Progesterone

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PROGESTERONE

The primary function of progesterone is to support pregnancy. The use of supplemental progesterone in pregnancy to prevent early miscarriage is still controversial and the FDA has not approved it for this use. This controversy has not prevented a large number of women with a history of problem pregnancies from using the nonprescription cream for that purpose with some success. Over the years various synthetic (prescription) progestagens have been used in infertility treatment as well as in birth control pills for contraception.

A second use of progesterone is in the treatment of pre-menstrual syndrome (PMS), fueling the recent popularity of the natural progesterone creams. PMS is a major problem for millions of women around the world and until recently there has been no effective treatment. There have been several scientific studies on the treatment of PMS with progesterone, though only a few small studies have shown relief of symptoms.

The realization that estrogen alone or estrogen with synthetic progestagens, when used as postmenopausal hormone replacement therapy, is associated with an increased risk of cancer (especially endometrial cancer) has encouraged more women past childbearing age to explore the possibility that bioidentical progesterone will more safely alleviate the symptoms of menopause than synthetic progestagens.

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VITAMIN C AND OSTEOARTHRITIS— ADVICE FROM ANIMAL STUDY MISINTERPRETED

Luke R. Bucci, Ph.D., CCN, CNS

Re: Kraus VB, Huebner JL, Stabler T, Flahiff CM, Setton LA, Fink C, Vilim V, Clark AG. Ascorbic acid increases the severity of spontaneous knee osteoarthritis in a guinea pig model. *Arthritis Rheum.* 2004 Jun; 50(6):1822–1831.

Duke University Medical Center, Durham, North Carolina 27710, USA.

This paper appeared simultaneously with press releases from Reuters Health desk on June 18, 2004. The lead author, Dr. Virginia Kraus, was interviewed and quoted as saying:

“In conclusion, this study highlights the potential drawbacks of long-term, high-dose ascorbic acid intake on joint health, suggesting that dietary intake should not be supplemented above the currently recommended dietary allowance (90 mg/day for men and 75 mg/day for women).” (1)

This statement is inappropriate given the level of evidence presented by the authors

The evidence for this final sentence of the article is entirely contained in their article, which used Hartley guinea pig osteoarthritis (OA) as a model. The authors studied three different levels of dietary ascorbic acid (Vitamin C) intake for 8 months in a guinea pig strain that spontaneously becomes osteoarthritis with 100% incidence. The authors reported that severity of OA was worse with increasing amounts of dietary ascorbic acid that are equivalent to 30, 200, and

well over 2500 mg of ascorbic acid daily for humans (based on plasma ascorbate levels). There are many reasons why this conclusion is inappropriate and cannot be extrapolated to human osteoarthritis.

- Use of an animal strain that will become osteoarthritic without fail does not necessarily mirror spontaneous osteoarthritis in humans. Animal strains that become osteoarthritic have a very large genetic factor that obviously causes osteoarthritis, whereas humans have genetic factors that contribute to, but do not normally cause osteoarthritis. Thus, the etiologies are different. Extrapolation from this animal model to humans is fraught with many difficulties that were not adequately expressed in the article, and certainly not in the press release.
- The authors showed that intakes of ascorbic acid equivalent to eating five servings of fruits and vegetables daily (around 200 mg) led to more osteoarthritis than an intake barely able to prevent scurvy (one animal actually did get scurvy). Yet the authors did not say that a healthy diet rich in fruits and vegetables worsens osteoarthritis, they said intakes OVER the recommended % Daily Value (DV) have potential drawbacks. Does this mean we should stop eating oranges? Why did the author not mention that option in the press release?
- Since dietary levels of Vitamin C intake normally obtained from healthy foods without supplementation increased OA

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- severity (according to the authors' results), how did a message come out in a press release to avoid Vitamin C supplements? One possibility is an anti-supplement bias.
- Further support for an anti-supplement bias is evident from their conclusion statement, which suggests that *supplementation* above the DV is problematic. This is irresponsible as many people ingest MORE than the DV for Vitamin C from foods alone. So is it OK to drink more orange juice and get more Vitamin C that way, but not from supplements? Thus, the authors have shown a clear and irresponsible anti-supplement bias.
 - Furthermore, in the Discussion, the authors mention the pro-oxidant properties of ascorbic acid, in an effort to explain why ascorbic acid would account for their observations.
 - The two references they chose to support pro-oxidant actions for ascorbic acid (with a weak qualifier of "Under some conditions...") were very poor choices. One reference was to a vehemently biased and mostly fallacious editorial by Victor Herbert in the scientific news journal *Nutrition Today* (5). His points have all been repeatedly debunked and refuted. In fact, some of his experiments have been shown to be rigged to produce pro-oxidant effects that have no relation to living systems. Their other "reference" was a letter to the editor of *Nature* – again, NOT a scholarly, peer-reviewed source. Thus, the authors relied on two *opinions*, and no valid, peer-reviewed scientific evidence, to give only one side of the ascorbic acid pro-oxidant issue. There are many articles that address this issue, and there are many human supplementation studies that DO NOT show pro-oxidant actions. The authors carefully selected low-quality citations that supported an unscientific bias against supplements.
 - The authors stated that there are no known long-term human studies of Vitamin C administration on osteoarthritis. This is incorrect. There is an article by James Greenwood, M.D. from 1964 reporting on several cases of large and significant clinical improvements of himself and his patients using high-dose (1–4 grams daily) ascorbic acid for long periods of time (over one year) in low back pain from disc degeneration (2). Dr. Greenwood reported that no safety issues were observed. So there is some evidence in humans that long-term, high-dose Vitamin C supplementation is not harmful to joints already showing signs of degeneration, and indeed, may have provided some benefits. In addition, there are several studies that examined relatively high-dose Vitamin C intake (0.5–1 gram daily) for prevention of the common cold that lasted 6–12 months. Again, no adverse effects were noticed.
 - The authors did discuss one epidemiological study on Vitamin C intake and osteoarthritis incidence, by McAlindon, et al in 1996 (3). This study found a reduced risk of cartilage loss from increasing Vitamin C intake. Osteoarthritis incidence and osteophyte presence were not significantly associated with Vitamin C (which means Vitamin C did not make them worse). While every epidemiological study has limitations, the authors tried to dismiss the validity of McAlindon's results.
 - The authors tried to explain McAlindon's positive results for Vitamin C preventing one marker of OA severity by rationalizing that maybe select subgroups of humans benefited from extra Vitamin C – notice this is a very pro-supplementation statement which contradicts their final conclusion.
 - The authors also rationalized McAlindon's results by implying that something else that people with high Vitamin C intakes were

doing actually prevented cartilage loss, rather than the Vitamin C itself. However, the authors volunteered no evidence to support their rationalization.

- One point the authors did not discuss, and indeed, did not mention, is that they studied guinea pigs, and guinea pigs are NOT human beings. The authors only provided plasma ascorbate levels as being directly comparable in humans and guinea pigs, which is sound in principle, but not in detail.
- The authors never discussed how spontaneous osteoarthritis in guinea pigs is very different from human spontaneous osteoarthritis. In other words, they did not address the key and crucial issue of extrapolation of guinea pig osteoarthritis to human osteoarthritis.
- The FDA convened a Food Advisory Committee meeting in June 2004 that was asked if animal models of osteoarthritis could be used to provide evidence of nutrient effects in human osteoarthritis. The august and esteemed rheumatologists, hand-picked by the FDA all concluded for the public record that animal studies have no relevance to humans (4).
- Thus, other experts in the human osteoarthritis field feel that results in guinea pigs cannot be extrapolated to humans, making the final conclusion and press release statements of the authors completely inappropriate. This inappropriateness is important since the final, take-home message to the public from the investigators was that Vitamin C is bad for your joints. This message contradicts the human research.
- From a mechanistic standpoint, the authors advocated that pro-oxidant actions of high-dose ascorbic acid concentrated in joints led to increased TGF-beta over time, which promoted increased degeneration, especially osteophyte formation. To this point, the authors did not measure TGF-beta in their animals. They pieced together other in vitro evidence of ascorbic acid activation of latent TGF-beta with injection of active TGF-beta into mice joints acutely causing more osteophytes as evidence of how Vitamin C might have accounted for their observations. This is more extrapolation across species as well as from in vitro studies. Thus, the authors would have to rely on mice, guinea pigs, human beings and plastic culture dishes being equivalent to support this line of reasoning.
- One point on this topic missed by the authors is that Vitamin C deficiency (lowest dose tested) in their guinea pigs did not increase osteoarthritis severity (compared to the guinea pig DV). This is not analogous to humans, who show degenerative changes in joints with prolonged Vitamin C deficiency compared to sufficient intakes. Thus, a key difference between guinea pigs and humans in ascorbic acid and joint degeneration was not evident to these investigators.
- The authors looked at bone mineral density, along with markers for bone turnover. They found "...no differences between dose groups for any of the measurements and no correlations with the histologic severity of OA." The authors did not emphasize this data, which did not make Vitamin C look bad, and purposefully chose not to exhibit this data, and only to briefly discuss it.
- The authors postulated that Advanced Glycation Endproducts (AGEs) in cartilage collagen might promote osteoarthritis, which is a current working hypothesis in the field of rheumatology. Even though the authors did not find any change in AGE levels in response to varying ascorbic acid intakes or plasma levels, they still did not believe their results. The authors then proceeded to say

- they may have missed "...subtle differences in AGEs accumulated in cartilage over only 12 months..." They concluded that their assay, which successfully found increases of AGEs in aging cartilage elsewhere, may not have been able to see miniscule changes that when added up over longer time periods, might account for more osteoarthritis. This argument is extremely weak and hypocritical considering their animals already had late stage osteoarthritis, with no correlation of AGEs with ascorbic acid intake or levels. In other words, they simply could not emotionally abandon what they thought would be a smoking gun implicating Vitamin C causing osteoarthritis that did not come to fruition.
- The authors also played fast and loose with statistical significance to emphasize their anti-supplement bias. They performed osmotic loading tests in vitro to cartilage at the end of the study, which is a measure of cartilage material properties. They stated "The high dose group had lower moduli values compared with the low-dose group..." consistent with greater chondropathy scores in the high-dose group, although this difference was not statistically significant ($P=0.12$)." Then the authors proceeded to say in the Discussion: "A trend of worsening chondropathy in association with higher ascorbic acid levels was also borne out by this biomechanical measure performed on a subset of the animals." Look carefully at this statement. They acknowledged that a P value of 0.12 was a trend, which is very highly debatable and hard to defend, since they only looked at a subgroup. The authors chose to spend considerable time and resources to explain why a nonsignificant result was a "trend." One can legitimately wonder what the authors would have concluded if high-dose Vitamin C had *improved* moduli scores with a P value of 0.12.
 - Furthermore, the authors made no mention of any long-term human studies examining effects of high-dose (over 1000 mg daily) supplementation studies of Vitamin C. Even a casual perusal of these studies would have found no evidence of adverse effects, and indeed, would most often find evidence of benefits for immune function, reducing incidence of upper respiratory infections, reducing biomarkers for incidence of many types of cancer, reducing cardiovascular disease risk, reducing asthma attacks, improving lung function, improving exercise performance, and other benefits. The fact that these well-documented benefits of Vitamin C supplementation were never mentioned makes their final conclusion unbalanced.
- Other publications directly refute the conclusions of Kraus. In June 2003, Lamers published an article on osteoarthritic Hartley guinea pigs given Vitamin C at low (2.5–3 mg/day), medium (30 mg/day) and high (150 mg/day) doses, similar to the doses used by Kraus (5). The authors used NMR spectroscopy fingerprinting to show that the high dose of Vitamin C had "...a noticeable effect on the development of OA..." Thus, data existing before the time of publication, using the same animal model and the same Vitamin C dose and that contradicts the conclusions of the authors, was not mentioned.
- A press report by Dorothy Pattison from the University of Cambridge was released in March 2003 concerning Vitamin C consumption and inflammatory polyarthritis in humans (6). The full article was published one month after the Kraus article, so the authors could not be expected to include a discussion of those results. However, this study found higher intakes of Vitamin C protected against risk of inflammatory polyarthritis in humans. In fact, Professor David Scott, president of the British Society for Rheumatology, stated: "It seems there is a particularly strong link between the risk of develop-

ing some forms of arthritis and a low intake of vitamin C. We feel these findings may have important implications for the role of diet in reducing the risk of inflammatory arthritis.” It should be pointed out that the Hartley guinea pig OA model used by Kraus more closely approximates human inflammatory polyarthritis than typical human OA. Thus, additional human data exists that directly contradicts the press release statement by Kraus.

