Specific Anti-Aging Factors for Natural Clinicians
by Stephen Holt, MD

Concepts of Aging
It is impossible to define the onset of “old age,” which is the result of many physiological and sociobehavioral changes.\textsuperscript{1,7} While many seek the “fountain of youth,” no one has found it. Aging is a complex process that can be modified only by multipronged interventions.\textsuperscript{1,7} Positive lifestyle is pivotal in the promotion of health and well-being. While one can extol the virtues and benefits of good lifestyle for health maintenance and longevity, the investment in “behavior change today for health tomorrow” is a difficult pathway of intervention. Mental and physical idleness result in loss of vitality. An important promoter of aging is lack of mind or body activity, resulting in the “disuse syndrome,” with its hallmark of premature aging.\textsuperscript{1-7}

Many theories of aging have been proposed, but no single explanation suffices (Table 1). Despite uncertainty about aging theories, modern anti-aging research has identified several key disorders or processes that promote tissue aging. These processes include immune impairment, sleep deprivation, obesity, adverse lifestyle, genetic programming, poor nutrition, hormonal deficiencies or deregulation, inflammation, oxidative stress to tissues, deficient methylation, and the formation of glycated proteins (Advanced Glycation End Products, or AGEs).\textsuperscript{1,8}

A wide range of natural substances had been identified that can provide favorable nutritional or chemical effects on several of these common disorders or processes that accelerate tissue aging.\textsuperscript{1,8,9-12} Modern research has identified many natural substances with anti-aging properties, but simple interventions or single supplements (or drugs) cannot address efficiently the multifactorial aspects of tissue aging.\textsuperscript{1,8,9-12} The intricate, biochemical cascades of events involved in aging require a synergistic approach to the formulation of anti-aging substances, specifically dietary supplements.

The objective of this article is to review and focus on anti-aging interventions using dietary supplements to induce youth-preserving improvements in body functions and structures. This compilation of information will permit the natural clinician to adopt a synergistic approach to the correction or retardation of tissue aging using evidence-based, dietary-supplement strategies.

Dietary Selections
The optimal “anti-aging diet” should be reduced in simple sugars and saturated fat, while being supplemented with omega-3 essential fatty acids (EFA).\textsuperscript{5,13,14} The diet should contain modest amounts of protein of mixed origin (vegetable, meat, dairy, and fish origin), high in fiber and dense in vital nutrients, such as vitamins, minerals, and phytochemicals. Perhaps the most important dietary adjustments involve the reduction of useless, dietary calories (e.g., simple sugars, saturated fat,

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<thead>
<tr>
<th>Table 1. Theories and Hypotheses of Aging with Comments about Age Promoters and Putative Age Eradicators\textsuperscript{1-12}</th>
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<tbody>
<tr>
<td><strong>HYPOTHESES OF AGING</strong></td>
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<tr>
<td>Free Radical Theories ........................................</td>
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<tr>
<td>Cross-Link Theories ..........................................</td>
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<td>Immunologic Theories .........................................</td>
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<td>Mutation and Error Theories ................................</td>
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<td>In-Built Programs of Tissue Aging ..........................</td>
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<td>Stress Theories ................................................</td>
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<td>Repair Budget Theories ........................................</td>
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<td>Miscellaneous ..................................................</td>
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or alcohol) and a restoration of the balance of omega-3 EFA to omega-6 EFA intake. The widespread, relative deficiency of omega-3 EFA and imbalance of omega-6:omega-3 dietary intake ratios have been implicated in proinflammatory states, increased risks of cancer or cardiovascular disease risk, and the general promotion of chronic disease, tenable theory of aging, due to free radical damage, is widely accepted as a cause of aging. The body has efficient ways during exercise. Many environmental oxygen species are formed during a few, multifunctional, natural antioxidants are ubiquitous in fruit, vegetables, and berries. To provide adequate antioxidant coverage, many physicians are using vitamin supplements (e.g., A, B complex, C, D, and E) combined in complex mixtures of berries, greens, and vegetable powders. These blended powders contain a vast array of antioxidant phytochemicals and micronutrients. This complex approach has started to replace the use of multivitamin supplements in the modern practice of Integrative Medicine. The key to antioxidant supplementation is to attempt to cover all body tissues with an antioxidant blanket of compounds that access many tissues (lipophilic and hydrophilic antioxidants). This approach should use antioxidants with different REDOX potentials, in order to maximize oxygen radical absorbance capacity (ORAC).

Cell membranes are particularly vulnerable to free radical damage. This circumstance demands the use of lipophilic antioxidants such as turmeric, vitamin E (tocopherols), or essential fatty acids of the omega 3 series (indirect antioxidants). Particularly valuable common antioxidants include pycnogenol, lutein, lycopene, ellagic acid, alpha lipic acid, co-enzyme Q10, green tea or coffee polyphenols, bioflavanoids, and isoflavones.

Co-enzyme Q10 (ubiquinone) is a powerful antioxidant with well-documented benefits in the management of cardiovascular disease (angina, congestive cardiac failure, hypercholesterolemia, etc.). This table presents an overview of antioxidants that are used in regimen and supplement form to cause tissue damage. Endogenous antioxidants can “mop up” free radicals. These antioxidants include superoxide dismutase (SOD), glutathione, catalase, selenium, and vitamins A, C, and E. Many benefits with adaptogenic effects on apoptosis.

<table>
<thead>
<tr>
<th>ADAPTOGEN</th>
<th>ACTIONS</th>
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<tbody>
<tr>
<td>Ginseng (Panax, Eleutherococcus)</td>
<td>Panax (Chinese/Korean), Eleutherococcus (Siberian), Panax quinguelorus (American) have variable antioxidant, brain-supporting, cholesterol-lowering, and estrogenic actions.</td>
</tr>
<tr>
<td>Ashwagandha (Withania somnifera)</td>
<td>Ashwagandha contains alkaloids and antioxidants that may have anti-inflammatory, cognitive-enhancing, anxiolytic, and aphrodisiac qualities.</td>
</tr>
<tr>
<td>Dandelion (Taraxacum officinale)</td>
<td>Dandelion extract has diuretic, liver-supporting, anti-cancer, antioxidant, blood glucose-balancing, and anti-thrombotic properties. It may inhibit ILG and TNF alpha (anti-inflammatory).</td>
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<tr>
<td>Ganoderma (lucidum, Reishi)</td>
<td>Ling Zhi (Reishi) mushrooms have anticancer, antiangiogenic, DNA-protective, anti-inflammatory effects.</td>
</tr>
<tr>
<td>Schisandra (chinensis)</td>
<td>Schisandra has anti-stress, anti-inflammatory, energizing, immune-stimulating, and hormone-balancing actions.</td>
</tr>
<tr>
<td>Rhodiola (rosea)</td>
<td>Rhodiola has anti-stress, memory-boosting, and antidepressant actions</td>
</tr>
<tr>
<td>Bacopa (monnieri)</td>
<td>Bacopa has anti-stress, brain-supporting, and rejuvenating properties.</td>
</tr>
<tr>
<td>Resveratrol (skin of red grapes)</td>
<td>Many benefits with adaptogenic effects on apoptosis.</td>
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Table 2: Botanical Agents That Have Adaptogenic or Biological Response Modifying Effects These natural substances can be combined in synergistic formulations to constitute a baseline, natural anti-aging approach.
Antioxidant may play a role in the management or prevention of macular degeneration, prostate or breast cancer, cognitive decline, Parkinson’s disease, skin aging, muscle weakness, and chronic fatigue syndromes. Idebenone is a modified form of CoQ10 that may have a greater antioxidant action than CoQ10.

Tissue Glycation

Glycation or glycosylation results from the undesirable combination of aldehydes, glucose, or fructose with proteins. During cell membrane damage by free radicals, aldehydes, such as malondialdehyde (MDA), are released. These aldehydes can cross-link sugars and proteins, causing protein aggregation with consequent loss of the functional and structural integrity of several tissue proteins. The linking of proteins with sugars or aldehydes involves a process of carbonylation. This process of protein linking and aggregation attracts further free radical damage, resulting in the formation of advanced glycation end-products (AGEs).