CONCLUSION

The authors made a major error by putting the message out that nobody should be taking supplements with more than the DV for Vitamin C or else put their joints at more risk for OA. They did not explore the crucial issue of just how well do guinea pigs with genetically spontaneous and severe arthritis extrapolate to humans. They ignored long-term studies showing health benefits of high-dose Vitamin C, they did not perform an adequate literature search on Vitamin C for joint health in humans, and they wished away human data that directly contradicted their final conclusion. Essentially, the authors did not base their final conclusion on sound science. Based on the evidence on hand, their message if heeded would lead to a higher

incidence of cancers, cardiovascular diseases, infections and osteoarthritis in humans.

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COENZYME Q₁₀ ORAL ABSORPTION— RESULTS OF A COMPARATIVE STUDY

PURPOSE

The purpose of the study was to compare the rates of assimilation of two coenzyme Q₁₀ formulations following an oral dose.

INTRODUCTION

Two coenzyme Q₁₀ formulations were tested. Formulation A, trademarked as Q-Gel Forte[®], consisted of 30 mg of encapsulated coenzyme Q₁₀ dissolved in vegetable oil contained in a soft-gel[™] capsule. Formulation B was a powdered preparation supplied as 100 mg coenzyme Q₁₀ per gelatin capsule.

SUBJECTS

Five healthy subjects who volunteered for the study consisted of four men and one woman between ages 24 and 55.

DESIGN

A simple pharmacokinetic design was employed to assess the absorption efficiency of each coenzyme Q₁₀ formulation. Each subject took a single oral 300 mg dose of coenzyme Q₁₀ immediately after the drawing of the initial (S_{0 hr}) blood sample. See Table 1 for formulations. Blood draws were repeated at 1 hour, 3 00

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hours and 6 hours (S_{1 hr}, S_{3 hr} and S_{6 hr}). Coenzyme Q₁₀ was assayed in the serum fraction of all collected blood samples. The change in coenzyme Q₁₀ concentration from baseline values (S_{0 hr}) was taken to represent the rate of intestinal absorption.

The study was conducted in three phases (Table 1). In phase I, fasting subjects took Formulation A without breakfast. Phase II consisted of taking Formulation B with a standardized breakfast. Phase III consisted of taking Formulation A with the same standardized breakfast. A 'wash-out' period of at least one week intervened between each phase of the study.

TABLE 1. Design of Study Phases

Study Phase	CoQ10 Formulation	Breakfast Eaten
Phase I	Formula A (Q-Gel)	No
Phase II	Formula B (Powder)	Yes
Phase II	Formula A (Q-Gel)	Yes

PROTOCOL

Each phase was conducted as follows: fasting subjects had their first blood draw (S_{0 hr}) samples around 9 am. Within 15 minutes of the first blood draw, each subject took a 300 mg oral dose of one of the two coenzyme Q₁₀ test formulations. All groups consumed water, and for those eating breakfast the coenzyme Q₁₀ test dose was consumed a sausage and egg biscuit. One hour following the 300-mg coenzyme Q₁₀ dose with or without the breakfast meal, another blood draw was taken (S_{1 hr}). Blood samples were taken again at 3 and 6 hours (S_{3 hr} and S_{6 hr}). Subjects were permitted lunch after the S_{3 hr} blood draw. The serum fraction of each

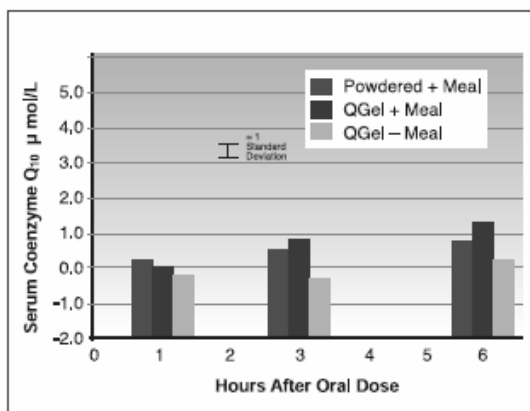


FIGURE 1. Coenzyme Q₁₀ absorption following an oral 300 mg dose of powdered CoQ₁₀ with breakfast (E); Q-Gel[®] with breakfast (G); and Q-Gel[®] without breakfast (C). Symbols show the means for five subjects.

blood sample was analyzed for concentrations of coenzyme Q₁₀ by high performance liquid chromatography (HPLC).

RESULTS

The plasma coenzyme Q₁₀ concentrations for samples S_{1 hr} - S_{6 hr} were adjusted by subtracting the S_{0 hr} coenzyme Q₁₀ concentration. The data (each data point is the mean coenzyme Q₁₀ concentration of five subjects) showing the coenzyme Q₁₀ absorption curves is summarized in Figure 1.

Data was statistically analyzed by the method of analysis of variance (ANOVA) with repeated measures. Assuming a probability of significance cut-off (p-value) of <0.05, no statis-

tically significant difference between the first two absorption curves was observed. However, the “Q-Gel with breakfast curve” was significantly different from the “Q-Gel without breakfast” curve, which demonstrates the important effect of the meal.

CONCLUSION

A meal is critical for the proper absorption of coenzyme Q₁₀. Without a meal, coenzyme Q₁₀ is very poorly absorbed. The amount of fat present in the Formulation B capsule (Q-Gel[®]) is not sufficient to promote absorption in the absence of a meal. If taken with a meal, the capsule type appears to have only a minimal impact on coenzyme Q₁₀ absorption.

IMPLICATIONS OF STRESS RESPONSE: MIND-BODY CONSIDERATIONS FOR CLINICAL PRACTICE

“What happens in the mind of man is always reflected in the diseases of the body.”

—Rene Dubos

In recent years the medical and psychological communities have become increasingly aware of the role that stress plays as an underlying cause of disease. Today we know that the majority of all visits to primary care physicians are in some way related to the adverse impact of stress.

It is currently recognized that one stress condition, stress-related metabolic syndrome—the most common cause of death in the Western world—occurs in more than 25% of American adults. In many of these people, genetics or overeating plays a role, while for others the effects of chronic stress builds until middle age, often culminating in metabolic syndrome (1). As most clinicians are aware, metabolic syndrome (also known as Syndrome X), commonly presents with various signs which can include dyslipidemia, insulin resistance, blood that clots easily, hypertension, increased body mass index (BMI) and an apple-shaped body with metabolically active abdominal (visceral) obesity—powerful predictors that in many cases can be associated in part with increased cortisol.

From this example can we assume that stress-related metabolic syndrome or any stress related condition is just an inevitable part of life? One of the major concerns with addressing such

issues is that few patients or clinicians have a clear understanding of how stress really affects us and how it can best be managed. For many people, stress is simply a word that defines a series of intangible and often undesirable situations, inescapable elements of life that we confront on a regular basis. Although stress is certainly a reality of life few people understand that it's ultimate effect on health and wellbeing has a great deal to do with the interactions of our mind and body and how we meet life's challenges.

HISTORICAL OVERVIEW OF STRESS

History tells us that the link between health and the mind and the body has been recognized for thousands of years. Hippocrates (the “Father of Medicine”), Aristotle and Plato were among the first to recognize that diseases begin first in the mind and the soul. Eastern philosophers, as well as Judeo-Christian, Hindu and other spiritual scriptures, similarly recognized such relationships.

Since the 19th century, mind-body parallels began entering into mainstream medical thought. Claude Bernard's (1813–1878) thesis of the “milieu interieur” (constancy of the internal environment) and Herbert Spencer's (1820–1903) concept of “survival of the fittest” both promulgated acceptance of the interconnectedness of the mind and physical body.

In the early 20th century a clearer understanding of the physiological effects of stress were researched by American physiologist, Walter B. Cannon (1871–1945). He found that when we experience stress whether from internal worry or external circumstances, the body triggers a “fight or flight” response. This reaction

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prompts nerve cell firing and outpouring of stress hormones (e.g.: cortisol and catecholamines) into the bloodstream. In addition, increases in cardiac output and blood pressure and activation of the sympathetic nervous system occur, as do effects on the hypothalamus-pituitary-adrenal (HPA) axis. Studying this “emergency response” of the autonomic nervous system, Cannon saw that survival was dependent upon the ability of the organism to remain in a state of “homeostasis.” It was this state of balance, or equilibrium, which was demonstrated to yield “staying power” and provide protective benefits.

The work of Canadian physician and endocrinologist, Hans Selye (1907–1982) built upon this early understanding. Selye presented our most significant modern day understanding of the physiology of stress and its effect on endocrine response. Author of more than 1,500 articles and 30 books on stress and related problems, he is sometimes referred to as the “Einstein of medicine,” because of his far-reaching insights in these areas. More than anyone else, Selye demonstrated the role of various responses in causing and combating much of the wear and tear people experience during their lives. He defined stress as the “non-specific response of the body to any demand made upon it” (2).

It is this wear and tear (also referred to as strains) that may have immediate or long-term effects on the organism. In his view, stress is not always detrimental. It can actually be a health enhancing positive or motivating experience—a “spice of life” (*joie de vivre*)—often termed “eustress.” When stress is acute and not protracted, normal adaptation can take place with upregulation of the immune system. Selye also found that stress could be neutral, termed “neustress.” However, it is the unpleasant or harmful, illness-provoking forms of stress, described as “distress,” that may be the contributing or causative factors promoting more rapid aging and cellular deterioration. With

chronic stress, an individual may also experience serious impairment or suppression of immunity.

IDENTIFICATION OF STRESS

To understand the stress concept, consider Selye’s definition of stress as “any” demand made upon an organism. He believed that stress cannot be totally avoided; it is a part of life, encompassing a wide range of life experiences—both good and bad. Thus, our deprivations, motivations, fears, frustrations, struggles, victories and joys of everyday life are all potential sources of stress. However, the impact, or “distress,” that life events will have on a person is dependent upon our individual characteristics such as personality, perceptions, adaptation, coping style and unique emotional-physiological responses to the particular stress. This work has been confirmed with more recent investigations on cellular telomeres, showing that the effects of chronic stress and the perception of life stress has the potential to shorten the life of cells and be a cause of an increased rate of aging.

Selye felt that anything that causes stress endangers life unless it is met with adequate responses. Conversely, anything that endangers life causes stress and can initiate the body’s attempt at adaptive responses. Ultimately, our adaptability and resistance to stress is required for our survival (2,3).

Stress can be identified as a variety of dissimilar situations that can be prompted by a wide range of circumstances that may include emotional arousal, physical effort, fatigue, pain, embarrassment and any number of other diverse states. Stressors can be conditions, situations, events or things that have the potential to trigger a stress response.

EXAMPLES OF COMMON LIFE STRESSORS

1. *Physical*—trauma, heat, cold, pain, injury, illness, allergies, exertion, intense focused atten-

tion, oxygen deprivation, immobilization, exercise, smoking, faulty diet, poor food quality, excessive free radical oxidation, insufficient sleep, hunger, hypoglycemia, malnutrition, under-nutrition, fasting, thirst, dysbiosis, infection, toxins, over-exertion, over-training, high-tension activities, tedious driving (e.g.: “white knuckle” driving conditions).

2. *Psychological/Emotional*—bereavement, chronic depression, fear, apprehension, joy, illness, isolation, loneliness, lack of adequate social support, personal performance (e.g.: achieving expectations, exams, public speaking), trauma, unrealistic expectations, personal frustration, juggling multiple life roles, lack of purpose or meaning in life, conflicts between personal values and those of culture or society, loss of job, financial burdens or obligations, time pressures, difficulties in marriage or personal relationships, tendency to “drive” oneself, family or relationship changes, caretaking responsibilities.

3. *Environmental*—poor living conditions, air, water and noise pollution, acid rain, severe cold or hot conditions, overexposure to toxic substances, electromagnetic fields, noise pollution, natural disasters.