These AGEs make cellular attachments that induce tissue destruction and the generation of disruptive end-products (e.g., nitric oxide or inflammatory mediators, including tumor necrosis factor [TNF] and undesirable interleukins [IL-6]).

The generation of AGEs can be interrupted by the use of carnosine that causes “carnosinylation.” This chemical reaction is protective against the process of carbonylation. Carnosine can combine with MDA, thereby inhibiting the process of glycation. Glycation results in severe compromise of tissue structure and function in many organs. The development of AGEs in metabolic syndrome X and diabetes mellitus explains the hallmark presence of premature aging in these disorders.

Glycation is clearly related to the development of atherosclerosis, beta amyloid deposition in the brain (typical of Alzheimer’s disease), and skin aging. Furthermore, glycation can involve cross-linking of sugars or aldehydes with both protein and DNA. This circumstance impairs the normal genetic functions of DNA.

Carnosine and its variants (anserine, homocarnosine, N-acetyl carnosine, and carcinine) contain alanine and histidine. Emerging evidence shows the benefit of carnosine in a variety of disorders or illnesses, including states of chronic inflammation, rheumatoid disease, hypertension, vascular thrombosis, peptic ulceration, delayed wound healing, skin aging, radiation-induced tissue damage, cancer, and cataracts.

Carnosine has shown well-defined, anti-aging properties by extending the lifespan of laboratory mice, and it has been shown to expand the lifespan of human cell lines grown in tissue cultures (fibroblasts), in several lab experiments.

Methyl Donation (Methylation)

The maintenance of the structural and functional integrity of several key chemical compounds in the body involves the donation of methyl groups. Examples of vital compounds that require methylation for optimal function include high-density lipoproteins (HDL), DNA, phospholipids, serotonin, and adrenaline. Without a continuing ability of the body to methylate many pivotal compounds, normal tissue functions cannot proceed. A common result of impaired methylation is the damaging accumulation of homocysteine. Homocysteine accumulates as a result of its lack of conversion to methionine (a methyl donor).

Eleven levels of homocysteine are found in states of inflammation and associated with several diseases, including cardiovascular disease, dementia, osteoporosis, diabetes mellitus, systemic lupus erythematosus (SLE), and other autoimmune disorders. These circumstances benefit from the availability of methyl donors such as S-adenosyl methionine (SAMe) or tri-methyl-glycine (TMG), which are present in popular dietary supplements.

Deregulation of methylation tends to occur with age, and exercise increases the need for methyl group donation. For these reasons, aging or over-exercised tissues may suffer protein and DNA damage. A particular problem occurs with collagen destruction in individuals who over-exercise. In competitive athletes, tendon, periarticular, and ligamentous disruptions result from compromised or sub-optimal methyl donation. Committed or elite athletes may benefit from methyl-donating supplements (TMG and SAMe) to engage in preservation of youthful musculoskeletal function.

Hormonal Deficiency or Imbalance

There is no evidence to support the naïve notion that hormone deficiencies provide a comprehensive explanation of the aging process. While specific hormonal deficiency or deregulation contributes to tissue aging in the mature individual, simple hormone replacements with human growth hormone (HGH), DHEA, melatonin, or sex hormones are not “stand-alone,” anti-aging interventions. That said, hormonal therapies show promising benefits for anti-aging when used in the correct context. The relative deficiency of several hormones that occurs with advancing years is perceived by some physicians as a simple opportunity to reverse aging by hormone supplementation. Other physicians perceive reductions in certain hormones as a normal healthy adjustment made by the aging body. Of course, neither perspective is completely correct, and these issues remain debatable among medical practitioners.

The administration of HGH has become very popular in anti-aging medicine, but its use remains controversial. While a number of studies have shown favorable physical and physiological outcomes with HGH administration, recent meta-analysis studies of HGH treatments fail to show acceptable safety and efficacy.

Proponents of growth hormone use in anti-aging medicine report muscle mass increase, gastrointestinal benefits, improved visual acuity, enhanced exercise tolerance, blood pressure reductions, improved libido, promotion of immune function, and enhanced cognitive activity. Such benefits are undeniable in anecdotal reports, but the duration of some of the recorded benefits of HGH may be limited, and the consequences of long-term use of HGH in anti-aging strategies remain uncertain.

The observed benefits of growth hormone supplementation must be balanced against known side effects, which are most often experienced...
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at high dosages of injected HGH. Adverse side effects of HGH include soft tissue swelling, entrapment neuropathy, diabetogenic tendencies, gynecomastia, fluid retention, acromegalic features, and hepatic enlargement. The risk of HGH as a promoter of cancer growth is a residual concern. Notable evidence exists that HGH treatments may enhance risks of colonic cancer. Claims that HGH can actually accelerate tissue aging remain challenged. On balance, it is clear that HGH treatments must be carefully planned and monitored by a knowledgeable physician. The formal prescribing guidelines for HGH use in anti-aging practice remain confusing, but many physicians believe that HGH administration is indicated when mature adults have documented low blood levels of HGH of IGF1.

Natural ways of boosting HGH release by applying hormonal or nutritional secretagogues are more portable than HGH injections in clinical practice. The value of amino acid secretagogues has been questioned in elderly humans. The classic way of enhancing the secretion of HGH involves the use of growth hormone-releasing hormones (e.g., GHRP-6). Other hormonal secretagogues include GHRH analogues, Ghrelin, and ProHGH, with or without GHRH cofactors. Some growth hormone-releasing products are administered by oral capsules or tablets, sublingual or oral sprays, with a variable evidence-base for safety and efficacy. Growth hormone-releasing co-factors include glutamine, combinations of arginine, lysine, and ornithine, L-dopa, or plant-derived “mimetics” (Mucuna pruriens), carnosine, homeopathic preparations, gamma hydroxy butyrate (GABA), yeast extracts, and mixed mineral supplements. The use of growth hormone secretagogues over extended periods of time may sometimes result in their ineffectiveness, as the pituitary or its effector mechanisms become tolerant to initial growth hormone-releasing actions.

De-Hydro-Epi-Androsterone (DHEA) is a hormone that is readily converted to several sex hormones (estrogen, progesterone, and testosterone). The decline in the endogenous availability of DHEA with age is associated with several disorders of aging including chronic inflammation, reduction in IGF1, immune impairments, neurodegenerative disorders (e.g., Alzheimer’s disease), and risks of death in the elderly. The administration of DHEA in several of these disorders of aging has been reported to produce an overall benefit. Adverse effects of DHEA administration include severe depression and growth-promoting effects of DHEA on the prostate and perhaps other organs.

While the benefits of DHEA supplementation appear attractive, this supplement should be administered under medical supervision because of its relatively narrow benefit/risk profile. The combined use of melatonin with DHEA may have added anti-aging benefits. Melatonin is a potent antioxidant hormone that may improve menopausal
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Symptoms, partially restore age-related declines in thyroid function, exert anti-cancer effects, and help restore the circadian rhythm of sleep. Recent research highlights the potential value of topical melatonin in reversing many changes found in aging skin.

The administration of conventional hormone replacement therapy (HRT) to women in the transition of menopause carries more risks than benefits, according to "The Women’s Health Initiative Study" in the US and "The Million Women Study" in Europe. More women are now prescribed so-called "bio-identical hormone therapy (BHRT)," but residual concern exists that there are insufficient studies of this form of therapy to make clear conclusions about safety and effectiveness. I have tended to reject the term "bio-identical" and substitute the term "bio-similar," which is a more accurate reflection of the circumstance. It is proposed that the benefits of BHRT outweigh the risks when hormones are used early in the transition of menopause and in the correct ratio of estrogens that mimic normal estrogenic patterns. Furthermore, the data may support the transdermal administration of "bio-similar" estrogens.