4. *Occupational/Job Stress*—work that does not match our innate capabilities, resources or needs, tedious work, boring or dangerous work, job insecurities, downsizing and layoffs, long or difficult commutes, inflexible work schedules, difficult time deadlines, shift work, heavy travel schedules, multi-tasking; excessive work loads, long work hours, prejudice or problems in the workplace, lack of adequate compensation, excessive involvement in work, poor communication, interpersonal problems, poor distribution of responsibility, job responsibility without proper authority (e.g.: the subordinate who has little decision-making authority, latitude or control over the outcome of job duties).

In today’s society the wide-ranging forms of stress that regularly confront us can undercut our resilience and lay many of our most basic needs on the line. In a most fundamental sense

stress disturbs our equilibrium and unless we properly adapt to life events, our internal stress mechanisms become activated. Whether we experience physical, mental or somatic stress responses (e.g.: anxiety-fear, grief-sadness-depression, or frustration-hostility-anger-rage) we will commonly experience stress induced corticosteroid stimulation. What is often overlooked is that emotional stress can be equally, and often more depleting to the individual than physical stress.

Such modern-day reactions to stress are often equated to the emergency responses of early cavemen. As wild animals or other predators approached, early man recognized his fears and either ran for safety or physically fought for his survival. In either situation, the body rallied various physiological systems to ensure safe resolution. Whether stress is associated with early caveman experience or exemplified by our modern-day life events, “fight-flight” emergency responses often occur.

In primitive times the fight-flight response occurred every few days or weeks, allowing sufficient time for the body to effectively recover. Today, stress can be continual, and for many individuals its relentless, on-going and often inescapable nature can prevent us from having sufficient time needed for the rest and recovery so crucial to well-being. As a consequence, individuals may suffer from stress-induced physical illness or forms of depression.

Our level of stress hardiness, the ability to stay healthy despite stress, is contingent upon many variables, both physical and emotional. Characteristics such as commitment, meaningfulness as it relates to the challenge, ability to feel in control and to manage stress (as opposed to feeling helpless), self-efficacy (belief in our personal ability to meet the challenge), the ability to express our own emotions, availability of social support and spirituality with its sense of optimism and hope are all important considerations that can have an impact on our ability to maintain long term wellness amidst stress (4).

STRESS RESPONSE

During the various stages of the stress response, dysfunction and “diseases of adaptation,” can occur. Selye found that ulcers, lowered immunity, shock and death could also be associated with chronic stress. Autopsy studies of experimental animals experiencing the various stages of stress revealed many pathogenic changes characteristic of a range of human health conditions including hypertension, arthritis, peptic ulcers and coronary artery disease. Chronic stress stimulation with activation of the pituitary adrenocortical axis and resulting increased stress hormone levels produced pathologic changes in the gastric mucosa, lymphoid tissues and adrenal cortex.

Newer studies similarly suggest that hypothalamic arousal with parallel activation of the hypothalamic-adrenal axis and central sympathetic nervous system can be responsible for abnormalities in the endocrine system, insulin resistance, central obesity, dyslipidemia and hypertension leading to diseases that include type II diabetes (5).

Studies have also found that stressful experiences and negative emotions including depression can promote production of interleukin-6 (IL-6) and other pro-inflammatory cytokines. Of concern is that IL-6 is directly linked to cardiovascular disease due to its role in the production of C-reactive protein (CRP). Interestingly, both IL-6 and CRP are also involved in the development of type-2 diabetes. (6,7). Thus, we can see the implications of stress or forms of personal dependency in the role of Type II diabetes and numerous other commonly observed stress-linked health conditions.

Most of Selye’s research focused on the hypothalamus-pituitary-adrenocortical (HPA) axis with the resultant release of a large amount of cortisone-like hormones in response to stress. Today it is recognized that there is also an intimate relationship between serotonin, the HPA axis and normal physiology such as the circa-

dian rhythm, as well as pathophysiological disorders such as depression, anxiety, eating disorders and chronic fatigue (8).

SELYE’S GENERAL ADAPTATION SYNDROME (G.A.S.)

Selye addressed the wear-and-tear of stress in a three-phase response called the “General Adaptation Syndrome (G.A.S.)” (3). General, because it produced hormones that have an arousal effect on the entire body; adaptive, because it stimulates the body’s defense mechanisms thus increasing the chances for survival; and syndrome, because the stress response is integrated. The G.A.S. appeared to be evoked by stimuli with strong psychosocial components.

Selye termed the initial stimulation of stress the “Alarm Reaction,” since it appeared to rally together the body’s defense resources in response to the offending stressor. This stage was characterized by the release of adrenal medullary (epinephrine release) and cortical hormones into the blood stream, and had a number of characteristic manifestations including tissue catabolism, blood sugar disturbances and gastrointestinal erosions. Most researchers today view this stage as the sympathetic response known as the fight-flight reaction.

A “Stage of Resistance” follows the alarm phase as a means to maximize protection against the persisting stress response. In this state characteristic signs of the alarm stage diminish and resistance rises above normal in an attempt to maintain homeostasis. Adaptive responses are maintained and body function is heightened. If the stress persists the supportive mechanisms of this stage will diminish.

Compelling evidence suggests that progressive dysfunction of the HPA axis with elevated levels of circulating cortisol is implicated with visceral obesity (9). Chronic stress is also associated with suppression of both cellular and humoral measures, and physical vulnerability (as a function of age or disease) to immune changes (10).

If the stressor resistance continues too long, mechanisms supporting this response eventually weaken and the “Stage of Exhaustion” begins. Here, the energy that has adjusted to long-term exposure to the stressor begins to exhaust, signs of alarm reactions reappear, and disease or death can occur. Selye found that severely overstressed animals experienced adrenal gland bleeding and signs of adrenal destruction before the animal finally dies from stress.

The stage of exhaustion, however, need not always be irreversible and complete as long as it affects only parts of the body. An example is the runner who experiences stress placed on the muscles and cardiovascular system during an exercise session. Coping must include limbering to ready each system for the task. The systems are then at their height of efficiency during running but eventually exhaustion will set in. This type of exhaustion will reverse itself when the individual has sufficient rest to return the body back to normal (11).

A collapse of body functioning or specific organs marks the Exhaustion Stage. In many individuals long term or ongoing stress will create this level of exhaustion or “burn-out.” The initial hyperactivation prompted by the stress response eventually exhausts into hypoactivation or adrenocortical hypofunction. The result can then be loss of HPA adaptation to stress, hypoarousal and disruption of the regulatory systems (12).

Selye recognized that the body’s adaptability (adaptive energy) is finite. Our individual reserves of adaptive energy vary from person to person and are much like an inherited bank account from which we can make just so many withdrawals (11).

Exhaustion can also include altered endocrine function which may consequently result in diminished resilience, detrimental effects on quality of life and added burdens on other endocrines including thyroid, T4-T3 conversion, and growth and other hormonal disturbances. Each of these disturbances may also

usher in the onset of a broad variety of conditions

Patients with inadequate adrenal function may also have a deficit in the protective ranges of cortisol required by the body. As a result, they may experience symptoms that are influenced by such decline (e.g.: fatigue, inflammation, allergies, infection, asthma, chronic pain, autoimmune disorders, cognitive dysfunction and other symptoms).

Selye did recognize that sleep and rest can restore resistance, but complete restoration is probably impossible. He equated exhaustion to a wear-and-tear that leaves some irreversible clinical scars; these accumulate to constitute the stages of aging (11).

Overall, Selye saw these three phases of the general adaptation syndrome as being analogous to our life stages: Childhood (Alarm Reaction Stage) with tendency toward lowered resistance, and excessive reactions; Adulthood (Resistance Stage) where adaptation occurs and resistance increases; and finally, Senility (Exhaustion Stage), characterized by irreversible loss of adaptation and eventual exhaustion (2).

CORTISOL AND KEY STRESS HORMONES

Although the adrenals produce approximately 150 hormones, cortisol is one of the most prominent, assisting in the homeostasis of the body and substantially increasing the resistance of the body to acute and chronic stress. Cortisol is considered the primary glucocorticoid, accounting for 95% of glucocorticoid activity

Almost all forms of stress will stimulate cortisol secretion; however differences exist between individuals in how they respond to the same stressor. The reason for this is generally due to the individual’s unique perception of the stress. With continued exposure to the same stimuli adaptation, attenuation of cortisol hormone release may also occur.

Produced in the middle cell layer of the adrenal cortex (zona fasciculata), cortisol production is controlled by the regulatory action of the Hypothalamus/Pituitary/Adrenal (HPA) Axis. Cortisol is stimulated by the anterior pituitary's production of adrenocorticotrophic hormone (ACTH). In turn, ACTH is regulated by the hypothalamic cortical-releasing hormone (CRH). These secretions are controlled by the classic negative feedback loop - as blood level concentrations of cortisol rise to a particular level, cortisol suppresses the need for further production of ACTH and CRH (13).

CRH → ACTH → CORTISOL

Cortisol tends to exhibit a diurnal rhythm, normally peaking in the early morning (e.g.: 6–8AM, maximum levels 5–10AM) and its lowest levels late in day through midnight. The circadian rhythm of cortisol release is established in infancy and regulated by our sleep-wake cycles. Normal sleep-wake cycles help normalize cortisol, while altered sleep-wake cycles can in turn induce cortisol disturbance. Sleep restriction can be associated with disturbances of cortisol levels with inappropriate cortisol increases during afternoon and evening hours along with reduction of the quiescent period (14).

Anxiety and arousal tend to increase muscle and sympathetic tone, increase catabolic hormones and brain catecholamines and alter overall functioning of the endocrine and immune systems especially in early stages before exhaustion. These shifts can aggravate or prompt any number of dysfunctions including muscle tension, pain, vasoconstriction (e.g.: Reynauds syndrome), insomnia, allergies, fatigue, hypertension, headaches (migraine, tension, temporomandibular joint disorder related), blood sugar imbalances, disruption of diabetic control, spastic colon, ulcers, anxiety, depression, cholesterol increases, and various other disturbances manifesting in the gastrointestinal, musculoskeletal, cardiovascular,

endocrine and immune systems. Excess cortisol production can also promote elevations in blood glucose (hyperglycemia) and increased liver gluconeogenesis with resulting increased liver glycogen storage.

SOME PHYSIOLOGICAL IMPLICATIONS OF GLUCOCORTICIDS

Carbohydrate Metabolism

- High circulating cortisol promotes tendency toward hyperglycemia
- Increases amino acids in blood (especially from muscle) and transport to liver
- Stimulates liver gluconeogenesis (formation of glucose from non-carbohydrate sources) by up to 6–10 times greater than normal (builds up liver glycogen storage).

Protein Metabolism

- Decreases protein anabolism (synthesis)
- Increases protein catabolism (breakdown)
- Decreases protein stores in all cells except liver (liver proteins increase)
- Possible negative nitrogen balance due to loss of protein from high cortisol levels (labile protein constituents mobilized rather than basic structural proteins).

Fat Metabolism

- Minor stimulation in mobilization of fatty acids in adipose tissue
- Mild increases in plasma free fatty acids
- Increases cellular fatty acid oxidation
- As a result of lipolysis, increased glycerol and lactate production encourages gluconeogenesis
- Utilization of fats replaces glucose as energy source. Glucose and glycogen is preserved.

Muscular System

- Maintains muscle strength initially.
- Reduces muscle strength if cortisol in excess.

Anti-Inflammatory Effects

- Inhibits inflammatory response via decreased capillary permeability, stabiliza-

tion of lysosomal membranes, decrease in fibroblast activity and the blocking of WBC's ability to release more inflammatory substances.

Immune System

- Suppresses lymphoid tissues and decreases lymph organ production of leucocytes, sensitizes lymphocytes and antibodies if cortisol produced in high amounts.
- Overall immunity decreases to almost all foreign substances
- Reduces immune activity with high levels of cortisol (reduction in eosinophils and lymphocytes)
- Enhances production or maintenance of red blood cell (RBC) production via increased cortisol.

Some Other Effects

- Anti-anabolic (i.e. catabolic) effect on lymph, bone, connective tissue and other body tissues
- Anabolic effects on liver and either anti-anabolism or catabolic effect in other tissues
- Inhibits DNA production in some tissues
- Increases appetite and gastric juice
- Necessary for normal brain function. (15)

As can be seen, glucocorticoids can significantly change biological functions, primarily in the direction of preparing the body for short-term and long-term survival.