Adaptogenic Herbs and Botanicals

The term adaptogen is often used in a loose manner in alternative medicine jargon. Adaptogens are most specifically defined as naturally occurring plant substances that assist in the adaptation of the body to continuing stress. However, this terminology is restrictive, and many natural substances exist that can act as biological response modifiers (BRM) in a favorable way. The terms adaptogen and BRM may be used interchangeably to advantage. A large number of nutrients or botanical agents have adaptogenic qualities (Table 2).

Clearly, a good, balanced nutritional intake of vitamins and phytochemicals is pivotal in a comprehensive adaptogenic body status.

Calorie Restriction or Calorie Restriction “Mimics”

Restriction of calorie intake combined with the maintenance of nutrient density of food has powerful anti-aging benefits in rodents and probably in humans. Experimental calorie restriction may improve protein metabolism with the elimination of cross-linked protein products by downregulation of “chaperone molecules,” with resulting increases in hepatic protein elimination. Calorie restriction has been associated with reductions in blood cholesterol and blood markers of inflammation and with improvements in glucose tolerance. Many of these benefits may be related to loss of adipose tissue, but the proposed actions of calorie restriction are legion (Table 3).

Several natural compounds and drugs have been proposed as agents that can mimic variably the effects of calorie restrictions. These putative, calorie-restriction mimetics include resveratrol, hydroxyecitrate, gymnema alkaloids, alpha lipoic acid, cinnamom (methylhydroxychalones), indoeacetate, metformin, and thiazolinediones. Much interest has focused on the anti-aging benefits of resveratrol. These benefits are potent and versatile. They include regulation of apoptosis, antioxidant actions, anticancer effects, cardiovascular benefits, and specific gene-regulating actions. The aging gene in question is SIRT1. This gene modulates tissue aging by inhibiting apoptosis. Resveratrol exerts complex, poorly understood effects on apoptosis regulation, with an ability to upregulate or downregulate cell death.

Toxicity and Premature Aging

The twentieth century witnessed the increasing use of synthetic chemicals, and the new millennium is a time to experience the adverse effects of these toxins (toxicants). Toxins are ubiquitous in our environment and the body tissues of animals and humankind. The association between toxic exposures derived from food, buildings, or consumer goods and chronic disease is becoming increasingly obvious in contemporary medical research.

Attempts to avoid or ameliorate exposure to environmental toxins by lifestyle change, consumption of organic vegetables, and body-cleansing programs are valuable anti-aging tactics. Integrative medicine now stresses the use of non-toxic alternatives to many items that contain health-damaging toxins. Among the undesirable actions of organic chemicals (toxicants) are the promotion of weight gain, propagation of oxidative stress to tissues, direct mutagenic effects, and the exertion of unwanted hormonal actions, e.g., xenoestrogens.

While not prominent in anti-aging advice, the avoidance of unnecessary pharmaceuticals and HRT for menopause appears to be a prudent recommendation. Adverse side effects of medications and iatrogenic drug catastrophes are a major cause of death and premature disability in the US. Furthermore, the use of conventional sex hormone replacement therapy, with animal estrogens and synthetic progestins, appears to have more risks than benefits in the management of menopause. The proposed safety of bioidentical hormone treatments remains to be defined, despite the rhetoric.

Immune Function

Immune senescence is characterized by both deficiencies and deregulation of immune function. Much interest in natural medicine has focused on the correction of Natural Killer cell function (NK cells), at the expense of considering needs to modulate other components of the aging immune system. While
immune function involves a complex cascade of bio-physiological events, attempts to enhance or modulate immunity, using natural medicines, has often focused inappropriately on the use of single agents of botanical or nutritional origin.

My colleagues and I have tested the hypothesis that complex immune functions are best addressed by synergistic formulations of multiple herbs, botanicals, and nutrients. In vitro and in vivo comparisons of dietary supplements with effects on immune function show that synergistic formulations of substances with known immune-modulating effects provide more potent and versatile effects than single or limited compositions of immune-stimulating supplements. This approach is summarized in Table 4, which identifies a combination of natural substances that are associated with specific research. This research shows profound stimulating effects on NK cell activity and cell-mediated immunity with associated actions on immune, molecular cascades. It is noteworthy that complex immune-modulating formulations can incorporate botanicals with antiviral properties (e.g., *Andrographis paniculata*) to further enhance immune protection. In brief, evidence has accumulated that improvement in immune function may promote longevity.