Over-secretion of cortisol has been linked to a number of conditions including obesity, hypertension, disturbances of other endocrines and reduced calcium levels which may lead to osteoporosis.

In addition to cortisol, the adrenals also produce epinephrine and norepinephrine along with other key substances and intermediary hormones including testosterone, estrogen, progesterone, pregnenolone, adrostenedione, dehydroepiandrosterone (DHEA) the mineral corticoid, aldosterone (adrenal cortex secretion) and a certain amount of dopamine.

It is important to note that steroid hormone biosynthesis involves enzymes controlled by adrenal physiology. DHEA is the most abundant steroid hormone produced by the adrenal cortex (synthesized directly from pregnenolone which is, in turn synthesized from cholesterol) and converted into either testosterone or estrogens by body tissues. Aldosterone is a hormone that maintains the body's sodium and water balance and its stimulation is greatly influenced by plasma volume. Dopamine mediates signals that appear to be involved with positive emotions and memory.

ADRENAL HYPOFUNCTION

In many patients who are unable to continually adapt following intense or prolonged periods of stress, adrenal dysfunction may become evident. Such individuals may be unable to maintain healthy energy levels.

Poor or diminished adrenal function is commonly accompanied by other endocrine dysfunctions and can be an underlying factor in various conditions including recurrent infections, poor stress tolerance ("crashing" with stress), fatigue, feeling "wiped out," difficulty in performing tasks, general immune suppression, inflammation, hypoglycemia, low blood pressure, and endocrine dysfunctions.

Adrenal insufficiency or low adrenal reserve is also seen as a major consequence of prolonged or chronic stress fixation (later stages of compensated stress response). It may also result from chronic physical over-training—when athletes move from excessive cortisol and protein catabolism to a state of physical exhaustion. In other individuals, low adrenal function may also be a consequence of early life trauma.

Addison's disease serves as a reminder of how severe diminished adrenal health can affect patients. In this disease, patients exhibit a very severe form of adrenal insufficiency with pathologically low cortisol. These individuals may have a disruption of the natural circadian

rhythm of cortisol, weight loss, apathy, hypotension, inability to cope with stress and other clinical manifestations (16).

The etiology of adrenocortical hypofunction can be complex. While chronic or unrelenting stress is regularly seen in adult patient care, addressing this issue may be widely overlooked and unexplored in clinical evaluations. Consequently, addressing such concerns may not even be considered in standard therapeutic treatment plans.

Although the individual's current life situation and stressors provide invaluable information, a patient's earlier life and the impact of any previous trauma may also need to be explored. For some individuals, early life situations and events can impact adrenal function. Frequent elevations in cortisol during childhood can down-regulate the HPA system and result in low rather than high adrenocortical secretion as the individual ages (17). Childhood situations such as attachment insecurities, parental anti-social behavior, chaotic home life, forms of neglect and abuse, changes in care giving, and other situations may thus have a long-term impact on the individual. Studies also suggest that small birth weight and gestational age can also influence cortisol secretion later in life (18).

In acutely ill patients adrenal insufficiency is more commonly associated with a variety of clinical situations. It may also be seen in some patients taking a number of commonly used medications including the ketoconazole, synthetic estrogens, oral contraceptives, anesthetic agents, and high doses of corticosteroid therapy (19).

Reinstating normal adrenal function can be a challenge. However, it can be addressed in generally healthy people with various methods including lifestyle changes, diet and supplements (as will be discussed) and often by pharmacological protocols.

Many physicians avoid using adrenal hormones because of the wide and varied side effects, especially with prolonged use. However, endocrinologist William Jefferies (20,21) and

other experts have found that certain individuals with diminished hormone production or low adrenal reserve may warrant supportive therapy with low dose—"physiological doses"—of natural hydrocortisone. This method is very different than significantly higher pharmacological doses of synthetic forms of cortisone therapy. Jeffries found that these very small but physiologically active doses appears to provide sufficient replacement in many patients, bringing them to normal levels while relieving demands off the ailing gland. Today some complementary physicians use this method while assisting the patient with necessary lifestyle changes aimed at functional improvement of the adrenals. The goal is to restore normal adrenal function over time. In highly susceptible patients, brief booster support may later be needed during times of stress or illness.

Laboratory Evaluations for Adrenal and Related Functions

- Cortisol/ACTH Evaluation
- Morning plasma cortisol (drawn fasting and before 9:30 AM)
- Cortisol—saliva or serum
- Dehydroepiandrosterone Sulphate (DHEA-S) saliva and serum
- Salivary circadian cortisol measures (often used as a measure of free-circulating cortisol)
- Neuroendocrine Profile (stress related neurotransmitters and hormones) saliva and urine
- Urine free cortisol
- Glucose Tolerance Test or Hemoglobin A1C (glycosylated hemoglobin) - to identify hypoglycemic or hyperglycemic tendencies.
- Complete thyroid evaluation including T3, Free T3, Reverse T3, T4 and TSH

Functional Adrenal Evaluations

- Postural Blood Pressure Evaluation (Ragland Analysis)
- Pupil Constriction in Response to Light Test (Rogoff's Sign Test)

STRESS AND BRAIN FUNCTION

Neurotransmitters are particularly sensitive to stress and emotional stimuli. During stress the turnover of certain neurotransmitters can be rapidly increased. The exhaustion stage of the G.A.S. response can prompt dysregulation of multiple neurochemical and neuroendocrine systems in a similar way in both stressed and depressed patients. Low neurotransmitter levels can result from chronic or prolonged stress, genetic predisposition, and diets low in amino acid precursors.

Both physical and emotional health is dependent on normalized brain cell communication. Research indicates that anxiety and some forms of depression can be linked to stress, yet in different ways. Anxiety primarily creates havoc in the limbic (emotional) centers of the brain often resulting in agitation or hyperactivity. Depression (especially in its major forms) can induce a feeling of helplessness and feelings in some individuals of being so overwhelmed that they may exhibit a form of psychomotor retardation (slowness). Much of this response is due to the effect of stress on the neurotransmitters and the mood and pleasure centers of the brain. Loss of natural vigilance and diminished psychomotor activity often seen in many depressed individuals can be the result of both prolonged exposure to stress and glucocorticoid hormones along with a depletion of norepinephrine.

Depression is traditionally believed to be due to an imbalance of neurotransmitters—primarily either serotonergic neurotransmitters (inhibitory) or dopaminergic (stimulatory in most cases). A response to antidepressants will depend on the neurotransmitter system most out of balance, and the choice of antidepressant medication selected.

Chronic, on-going stress can reduce serotonin and disturb the regulation of mood and sleep cycles. Although moderate stress can stimulate glucocorticoids and increase dopamine release—thereby increasing a sense of well-being—with chronic stress and continual gluco-

corticoid exposure, dopamine production can decline and feelings of pleasure may diminish.

PHYSIOLOGICAL EFFECTS OF EPINEPHRINE AND NOREPINEPHRINE

PREPARATION FOR FIGHT-FLIGHT RESPONSE

Most activities rely on both hormones, some more on one hormone than the other.

Central Nervous System (CNS)

- Enhanced anxiety/arousal (primarily epinephrine)

Respiratory

- Breathing stimulation (epinephrine influence most potent)
- Increased respiration

Gastrointestinal

- Decreases smooth muscle tone and inhibits gastrointestinal tract peristalsis, slowing digestion

Circulation

- Increase heart rate
- Both constrict blood vessels of periphery (skin) and splanchnic bed.
- Lowering of eosinophil count (primarily epinephrine aided by cortisol)
- Skeletal muscle blood vessel dilation (primarily epinephrine) and constriction (primarily norepinephrine)
- Both increase perspiration and cause dilation of the pupils

Blood Pressure

- Increased systolic blood pressure (primarily epinephrine)
- Increased peripheral resistance/vasoconstriction effecting blood pressure (primarily norepinephrine)
- Increased contraction and heart rate

Metabolism/Other Effects

- Increased basal metabolic rate (BMR)—up to 100% above normal (primarily epinephrine)

- Increased blood glucose (hyperglycemia) (primarily epinephrine)
- In pancreas both can inhibit glucose-induced secretion of insulin
- Stimulation of salivation and lachrymal glands (primarily epinephrine)
- Enhanced glycogenolysis (conversion of glycogen to dextrose in liver) and gluconeogenesis (formation of glucose from non-carbohydrate sources occurring in the liver (primarily epinephrine) (15).

Several new forms of laboratory evaluations can help determine whether and to what extent brain neurotransmitters may be out of balance. While low levels of certain neurotransmitters may be seen in some stressed individuals, abnormally high levels can also exist and be involved with such conditions as hypertension, anxiety, hyperactivity and various other conditions.

Other new ways to evaluate the degree of brain imbalance, electrophysiological function and positive brain wave levels is Brain Electrical Activity Mapping (BEAM) or the Quantitative EEG (QEEG) used in conjunction with neurofeedback (EEG). Often dietary change, supplements, prayer, meditation, exercise and spirituality may help rebalance this system. In some cases, the Cranial Electrical Stimulation (CES) may sometimes be used with certain patients as determined by the physician specializing in this approach.

Protecting brain cells is another concern during stress. High levels of glucocorticoids produced during the stress response have been shown to destroy brain cells and can cause damage to the hippocampus, the area of the brain associated with learning and memory. Depression is another concern since it is also known to be accompanied by changes in glucocorticoids (22).

Neurotoxic substances (e.g.: heavy metals, amphetamines, pesticides and some drugs) may cause damage to the nervous system by reducing the number of active receptors. Neurotransmitter related disorders occur when current levels of

neurotransmitters are unable to properly relay electrical signals between neurons. Balanced brain function and optimal health therefore depend on a proper balance of the inhibitory and excitatory neurotransmitter system. Low levels of neurotransmitters can result from prolonged stress, genetic predisposition, and diets low in amino acid precursors. Ultimately our neurotransmitter balance is greatly affected by lifestyle, diet, nutrient levels, stress, genetics and hormones.

Neurotransmitter and Brain Function Evaluations

- Saliva Neurotransmitter
- 24 Hour Urine Neurotransmitter
- Brain Electrical Activity Mapping (BEAM)
- QEEG and Neurofeedback (EEG)

SLEEP REPLENISHMENT

Insomnia affects 9–12% of the adult population and may be a major factor not only in poor stress tolerance and poor performance, but for some individuals it may also herald the onset of depression. It is clear that sufficient amounts of sleep and adequate amounts of specific levels of sleep is associated with improved quality of life, productivity, clearer thinking, better cognition, improved learning and memory and greater safety in regard to personal functioning. As Selye and other authorities have found, sufficient sleep and rest is also vital to stress-resilience, immune protection and is needed to attenuate the effects of stress related reactions.

In a study of adult insomniacs, stress (evidenced by cortisol and catecholamine output) was correlated with insomnia. The authors concluded that in chronic insomnia, the HPA and sympathetic nervous system are both positively related to the degree of sleep disturbance (23).

We experience several types of sleep patterns: slow wave, rapid eye movement (REM) and

non-rapid eye movement (non-REM), each important to normal sleep. Timing of REM is a known biological marker in studies assessing serious depression. REM sleep is often equated with our most active dream states. REM appears to be crucially important to our well-being, providing us the ability to work through daily life events and the emotions we experience. REM sleep deprivation by itself may also effect the expression of steroid metabolism-related genes in the adrenal gland, suggesting a relationship between REM sleep and adrenocortical steroid metabolism (24).

Individuals with chronic insomnia have been shown to have an altered immune defense with lower levels of CD3+, CD4+ and CD8+ cells (25). Similarly, the quality and depth of sleep are important determinants to immune function. Studies also suggest that melatonin, a sleep related hormone, may also be involved in these responses with the regulation of human immune functions by modulating the activity of Th1 cells and monocytes via nuclear receptor-mediated transcriptional control (26). Melatonin is also intimately involved with neurotransmitter modulatory activity. Known to be produced by the pineal gland, melatonin levels increase during hours of darkness when we see no light (e.g.: during sleep). Newer research suggests that it is also produced in the retina (27) and significant amounts produced in the gastrointestinal system (28). Sufficient melatonin results in improved sleep, which in turn provides better stress recovery and enhanced T-cell stimulation. With better sleep, stress resistance and immunity can be improved (29).

To reset the body clock it often helps to go to sleep the same time each night. Sleeping in a sufficiently dark, cool and quiet environment is also beneficial, as is refraining from alcohol, spicy food, dietary stimulants (e.g.: cola, coffee, strong tea or chocolate), and disturbing or intense mental stimulation before bed. Often a balanced dinner that includes sufficient complex carbohydrate will also help insure restful sleep

by offsetting chances of hypoglycemic response that may occur during the night. For other individuals, avoiding food several hours prior to sleep may insure better sleep.

Another popular method to improve sleep is retraining the natural sleep-wake cycles. This can be achieved by using only bright light in the early morning to induce phase responses to the clock, and sometimes melatonin therapy in the evening before bed (e.g. 11PM) to help advance sleep time and improve sleep onset and sleep duration. In time, sleep cycles may return to normal and melatonin treatment may be discontinued. Melatonin is also commonly used for very short periods of time to offset the effects of jet lag.

Magnesium is another factor in this process and is seen as an important mineral involved in the stress process and maintaining normal biological rhythms including sleep cycles (30). Found in many foods including green vegetables, whole grains and nuts, it remains a critically important nutrient in many areas of health. Although dietary sources are important, some individuals may need the higher amounts that can be obtained through supplementation.

Vitamin B12 also plays a role in the development and treatment of insomnia (31), and may need to be assessed in patients. Found in significant quantity in eggs and other animal proteins, B12 is commonly found to be deficient in the elderly and in patients who may have dietary imbalances or who follow a strict vegetarian diet. In such individuals B12 injections or supplemental sources may be needed.

The amino acid tryptophan is a precursor to serotonin and also a key influencer of sleep. Found in turkey, chicken, milk, cheese, oats and wheat germ it can easily be provided in the diet. Diets that are high in carbohydrate and low in protein will also tend to increase plasma tryptophan. Because of this, sufficient complex carbohydrate with dinner can help some individuals achieve better sleep. To ultimately perform its function, tryptophan requires various micronu-

trients including adequate folate, magnesium and B6.

Clinical Evaluations of Melatonin and Amino Acids

- Salivary Circadian Melatonin
- Plasma or Urine Amino Acid levels
- Serum amino acids
- Urine organic acid test
- B12 (along with folic acid)

BOTANICAL SUPPORT

Many herbs have unique properties that can help offset the effects of stress. The Ayurveda herb, ashwagandha (*Withania somnifera*), has traditionally been known for its adaptogenic and rejuvenating benefits. Studies demonstrate that ashwagandha protects against inflammation, stress, exhaustion and insomnia. It may also provide antioxidant immunomodulatory, hemopoietic and rejuvenating properties. Its positive influence extends to the endocrine, cardiopulmonary and central nervous systems (32, 33). Clinical trials and animal research supports its use for various conditions including some cognitive disorders.

Ginkgo biloba is another herb with stress-tolerance benefits. As opposed to pharmacologically manufactured or synthetic drugs (which provide a single target for a single receptor as the mechanism of action), a standardized Ginkgo biloba extract (EGb761) used for one study was able to up- or down-regulate signaling pathways, gene transcription, cellular metabolism and other actions and thus assist in the regulation of the general physiological status in response to stressors posed by both intracellular and extracellular conditions (34). The use of Ginkgo biloba and its active constituents, ginkgolides, appear to improve vascular and cerebral blood flow, fatigue and to exhibit anti-stress benefits. Caution exists with a potential for a bleeding anti-platelet effect especially if

used with anticoagulant and anti-platelet drugs.

Ginseng has traditionally been known to be a tonic for enhancing stamina and forestalling fatigue. Ginseng's saponin content seems to support homeostasis and influence HPA activity through the binding of corticosteroid to certain brain regions (35), although it has commonly been known to have contraindications, including for those with bleeding conditions and for those taking MAO inhibitors. In excess, ginseng can also cause nervousness, hypoglycemic reactions in people taking insulin or sulfonylureas, sleeplessness, amenorrhea and changes in libido—all suggestive of excess production of cortisol and changes in androgen levels.

Rhodiola (*Rhodiola rosea*), sometimes known as "Arctic Root" is also known for its ability to normalize catecholamine, reduce stress-induced fatigue, improve mental performance, enhance work performance and have both immune and CNS effects. Research suggests that it is an adaptogen and has effects on monoamines (serotonin, dopamine and catecholamine) and beta endorphins (36). One study found that its use increased visual and audio perception and short-term memory after two weeks of use (37).

Due to its adrenocorticoid-like activity, licorice (*Glycyrrhiza glabra*) may be helpful in the short term for some stressed individuals who have diminished adrenal function. Licorice has traditionally been used for inflammation of the upper respiratory mucous membranes, gastric and duodenal ulcers, bronchitis, chronic gastritis, primary adrenocortical insufficiency and other conditions. It also appears to have antiviral effects. Due to its multiple pharmacological actions, use of licorice may require caution for certain individuals. It is contraindicated in some patients including hypertensives, diabetics, those with cardiac disorders and pregnant and lactating women. Prolonged use can also may cause sodium and water retention due to hypokalaemia (38).

St. Johns Wort (*Hypericum perforatum*) has

been widely used for mild depression; however studies do not support its efficacy in major depressive disorders (39). It should not be used with other medications. Its use may decrease prothrombin time (PT/INR) as seen in patients treated with coumadin and, theoretically, concomitant use of large amounts with tyramine-containing foods may cause a hypertensive crisis. In addition, an increase in photosensitivity may occur along with several potential side effects including headache, constipation, confusion, and dizziness.

A number of commonly used herbs also provide mild hypnotic/CNS tonic effects. Often called nervines, these include hops, chamomile, passionflower, skullcap and lemon balm. Since many herbs, like nutrients and other interventions, may have potential interactions or contraindications their use should be with appropriate precautions and as needed, with medical supervision.

HOMEOPATHY

A German physician, Dr. Samuel Hahnemann, developed homeopathy almost 200 years ago. The practice of homeopathy is based on the Law of Similars, meaning "like cures like." In this theory highly dilute concentrations of specific preparations are used to address problems of the mind, body and emotions. These preparations assist the individual in managing the various dimensions of stress and its symptoms. Just as sustained emotional stress can cause disturbances in immune function, difficulties with digestion and assimilation of food and sleep disturbances, the reverse is also true: physical problems can occur as a result of emotional responses and anxiety.

Homeopathic evaluations consider not only presenting symptoms and complaints, but also consider the behavioral tendencies and personality traits in the analysis. With proper homeopathic remedies and other lifestyle readjustments, greater balance can also be achieved through this intervention.

NUTRITIONAL IMPLICATIONS

As has been mentioned, integrated changes in the endocrine and vascular systems occur during times of stress in an attempt to maintain homeostasis. These occur in varying magnitudes and durations as a result of distress. Biochemical imbalance and changes in circulating hormones that result from stress induced hyperarousal can also impact nutritional status. These changes can, in turn influence the metabolism and consequently, the supportive requirements not only for calories but also for anti-oxidants and auxiliary micronutrients. An important aspect of clinical care may also include addressing the damaging effects of stress on the gastrointestinal tract including gastric irritation, altered bowel function (constipation or diarrhea) and dysbiotic conditions.

Since the effects of stress place heightened physiological demands on the individual, the influence of stress can be especially detrimental for the individual who may initially have few nutritional reserves. There exists an inverse relationship between stress and the status of many nutrients, with stress depleting many important nutrients. Resulting poor nutrient status can further compromise stress coping ability.

Although directly addressing the root causes of the added stress burden is crucial to therapy, conditioning with dietary interventions and maintaining hormonal balance can provide the body with greater support to help offset the detrimental effects of stress. As stress increases, caloric needs tend to increase, primarily due to potential protein-calorie need increase. Reduction or elimination of various sources of caffeine (e.g.: cola, coffee, strong tea, cocoa and chocolate) and refined carbohydrate and simple sugars is an important consideration to prevent loss of essential nutrients, inappropriate elevation of insulin levels and consequential excess epinephrine release which may lead to dysglycemic responses and added adrenal stress.

Avoiding alcohol and caffeine is also impor-

tant since these can reduce melatonin levels that are needed to help mitigate insomnia (40). Sufficient fiber (especially soluble forms such as that derived from beans/legumes, many fruits and vegetables and certain whole grains such as oats and barley) will help regulate glucose uptake by slowing down the absorption of carbohydrates. Since many of the effects of stress influence the digestive system, inhibition of digestive enzymes may be an added challenge for some highly stressed patients.

Immunologic protection, a major concern during stress, appears to be dependent on overall macronutrient and micronutrient status. Studies illustrate that athletes, for example, can counter the effects of physical stress by eating a well-balanced diet that includes adequate amounts of protein and carbohydrate, sufficient to meet their energy requirements. Consuming carbohydrates during times of physical stress induced by exercise appears to attenuate the rise in stress hormones, such as cortisol, and appears to limit the degree of exercise induced immunosuppression, at least for non-fatiguing bouts of exercise (41).

Micronutrients:

More generalized studies have shown that vitamin B6, pantothenic acid, folic acid, vitamin C, vitamin A (42,43,44,45,46), and vitamin E (47,48) support immune function. Micronutrient status has also been shown to be of paramount importance in the management of critically ill patients (49), with nutrients helping in the resistance to infections, aiding antibody formation and improving some white cell functions. Depressed individuals commonly have B vitamin deficiencies. Particularly important are folic acid and B12, which play several roles in the formation of precursor molecules that allow the brain to manufacture serotonin and dopamine. Inositol is one nutrient that helps support healthy serotonin metabolism and can be beneficial in some cases of depression, agoraphobia, and panic disorders (50,51).

Similarly, catecholamine oxidation and elevated serum lipid peroxide concentrations can also initiate stress response, prompt disturbances in endocrine function and produce more rapid aging (52) and chronic health problems. Stress stimulates sympathetic activity and can lead to mineral alterations. Initially, stress will increase the adrenal cortex secretion of aldosterone, its principle mineral corticoid. This can lead to increased water imbalances. Sufficient fluid and plasma volume are the main actions of aldosterone physiology. The impact of aldosterone also extends to elevation of blood chloride and bicarbonate.

Vitamin C seems to be particularly important to individuals confronted with stress. It is found in high concentrations in the adrenal cortex. Its absence there seems to lead to inefficient utilization of steroids (53). Neurological studies also suggest that vitamin C and vitamin E supplementation may protect against vascular dementia and may improve cognitive function in late life (54). Vitamin C, along with pantothenic acid, supports adrenal function, while healing and other supportive functions are dependent on sufficient protein, zinc, calcium and other nutrients, many of which may decline as a result of the stress response.

Also, vitamins C, E, glutathione, carotenoids, selenium and other free-radical quenching nutrients can diminish oxidative damage and provide antioxidant protection.

Amino Acids

As indicated, the catabolic effect of stress will increase muscle and tissue breakdown. Due to this effect, overall protein and amino acids may also need to be evaluated. Accelerated glucocorticoid production can also accelerate gluconeogenesis as much as ten-fold, thereby promoting an increase in blood glucose (15).

Shifts in amino acid status may also influence neurotransmitters, cellular energy production, bone and connective tissue, muscle activity, the formation and regulation of enzymes, blood

transport proteins and the formation of antibodies. Particularly crucial to the stress response are the aromatic amino acids—phenylalanine, tyrosine and tryptophan.

Phenylalanine is an essential amino acid that converts into tyrosine. Both are precursors to catecholamines in the body—each having an influence on mood and behavior. Like tyrosine phenylalanine can be synthesized into dopamine, epinephrine and norepinephrine. Studies indicate that norepinephrine can inhibit ACTH production through the suppression of corticotropin releasing factor (CRF) in the hypothalamus. Pre-treatment with supplemental tyrosine not only prevents behavioral depression and hypothalamic norepinephrine depletion after acute stress, but also suppresses the rise in corticosterone (55). Tyrosine has been shown to prevent substantial decline in various aspects of cognitive performance and mood associated with various types of acute stress. (56) Tyrosine rich foods include many of the same foods rich in phenylalanine. Significant amounts can be found in wild game, fish, chicken, turkey, duck, pork, yogurt, pumpkin seeds, ricotta cheese, egg, cottage cheese, rolled oats and wheat germ. Since phenylalanine and tyrosine promote cell division taking these in supplement form is contraindicated in melanoma and possibly other cancers. In addition, persons with PKU (phenylketonuria) and certain genetic deficiencies that prevent metabolizing phenylalanine must also avoid all sources of phenylalanine. In such situations a closely monitored program is needed.