### Sleeplessness

Sleep deprivation has many adverse, social, psychological, psychiatric, and physical consequences. Sleeplessness has been associated with alterations in appetite that promote weight gain, the induction of inflammation and chronic stress, together with linkage to several chronic diseases. Unobtrusive consequences of lack of sleep include mood change, depression, poor mental function, and metabolic changes similar to syndrome X. An association exists between abnormalities of sleep and premature death. Standard prescription sleeping pills or over-the-counter hypnotic drugs are common causes of iatrogenic problems. Natural approaches to induce restful sleep are to be preferred over pharmaceutical approaches. Such interventions include lifestyle change, behavioral modifications, and the use of synergistic combinations of herbs and nutrients that are part of “the Sleep Naturally Plan.” Certain herbs with adaptogenic or antioxidant properties can be selected as natural ways of promoting healthy sleep. This approach is a viable alternative to using hypnotic drugs, which may carry inherent risks of premature death.

### Anti-Aging Nutraceutical Strategies

In view of the many factors that contribute to aging, a holistic approach to anti-aging is required, with due consideration for positive lifestyle change. The challenge in using remedies of natural origin as recuperative factors involves the creation of synergistic, natural formulations that can be administered in a convenient, cost-effective format that may result in reasonable patient compliance. Such formulations should include sufficient ranges and amounts of evidence-based, anti-aging agents that can access the multiple aspects of the physiological and chemical cascades of aging. In summary, this combined approach requires a group of nutraceutical, anti-aging factors that can be administered in a convenient, well-tolerated protocol (Table 5).

### Conclusion

A focus on a holistic approach to anti-aging using positive lifestyle change and natural medicine is a key initiative in modern health care. Once relegated to the realms of quackery, remedies of natural origin play a major role in the promotion of longevity. The physician involved in anti-aging medicine should consider “staged strategies” of intervention starting with the most natural and simplistic approach of healthy lifestyle recommendations, followed by well-designed and tailored nutritional approaches. Popular hormonal interventions can be exercised in these staged strategies, but physician supervision must be involved in interventions that alter endocrine profiles.

### Notes

Anti-Aging Factors


Table 5: The Author’s Recommendations for the Rational Use of Combination Supplements in Anti-Aging Medical Practice.

<table>
<thead>
<tr>
<th>Poor nutrition</th>
<th>Anti-aging factors to correct pivotal biochemical imbalance, incorporating methyl donation and antioxidants to interfere with tissue glycation and oxidative stress. Recommendations include putative secretagogues or HGH “helpers.”*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep deprivation</td>
<td>Initial lifestyle change with combination synergistic formulations of melatonin, 5 HTP, adaptogenic, or sedative herbs</td>
</tr>
<tr>
<td>Membrane lipid damage and prevention of chronic disease and inflammation</td>
<td>Omega-3 essential fatty acids in enteric-coated fish oil capsules (at least 2g/day of 30:20 ratio of EPA/DHA)</td>
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<tr>
<td>Immune impairment</td>
<td>Use of complex formulations that modulate immune cascades with antiviral activity</td>
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<tr>
<td>Hormonal declines</td>
<td>Evidence-based GH secretagogues and DHEA</td>
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<tr>
<td>Combat diseases of premature aging</td>
<td>Cardiovascular health promotion; management of obesity, metabolic syndrome X, and diabetes mellitus; cancer prevention</td>
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*Courtesy of Holt MD Technologies

Stephen Holt, MD, is a clinician, researcher, and best-selling author. He is a Knight of Grace of the Holy Order of St. John and the recipient of many honors and awards for medical teaching and research. He is a scientific advisor to Natural Clinician LLC, Little Falls, NJ, a company that sells health care products. Dr. Holt is regarded as a pioneer of Integrative Medicine, and he is the President of the World Organization of Natural Medical Practitioners (www.wonmp.us).