Since high cortisol can suppress thyroid function (57), the beneficial effect of tyrosine on production of thyroid hormones may be an additional consideration. Amino acid levels along with a complete thyroid panel plus cortisol levels may be particularly important to include in clinical assessment.

Serotonin acts as a neurotransmitter influencing sleep, appetite and mood (58,59). Serotonin is produced in the body from L-trypto-

phan through its conversion into 5-hydroxytryptophan (5-HTP). It is required for gut motility, and low levels can be linked to constipation, diarrhea, carbohydrate cravings, depression, fatigue, insomnia, impulsiveness and behavioral disorders. Tryptophan is found in plentiful amounts in wild game, pork, duck, turkey, chicken, avocado, cottage cheese and egg.

For individuals with reduced cortisol output, sufficient dietary protein is an important consideration. Studies show that higher protein diets support cortisol output while high carbohydrate diets exhibit an inverse relationship with cortisol (60). Important to note is the bioavailability of protein sources and the competitive action of individually supplemented amino acids for entrance into the brain.

L-Theanine is a little known amino acid found in the leaves of green tea. Believed to help promote relaxation, it is sometimes used to reduce stress-induced restlessness (61). It should be noted however that green tea as a beverage generally contains caffeine, a non-relaxing and stimulating ingredient.

Similarly, gamma-aminobutyric acid (GABA) may provide similar relaxing benefits in its ability to inhibit anxiety and reduce nervousness. GABA levels are enhanced with sufficient glutamine-rich foods, the amino acid that is a precursor to GABA. These foods include complex carbohydrates, especially whole grains, rice bran, almonds, halibut, spinach, banana and potato.

Acetyl-L-carnitine also shows growing importance for improved energy, concentration and learning as well as the effects of stress.

Fatty Acids

Proper balance of fatty acids and phospholipids is also essential for cell membranes, brain and nervous system health. The dietary composition of fatty acids will ultimately determine membrane fluidity and the way in which membrane receptors communicate and receive neurotransmitters. Membrane fluidity depends on

sufficient unsaturated fatty acids—omega 3, omega 6 and omega-9. Since omega 6 fatty acids (e.g.: corn oil, certain vegetable oils) can be converted into pro-inflammatory prostaglandins through arachidonic acid, sufficient omega 3 (fish oils, flaxseed) intake can help to blunt omega 6 competition and provide anti-inflammatory, cell strengthening and immune support through its EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) constituents.

The phospholipid, phosphatidylserine (PS) is also a major fatty acid for brain health. PS seems to play a major role in improving cell membranes, assisting in the effective metabolism of glucose for energy and supporting the binding and releasing of neurotransmitters. Studies illustrate that administration of PS appears to blunt stress-induced activation of the HPA axis (62).

Laboratory Evaluations

- Organic acids in urine (nutrients, toxicants, and cell regulators) as neurotransmitter metabolism markers.

MIND-BODY INFLUENCES

Many individuals intensify or worsen their stress levels with ineffective coping strategies and maladaptive behaviors. They may engage in various forms of abusive behavior (excessive levels of exercise, food intake, work or recreation), or substance abuse (alcohol, food, smoking, drugs), as an integrated portion of their stress syndromes (63). High levels of stress can also prompt certain food cravings in patients—with many seeking stress relief by consuming excessive amounts of calories and refined/processed carbohydrates that can result in nutritional imbalances and/or weight gain related issues. Such responses, sometimes reflective of their lack of control, can be habituated and interwoven with neurotransmitter imbalances.

Although many tangible stressors can often be easily modified to diminish impact, less tan-

gible stressors can often take more time and personal effort to alter. Methods to eliminate and more effectively cope with existing stressors can be achieved through counseling and attention to diverse variables that may be intertwined with the individual's stress related condition. The work of behavioral medicine, which has grown out of the field of psychoneuroimmunology (PNI), addresses these interwoven aspects of the mind-body connection.

Explaining to patients that there is no quick fix or magic bullet to reverse the health disorders related to stress helps them to understand that the healing process takes time and requires their active involvement. Reversing health conditions means reversing the very factors that precipitated their stress related diagnosis. This means reversing unhealthy thought patterns and irrational beliefs, changing harmful behaviors and habits and altering the lifestyle factors that are a part of their underlying health challenges. For example, a patient may present a stress profile that includes abnormally long work hours, hectic commutes, poor diet, financial pressures, inadequate sleep, and inadequate exercise. Each of these factors needs to be addressed and accompanied by lifestyle modifications and improved stress coping skills. Establishing a comprehensive program that helps patients to normalize work hours, make job and lifestyle changes, improve diet, incorporate budget guidelines (e.g.: living within their means) and create a schedule that includes sufficient sleep, relaxation, fresh air, and appropriate levels of sunshine and exercise can be vital to their health recovery. These steps can be equally as important as other interventions.

EMOTIONS

Part of the stress management process is the clarification of how the role of emotions and thoughts are involved in the stress response. Many people fail to recognize that emotions and thinking are not disparate processes. Emotion,

especially when it is sustained, does not exist on its own. It is linked to our thoughts and appraisals. Therefore, attention to our “self-talk” (internal dialogue) becomes crucial to understanding emotions and behavior.

Epidemiological evidence suggests that our thinking and our emotions are intimately linked to our health. One example is the high rate of heart attacks on Monday morning as the work week begins. Similarly, the formation of plaque in the arteries is now known to be linked to action of the immune cells and the action of peptides that can either increase or decrease plaque formation in response to emotions.

The continual suppression of emotions during fight or flight reactions can have both damaging and toxic effects. Toxic metabolites interfere with neurotransmission, causing depression. With periodic detoxification crises, excess norepinephrine floods synapses, overexcites postsynaptic neurons and can cause a range of symptoms from mild anxiety to hostile behavior.

Recovery from some conditions is considered by some researchers to be a detoxification process that can be facilitated by therapy to re-experience traumas, release them and redirect repressed emotions (64).

Today we know that our emotions are mediated through neuropeptides and receptors, biochemicals that are messengers that carry information throughout the body and influence our health. These chemicals create the mind-body unit. Researchers have found that with beneficial emotional change, neurotransmitters and neuropeptides can be favorably influenced (65).

The role of mirthful laughter, for example, has been shown to reduce levels of cortisol and other classical stress related neuroendocrine changes and may have implications for the reversal of the neuroendocrine and classical stress hormone response (66).

For other individuals, prayer (67) is the first choice in finding inner peace during life's stress and personal storms. Spirituality - our search

for meaning and purpose, our relationship to self and connectedness to others, the universe, or the Divine - has traditionally been of major benefit to individuals seeking greater inner peace, and recovery. Optimism and hope are major elements of those with spiritual connection. People who are optimistic and hopeful tend to see themselves as having the ability to overcome life's challenges. They generally see an order in life with a belief that a higher power is watching over them.

One benefit of counseling and psychotherapy is that negative thoughts and emotions can be replaced with healthier, more positive and productive ways of thinking. Such changes can result in healthier cognitive and limbic integration and health enhancement. This may hold special significance for the elderly who may be more vulnerable to negative emotions due to their lack of social support systems.

A more comprehensive therapeutic program for stress management may include any number of psychotherapeutic and mind-body therapies in addition to medical, lifestyle and nutritional support. These may include various interventions such as behavior modification, cognitive therapy (Beck) and restructuring (identifying and changing irrational beliefs), humanistic (Rogerian) psychotherapy, Rational Emotive Therapies (RET/Ellis), lifestyle adjustment, time-management, moderate exercise, biofeedback therapy, and various forms of relaxation techniques aimed at shifting psychophysiological parameters.

Studies have demonstrated the success of comprehensive stress management techniques in conjunction with nutrition and moderate exercise as being vital to disease prevention and reversing atherosclerotic lesions in many patients (68). Overall, when the individual has a multidimensional holistic program that includes talk therapy or counseling along with other approaches the chances of long-term success are enhanced.

PHYSICAL EXERCISE

Exercise must also be recognized as having beneficial effects on stress if the level and intensity are correct for the individual. Although light exercise can be immuno-enhancing, highly strenuous or competitive physical activity can lead to physical exhaustion, reduced immune strength and diminished adrenal reserves, especially if performed in excessive amounts or if combined with other stressors.

Although strenuous exercise can temporarily stimulate cortisol (69), research shows that engaging in more moderate physical activity appears to provide a buffer for stress and relief from the physical symptoms and anxiety associated with stress (70). Sufficient carbohydrate consumption (e.g. carbohydrate drinks) during prolonged exercise may also help to attenuate some of the immunosuppressive effects that can occur in individuals engaged in high intensity and lengthy exercise sessions.

Exercise is well known as a way to increase the “feel good” chemicals known as enkephalins and endorphins (chemically similar to morphine). Although these neurotransmitters are known to provide pain relief and the classic natural “runners high,” they may also play a role in alleviating depression and in providing mood-enhancing benefits. Studies also indicate that physical exercise will increase norepinephrine over epinephrine, also possibly contributing to improvement in outlook, mood and greater feel-good effects. Overall, strength training and aerobic exercise appear to exert the greatest antidepressive effects (71).

MIND-BODY THERAPEUTIC INTERVENTIONS

A number of mind-body interventions can assist patients in reducing and managing their stress burdens. Many of these also help individuals retrain maladaptive behaviors and learn healthier ways to respond to life events. How-

ever, since symptomatic relief can mask an underlying problem, it is important that a physician evaluate all patients before therapies are selected.

Although some relaxation techniques have been used for centuries, the official introduction of relaxation into healthcare began in the late 1920's and early 1930's. The use of biofeedback and relaxation therapies is an example of approaches that can help patients improve autonomic nervous system response and create greater physiological homeostasis. Biofeedback techniques developed in the 1940s entered the medical community in the late 1960's and early 1970's, with laboratory procedures evolving into our current knowledge of methods to measure and alter brain activity, blood pressure, heart rate and other body functions. Although many of these physiological functions were originally believed to be “involuntary,” many have been shown to actually involve control by voluntary action.

Biofeedback techniques, originating from these early advances, are now being widely used to treat an increasingly large array of medical conditions. Today, various forms of biofeedback training and relaxation exercises are integral components to many stress management programs. Efficacy has been demonstrated for biofeedback in many areas including anxiety, asthma, attention deficit, chronic pain, headache (tension and migraine), hypertension, hyperhidrosis (excess sweating), hyperactivity, insomnia, irritable bowel (IBS), learning disabilities, muscle spasm, myofascial pain and temporomandibular joint disorder (TMD or TMJ), repetitive strain, tinnitus, tremors, tics, Tourettes, urinary incontinence and other conditions.

Techniques adjunctively used in biofeedback training include diaphragmatic (abdominal) breathing; progressive muscle relaxation or PMR (Jacobson), autogenic training (Schultz and Luthe), systematic desensitization (Wolpe) and open focus (Femme). Meditation, guided

imagery and other techniques can also adjunctively help patients to recognize and reduce harmful responses to stress. Biofeedback therapists and the treatment team can help determine which approach and biofeedback modality are best suited to the individual.

In simple terms, biofeedback patients learn how to alter muscle tension, blood pressure, heart rate, brain activity or other functions not normally controlled voluntarily. This is done with the assistance of various forms of complex biofeedback instrumentation, monitoring procedures and guided instructions and relaxation techniques taught by a therapist. Each form of biofeedback has unique applications and methods of monitoring. For example, neurofeedback biofeedback, which deals with brainwaves (the electrical wave patterns in every person's brain), will measure cycles per second of brain waves—beta, alpha, theta and delta—along with their amplitude (strength) and frequency (speed). Measurement, evaluation and the individual's training program will be designed to improve any number of functions or conditions. These may include such listening, learning, impulsivity, motivation, self-esteem and reduction of addictions. Other forms of biofeedback similarly address health concerns through their own form of instrumentation and methodology.

The goal is to teach patients new methods of self-regulation and self-mastery. Biofeedback is considered a very safe therapy, however it may possibly be contraindicated for persons with certain medical (e.g.: those with pacemakers or cognitive impairment) or certain psychiatric conditions (e.g.: psychosis and major affective disorders).

Within the framework of biofeedback therapy most patients who are trained by a professional counselor or therapist are not only commonly educated about how the unique form of biofeedback will assist them, but they may also be counseled regarding changing negative behavioral or cognitive patterns. Those who are Biofeedback Certification Institute of America,

Certified (BCIAC) have met stringent requirements of education, training and professional standards.

TRADITIONAL BIOFEEDBACK METHODS

(Exact modality choice may vary from patient to patient)

- Electromyographic (EMG) Biofeedback: Muscle related measurement and training
- Temperature (Thermal) Biofeedback: Assists the patient with an objective of diminution of vessel resistance
- Galvanic Skin Response (GSR) or Electrodermal Response (EDR):

Focus is on skin resistance

NEWER BIOFEEDBACK METHODS

- Electroencephalographic- (EEG): Neurofeedback brainwave training
- Heart Rate Variability (HRV): Focuses on neurocardiac function

SPECIALTY BIOFEEDBACK METHODS

- Quantitative Electroencephalography (QEEG):
An extension of traditional EEG neurofeedback. Evaluates how the brain functions.
Used with EEG neurofeedback.
- Hemoencephalographic Neurofeedback (HEG):
Measures blood flow in brain.

Although EMG and Thermal biofeedback are the most commonly used therapies, all forms of biofeedback demonstrate the power of the mind to alter and improve physiological function. Not only can patients learn to relax at will, but also ultimately they learn to control the body's capabilities to achieve homeostasis and better health.

RELAXATION METHODS

Biofeedback is often taught along with various relaxation techniques (72). Some of these have special application while some are contraindicated for particular conditions (PMR, for example, requires caution with hypertensives, hypotensives and certain for individuals with certain psychological conditions including depressives and patients who experience hallucinations).

The practitioner may provide the patient with appropriate guidance when suggesting specific complementary therapies (73). In many instances, relaxation and biofeedback therapy are often combined with guided imagery, especially when pain reduction is involved. This technique incorporates the use of mental images that can have visual, auditory, olfactory, gustatory and/or tactile-proprioceptive qualities. Images can be experienced in dreams, fantasies or during states of full awareness.

The relaxation response, a physiological response that is the opposite of Canon's fight-or-flight response, results in decreased metabolism, blood pressure and breathing rate. Awareness of this response is built on the work of Swiss Nobel Laureate, Dr. Walter R. Hess. Although no formal technique is needed, the response occurs in a two-step process when we are under stress. Described by Herbert Benson, the first step includes the repetition of a word, phrase or muscular activity (e.g.: mantra, prayer, movement). Second, when everyday thoughts intrude, there is a passive return to the repetition. On a regular basis, elicitation of the relaxation response has been shown to bring alleviation of many stress-related symptoms. The late Charles Stroebel, MD, Ph.D., Yale trained physician and past-president of the Association of Applied Psychophysiology and Biofeedback, similarly explored the effects of relaxation in his acclaimed book, *QR: The Quieting Reflex* (74).

A combination of deep relaxation along with

symbolic representation of conflict and resolution can be used to enhance the educational stress management approach. In pain patients, it is important to note that anxiety and depression often heighten the perception of pain while reducing pain tolerance.

Imagery can assist patients to restructure their appraisal of the situation, relieving discouragement and feelings of helplessness or hopelessness while increasing energy and focusing attention on living without pain. The interpretation of imagery in patients with psychic pain however requires knowledge of psychotherapeutic applications (75).

BREATHING

Breathing is the only vital life function that we can regulate voluntarily, yet it often falls into a state of dysregulation. In many instances shallow breathing or breathing which is too rapid may be due to medical conditions and, as a result, requires physical compensation. Individuals with pulmonary disorders, allergic reactions, diabetes, kidney disease, heart disease and various other conditions may be amongst those who experience irregular breathing as a physical need. In such individuals slow breathing may not be safe.

However, when individuals do not have medical conditions that are causing breathing disturbances, such irregular breathing may be a result of stress response. Research has found that the way we breathe, including rate and rhythm, affects our pulse, cardiovascular function and blood pressure. Conversely, in some instances, disturbances in oxygen delivery (sometimes with resulting hypoxia) to the body and brain can prompt anxiety, dizziness, phobias, pulse changes and disturbances of acid-alkaline balance.

When indicated, breathing therapy can be helpful for many individuals seeking to correct their stress induced breathing-linked symptoms.

MEDITATION

In some patients short meditations of approximately 15–20 minutes practiced daily over an extended period of time may be helpful. Used to “quiet the mind,” various forms of meditation incorporate a focusing of attention that leads to a state of quietness. One form of meditation involves the prayer bead and the orderly repetition of specific prayers. The Catholic rosary is one well-known form of meditative prayer. This involves a process of attention with an aim at achieving a heightened level of focused attention in a calm, non-analytical manner. Through meditation there can be an overall decrease in the hyper-sympathetic arousal responses commonly occurring with stress. In addition, meditation may have increased positive influences on serotonin and melatonin levels and brain waves, reflective of calmness, creativity and imagery. Although it should be avoided in depressed, suicidal, psychotic or psychologically fragile patients, meditation can assist many patients with pain and poor levels of stress management (76).

The physical and mental relaxation benefits achieved during daily meditation can generate reproducible effects with increased EEG alpha activity (indicative of calm relaxation, passive attention and feelings of serenity), improved skin resistance, reduction of sympathetic activity and reduced respiration and oxygen consumption. The benefits also extend into the area of psychoneuroimmunology.

Mindfulness-based stress reduction (MBSR) is a structured method that employs mindfulness meditation to alleviate suffering and help improve coping (77). Meditation is based on the basic principle of clearing the mind. Various guidelines can help the individual to tame the restlessness of the mind, but there is no one single way to meditate.

In one study, patients with symptoms of anxiety and panic were able to reduce these symptoms following an 8-week mindfulness medita-

tion program with a 3-year follow-up finding that continued practice produced long-term beneficial effects (78).

As with biofeedback and many forms of relaxation training, patients on certain drug protocols will need close monitoring since many patients may eventually need reduced amounts of some medications as they utilize the new skills they are taught and obtain the therapeutic benefits.

HYPNOSIS

Hypnosis may also be of benefit to many individuals who experience the harmful effects of stress. Research shows its effectiveness in a variety of disorders and conditions (79). Especially helpful to pain patients, hypnosis can be highly effective in teaching patients to alter their perception of their discomfort. According to experts, hypnosis can be a very natural process, but it is not recommended for particular individuals such as those who have psychotic process. In such cases it could precipitate an acute event although hypnosis itself does not cause psychosis (80).

In 1996 the National Institutes of Health (NIH) panel ruled that hypnosis was effective for pain relief in cancer and other chronic conditions and was potentially beneficial for mental well-being, accelerated healing and stimulating immune function.

CONCLUSION

Stress is a part of life. Its inescapable nature reminds us that we will continually be confronted with the ongoing challenges of life. It is our ability to cope with these situations that is tantamount to maintaining good health. Although allopathic interventions may often be necessary for some patients, this approach, when used alone, often remains a palliative, symptom-based solution to far more complex life situations. With greater understanding of

how stress affects both body and mind, we can more effectively assist individuals by providing them with more comprehensive evaluations, treatment protocols and referrals for specialized care. By addressing the underlying factors of stress response including biochemical, physiological, emotional and behavioral factors patients can gain new personal insights and find more clearly defined avenues to wellness.

Note: Concomitant use of certain supplements, herbs and therapies may mimic, magnify or oppose the effects of drugs therapies. Therefore, health care providers should always exercise caution with patients regarding single or combination therapies. Many therapies may not be indicated for certain patient types; therefore clinicians should explore all potential interactions and contraindications before implementing protocols. Additionally, some therapies may ultimately lead to needed changes in medication as the patient or client improves in their condition; therefore they should be followed and monitored closely by their physicians.

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LITERATURE BRIEFS

Food supplements for ocular health

The role of nutritional supplementation in prevention or progression of ocular disease is of importance to patients and health care professionals alike. Antioxidants are suitable supplements for those with a family history of glaucoma, cataract, or age-related macular disease, or those with lifestyle factors predisposing to onset of these conditions such as smoking, poor nutritional status, or high levels of sunlight exposure. Antioxidant supplements are also suitable for those with early stages of age-related ocular disease. A literature search of PubMed found articles supporting use of vitamins A, B, C and E; carotenoids including beta-carotene, lutein, and zeaxanthin; minerals such as selenium and zinc; and the herb Ginkgo biloba. B vitamins have been linked with a reduced risk of cataract and studies have provided evidence supporting a protective role of vitamin C in cataract prevention.

Bartlett H, Eperjesi F. An ideal ocular nutritional supplement? *Ophthalmic Physiol Opt.* 2004;24:339–49.

Vitamin and mineral supplements and blood pressure in diabetics

Four groups of Type 2 diabetic patients were given supplements of magnesium + zinc (200 mg, 30 mg) or vitamin C + E (200 mg, 150 IU), or both the vitamins and the minerals, or a placebo for 3 months. The combination of both vitamin and mineral supplementation significantly decreased the blood pressure more than the vitamins alone or the minerals alone, plus the combination of vitamins and minerals also increased serum potassium and decreased serum malondialdehyde.

Farvid MS, Jalali M, Siassi F, Saadat N, Hosseini M. The impact of vitamins and/or mineral

supplementation on blood pressure in type 2 diabetes. *J Am Coll Nutr.* 2004;23:272–9.

Vitamin and mineral supplements and serum HDL in diabetics

Four groups of Type 2 diabetic patients were given supplements of magnesium + zinc (200 mg, 30 mg) or vitamin C + E (200 mg, 150 IU), or both the vitamins and the minerals, or a placebo for 3 months. After 3 months mean serum levels of HDL-C increased significantly in the MV group by 24% and apo A1 by 8.8%. Serum levels of total cholesterol, LDL-C, triglyceride, and apo B were not altered. It is concluded that supplementation of these micronutrients could be recommended for the type 2 diabetic patients.

Farvid MS, Siassi F, Jalali M, Hosseini M, Saadat N. The impact of vitamin and/or mineral supplementation on lipid profiles in type 2 diabetes. *Diabetes Res Clin Pract.* 2004;65:21–8.

Natural phytonutrient supplement and serum folate and antioxidant levels

Low plasma levels of antioxidants are associated with increased risk for diseases such as heart disease and cancer. In a double-blind crossover study, healthy middle-aged, men and women took a natural phytonutrient preparation derived from fruits and vegetables while urine levels of 8-oxo-7,8-dihydro-2'-deoxyguanosine (a measure of oxidative stress) was monitored. Blood levels of beta-carotene, vitamin C, vitamin E, selenium and folate were also measured. No significant group changes were noted for 8-oxo-7,8-dihydro-2'-deoxyguanosine concentration in urine but significant increases in blood nutrient levels beta-carotene, vitamin C, vitamin E, selenium and folate were observed after supplementation.

Kiefer I, Prock P, Lawrence C, Wise J, Bieger W, Bayer P, Rathmanner T, Kunze M, Rieder A. Supplementation with mixed fruit and vegetable juice concentrates increased serum antioxidants and folate in healthy adults. *J Am Coll Nutr.* 2004;23:205–11.

Vitamin supplements for the aging population

A diet rich in vitamins is associated with improved health, although the results from controlled trials use with the of various dietary supplements are less impressive. The discrepancy is probably explained by the fact that superior dietary composition and supplement use are usually found in a cluster of healthy behaviors. An alternative hypothesis is that there are as-yet-unknown essential organic compounds in certain foods. It is prudent to recommend a daily intake of fruits and vegetables as a likely source of essential nutrients, but vitamin supplements should be encouraged in situations where there is poor compliance or high risk of vitamin deficiency.

Thomas DR. Vitamins in health and aging. *Clin Geriatr Med.* 2004;20:259–74.

Supplement use increases

The percentage of adults using any daily vitamin or mineral supplement increased from 23.2% in 1987 to 33.9% in 2000. In addition, 6.0% of respondents in 2000 reported using a nonvitamin/nonmineral supplement daily

Millen AE, Dodd KW, Subar AF. Use of vitamin, mineral, nonvitamin, and nonmineral supplements in the United States: The 1987, 1992, and 2000 National Health Interview Survey results. *J Am Diet Assoc.* 2004;104:942–50.

Dietary supplements that reduce blood pressure

A review of peer-reviewed trials of commonly available dietary supplements used in the treatment of hypertension disclosed that the agents with some evidence of benefit include coenzyme Q10, fish oil, garlic, vitamin C, and L-arginine. Agents were deemed to be of benefit if

a systolic blood pressure reduction of 9.0 mm Hg or greater and/or a diastolic blood pressure reduction of 5.0 mm Hg or greater was observed.

Wilburn AJ, King DS, Glisson J, Rockhold RW, Wofford MR. The natural treatment of hypertension. *J Clin Hypertens (Greenwich).* 2004;6:242–8.

Ascorbic acid and cancer

Ascorbic acid is the nutrient supplement most commonly used by cancer patients. A comprehensive review of the literature shows that 6 uncontrolled studies suggest ascorbic acid may increase survival, whereas 2 controlled trials have yielded null results. Controversy persists in the alternative cancer community.

Block KI, Mead MN. Vitamin C in alternative cancer treatment: historical background. *Integr Cancer Ther.* 2003;2:147–54.

Vitamin K supplements and coagulation

Oral anticoagulants exert their effect by blocking the utilization of vitamin K. In systematic dose-response studies, healthy volunteers who had been stably anticoagulated and maintained on their individualized doses for 13 weeks were given weekly incremental doses of 50 to 500 mcg of vitamin K(1). The threshold K(1) dose causing a lowering of the international normalized ratio (INR) was 150 mcg/day, and circulating undercarboxylated osteocalcin did not decrease until 300 mcg/day. A short-lived response after meals of spinach and broccoli suggested an inefficient bioavailability from these 2 sources. We conclude that short-term variability in intake of K(1) is less important to fluctuations in the INR than has been commonly assumed, and that food supplements providing 100 mcg/day of vitamin K(1) do not significantly interfere with oral anticoagulant therapy.

Schurgers LJ, Shearer MJ, Hamulyak K, Stocklin E, Vermeer C. Effect of vitamin K intake on the stability of oral anticoagulant

treatment: dose-response relationships in healthy subjects. *Blood* 2004;104:2682–9.

Iodine supplement for pregnant women

Nearly two-thirds of the population of Western and Central Europe live in countries that are iodine deficient. Damage to reproductive function and to the development of the fetus and newborn are the most important consequences of iodine deficiency. A compilation of research on iodine nutrition and iodine supplementation of pregnant women in Europe was done of all published studies since 1990. Less than 50% of pregnant women receive iodine supplements, resulting in adverse effects on the thyroid function of the mother and newborn, and on the mental development of the offspring. The iodine content of prenatal supplements in Europe varies widely; many commonly used products contain no iodine. Prenatal supplement manufacturers should be encouraged to include adequate iodine (approximately 150 mcg/day) in their products.

Zimmermann M, Delange F. Iodine supplementation of pregnant women in Europe: a review and recommendations. *Eur J Clin Nutr.* 2004;58:979–84.

Lutein from yellow carrots and from supplements

Lutein is a hydroxy-carotenoid comprising the macular pigment of the human retina. Lutein uptake and clearance in humans fed white carrots (containing no lutein), yellow carrots (providing 1.7 mcg/day lutein) and a lutein supplement of 1.7 mcg/day were evaluated. Lutein from yellow carrots was only about 65% as bioavailable as that from lutein supplements but yellow carrots maintained peak serum beta-carotene concentration.

Molldrem KL, Li J, Simon PW, Tanumihardjo SA. Lutein and beta-carotene from lutein-containing yellow carrots are bioavailable in humans. *Am J Clin Nutr.* 2004;80:131–6.

Fish oil and cachexia

Fish oil fatty acid supplements were administered at high doses (7.5 g eicosapentaenoic acid plus docosahexaenoic acid for a 70 kg individual, more than twice the doses used in published Phase III studies) to slow weight loss and to improve quality of life in patients with malignancy-related cachexia. A majority of patients did not gain weight but a small but definite subset of patients had weight stabilization or weight gain.

Burns CP, Halabi S, Clamon G, Kaplan E, Hohl RJ, Atkins JN, Schwartz MA, Wagner BA, Paskett E. Phase II study of high-dose fish oil capsules for patients with cancer-related cachexia. *Cancer* 2004;101:370–8.

Fish oil supplements and IgA nephropathy

Fish and marine oils are the most abundant and convenient sources of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the two major n-3 fatty acids that serve as substrates for cyclooxygenase and lipoxygenase pathways. Although the pathophysiology of IgA nephropathy is incompletely understood, it is likely that n-3 PUFA prevents renal disease progression by interfering with a number of effector pathways triggered by mesangial immune-complex deposition. In IgA nephropathy, efficacy of n-3 PUFA contained in fish oil supplements has been tested with varying results. The largest randomized clinical trial performed by our collaborative group provided strong evidence that treatment for 2 years with a daily dose of 1.8 g of EPA and 1.2 g of DHA slowed the progression of renal disease in high-risk patients. These benefits persisted after 6.4 years of follow up.

Donadio JV, Grande JP. The role of fish oil/omega-3 fatty acids in the treatment of IgA nephropathy. *Semin Nephrol.* 2004;24:225–43.

Mercury, cadmium and arsenic in Korean calcium supplements

The mercury (Hg), cadmium (Cd) and arsenic (As) contents for 55 brands of calcium supplements available on the Korean market were measured. Calcium sources were bone, milk, oyster/clam shell, egg shell, algae, shark cartilage or chelated calcium. Shark cartilage had the highest content of Hg (0.06 mg/kg) and Cd (0.13 mg/kg). The means for Hg, Cd and As were 0.01, 0.02, and 0.48 mg/kg, respectively, estimated to contribute less than 0.4% of tolerable daily intakes.

Kim M. Mercury, cadmium and arsenic contents of calcium dietary supplements. *Food Addit Contam.* 2004;21:763–7.

Complementary and alternative therapies in the military

A high percentage of soldiers, retirees, and dependents are using complementary and alternative medicine therapies, most commonly massage and herbal/food supplements. The implications of such high usage within the military suggests a need for nurses and providers to become educated to better assist patients in making appropriate choices between different forms of medical treatment.

McPherson F, Schwenka MA. Use of complementary and alternative therapies among active duty soldiers, military retirees, and family members at a military hospital. *Mil Med.* 2004;169:354–7.

Nutrient intake and malignant melanoma

Malignant melanoma has been one of the most rapidly increasing cancers within the United States, with few modifiable risk factors. Newly diagnosed patients with melanoma (n = 502) were requested to complete a food frequency questionnaire, which assessed diet over the previous year. A reduced risk for melanoma was found in persons with high intakes of vitamin D, alpha-carotene, beta-carotene, cryptoxanthin, lutein, and lycopene. High alcohol con-

sumption was associated with an increased risk for melanoma. These dietary risk factors are modifiable.

Millen AE, Tucker MA, Hartge P, Halpern A, Elder DE, Guerry D 4th, Holly EA, Sagebiel RW, Potischman N. Diet and melanoma in a case-control study. *Cancer Epidemiol Biomarkers Prev.* 2004;13:1042–51.

Fatty acids and branched-chain amino acid catabolism during exercise

Branched-chain amino acids (BCAAs) are essential amino acids that can be oxidized in skeletal muscle and such oxidation is promoted by exercise. BCAA supplementation before and after exercise has beneficial effects for decreasing exercise-induced muscle damage and promoting muscle-protein synthesis. Administration of ligands for peroxisome proliferator-activated receptor-alpha (PPARalpha) in rats caused activation of the hepatic branched-chain alpha-keto acid dehydrogenase complex in association with a decrease in the kinase activity, which suggests that promotion of fatty acid oxidation upregulates the BCAA catabolism. Long-chain fatty acids are ligands for PPARalpha, and the fatty acid oxidation is promoted by several physiological conditions including exercise. These findings suggest that fatty acids may be one of the regulators of BCAA catabolism and that the BCAA requirement is increased by exercise.

Exercise promotes BCAA catabolism: effects of BCAA supplementation on skeletal muscle during exercise. *J Nutr.* 2004;134(6 Suppl): 1583S-1587S.

A vitamin, mineral, herb dietary supplement and diabetes

A dietary supplement formulated with a synergistic combination of vitamins, minerals and herbals was tested in a group of 15 patients with uncontrolled diabetes type II. The supplement was given for 30 days. Fasting blood glucose was measured prior to the supplementation and at

the end of the 30 days treatment period. Blood glucose was significantly reduced in all patients with no adverse effects.

Gonzalez MJ, Ricart CM, Miranda-Massari J. A vitamin, mineral, herb dietary supplement effect on blood glucose in uncontrolled type II diabetic subjects. *P R Health Sci J.* 2004;23:119–20.

Bacterial vaginosis

Bacterial vaginosis is a common condition in women, representing an imbalance of the vagi-

nal microflora, lactobacilli depletion, and excess growth of mainly anaerobic Gram-negative pathogens. A randomized, placebo-controlled trial of daily oral intake of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus fermentum* RC-14 showed the lactobacilli-dominant microbiota was restored in 2 months.

Reid G, Burton J, Hammond JA, Bruce AW. Nucleic acid-based diagnosis of bacterial vaginosis and improved management using probiotic lactobacilli. *J Med Food.* 2004;7:223–8.

BOOK REVIEWS

Handbook of Nutrition and Immunity M. Eric Gershwin, M.D., Penelope Nestel, Ph.D. and Carl L. Keen, Ph.D., Eds. Humana Press, Totawa, NJ, 2004. Hardback, 365 pages, \$89.50. ISBN 1-58829-308-4

This is a great book if you missed the last 8–10 IAACN Scientific Symposia. It has a lot of the information covered in those meetings, although it is rather weak in the “nutrition” aspect of immunity. The nutrition concepts were “cutting edge” several years ago, but anyone who has been interested in clinical nutrition for the last few years should already know just about everything covered in this book.

The “immunity” portion of the book seems more up to date than the nutrition portion but is still somewhat dated. The chapter on prebiotics and probiotics is good, as is the chapter on acute

respiratory infections. If you should need to know more about the effects of malaria on immune function, you are in luck - there is an entire chapter on that subject. There is also a chapter on the effects of HIV infection on immunity, but there doesn't seem to be much fresh information in it.

A feature that I think should be included in every new book is a CD containing a eBook version that you can download to either your PC or PDA. In an age when information retrieval critically important this is distinct benefit to a busy practitioner. Be aware that the CD can only be used once for a PC and once for a PDA, so choose carefully where you want to download.

James Heffley, Ph.D., CCN, DANLA
Austin, TX

BOOKS RECEIVED

We're Killing Our Kids: How to End the Epidemic of Overweight and Sedentary Children

Todd Hollander, Worthy Press, Atlanta, GA 30356. 2004, Paperback, 192 pages (uncorrected proof) \$19.95. ISBN: 0-9753166-4-8

Cracking the Metabolic Code: 9 Keys to Optimum Health

James LaValle, R.Ph., CCN, ND with Stacy Lundin Yale, R.N., B.S.N. Basic Health Publications. North Bergen, NJ. Paperback, 2004, 608 pages, \$17.95. ISBN 1-59120-011-3

The Edge Effect: Reverse or Prevent Alzheimer's, Aging, Memory Loss, Weight Gain, Sexual Dysfunction and More

Eric Braverman, M.D. Sterling Publishing Co, Inc, NY. Hardback, 2004, 294 pages, \$19.95. ISBN 1-4027-1205-7

Reversing Hypertension: A Vital New program to Prevent, Treat, and Reduce High Blood Pressure

Julian Whitaker, M.D. Warner Books, NY. Paperback, 304 pages, \$14.95. ISBN 0-446-67663-2

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