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WORLD SOCIETY OF ANTI-AGING MEDICINE
Consensus Group of Experts on Nutritional Therapies

CONSENSUS # 1 on "FATTY ACID TESTING AND TREATMENT" of October 30, 2006

After having reviewed the scientific literature and exchanged experiences between physicians from all over the world who are competent in nutritional therapies, we, members of the Consensus Group of Experts of the World Society of Anti-Aging Medicine, think the time is ripe to reconsider current concepts on corrections of fatty acid deficiencies and excesses as they can be measured in a fatty acid profile.

Fatty acids accomplish important functions in our body: they are major components of cell membranes, and they play fundamental roles in the cardiovascular, immunological and nervous systems. Fatty acid deficiencies have been shown in several studies to increase cardiovascular diseases (including myocardial infarction, cardiac arrhythmias, and abnormal lipid profiles such as hypercholesterolemia or hypertriglyceridemia), to facilitate the appearance of psychiatric and neurological diseases, and to increase insulin resistance. Several serious studies have suggested that individuals presenting fatty acid deficiencies may have increased cardiovascular mortality. On the other hand, excesses in trans fatty acids have been shown to be detrimental to health: increases in cardiovascular diseases and mortality, a possible increased cancer risk, a higher incidence of diabetes, etc. Excesses in arachidonic acid increase inflammatory processes; they may alter health and possibly accelerate aging. Excesses in several saturated fatty acids (such as myristic acid) have been demonstrated as atherogenic and hypercholesterolemic.

The evidence is sufficient to justify testing (i.e. realize a fatty acid profile) and corrections of fatty acid deficiencies and excesses.
The evidence is sufficient to guarantee the physician a **freedom of choice in fatty acid profile testing**.

As fatty acid imbalances can contribute to serious adverse consequences on the quality of life and health of patients, we recommend that physicians, in light of the solid evidence here collected, request for their patient **a fatty acid profile test** (including the dosage of myristic acid, palmitic acid, stearic acid, margaric acid, pentadecylic acid, oleic acid, palmitoleic acid, elaidic acid, trans-vaccenic acid, linoleic acid, gamma-linolenic acid, dihomo-gamma-linolenic acid, arachidonic acid, docosapentaenoic acid, alpha-linolenic acid, stearidonic acid, eicosapentaenoic acid, docosahexaenoic acid)) **whenever a fatty acid imbalance is suspected,** such as in case of fatigue, depression and other psychiatric disorders, dry skin, cardiovascular pathology (familial or personal history), rheumatic diseases, insulin resistance, etc. Such a test must be done by measuring the profile of fatty acids included in serum phospholipids (and not just by evaluating free fatty acids) and should be done after a 12 hours fast. If these conditions are respected, it generally offers a stable picture of the fatty acids that a patient consumes (food and possibly supplements) during the preceding weeks, which enables the physicians to adapt either the patient's diet or their advice and treatments.

Treatment of fatty acid imbalances or toxic excesses indeed consists of **dietary advices** such as increasing the intake of fish, of specific cold-pressed vegetable oils and other sources of polyunsaturated omega 3 and 6 fatty acids, of monounsaturated omega 9 or, if necessary, of certain saturated fatty acids; and reducing the intake of sources of fatty acids that may be in excess such as arachidonic acid and trans fatty acids (these may also be produced by faulty cooking processes). Evidence suggests that diet adjustment in our modern society is often not sufficient to optimize the fatty acid composition of our body and makes **fatty acid supplementation** compulsory, in particular among patients showing signs and symptoms possibly linked to fatty acid disturbances. Such a supplementation is best done individually according to a fatty acid profile. Generally, several months of daily intake of fatty acid supplements are necessary before the correction takes place.

CONSENSUS # 2 on "OXIDATIVE STRESS TESTING and SUPPLEMENTATION with ANTIOXIDANTS" of October 30, 2006

After having reviewed the scientific literature and exchanged experiences between physicians from all over the world who are competent in nutritional therapies, we, members of the Consensus Group of Experts of the World Society of Anti-Aging Medicine, think the time is ripe to reconsider current concepts on tests for antioxidant capacity and free radical damage, and supplementation with antioxidants.

Free radicals are generated by the loss of an electron, leaving a molecule with an odd, unpaired electron. This molecule is very unstable and tends to react quickly with other compounds, trying to capture a needed additional electron to gain stability. Generally, free radicals attack the nearest stable molecule, "stealing" its electron, and, which may spread through waves causing free radical damage. This is believed to be one of the essential mechanisms behind senescence and many diseases such as diabetes, cardiovascular diseases, cancer, neurodegenerative diseases (Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease), stroke, asthma, psoriasis, pancreatitis, cataract, in case of transplant as well as in case of emotional stress. In an increasing number of studies, free radical damage, also called "oxidative stress" reflecting increased levels of free radicals, has been reported. Increased levels of free radicals generally result from lower levels of antioxidants and antioxidant enzyme systems. Health is generally associated with adequate levels of compounds (vitamins, trace elements and others) and enzymatic systems with antioxidant activity, plus low levels of lipid peroxides, oxidized lipoproteins, malonaldehyde, 8-OH-deoxy-guanosine and other markers of free radical damage. Laboratories specialized in Nutritional Biology have developed tests to measure the serum levels of these free radical markers as well as those of antioxidants such as vitamin A, vitamin C, vitamin E, beta-carotene, coenzyme Q10, zinc, copper, selenium, plus antioxidant enzymes such as superoxide dismutase and glutathione peroxidase. The testing also measures several markers of free radical damage in order to evaluate the net result of the oxidative stress and the antioxidant protection.
Every month, new evidence accumulates to show that adequate antioxidant supplementation can correct the disease-associated and the age-related increases in oxidative stress. In animal studies, antioxidant supplementation has been shown to reduce the progression of cancer, cardiovascular diseases, diabetes, and many other diseases, and even to increase lifespan. Some prospective human studies have shown beneficial results on the incidence and progression of diseases too, although not always as consistent as the animal studies data. In some important human studies, a high dietary intake of specific antioxidant nutrients has been shown to reduce overall or disease-specific mortality.

Recommendations: In face of the growing body of evidence, we recommend **testing** oxidative stress markers, antioxidant nutrients and antioxidant enzymatic systems, in any patient who is suspected, based on familial or personal history, to present or develop the above-mentioned diseases, to show signs of aging and/or to be in a chronic stressful environment. We recommend the physician to work with a laboratory where quality and experience in these tests handling are high (especially sampling and transport).
We recommend also the **treatment** of any oxidative imbalance to be discovered with the tests. Besides dietary advices to reduce free radical pathology such as increasing the intake of fruits and vegetables and avoiding foods cooked at excessive temperature for example, it is of primary importance to prescribe the appropriate antioxidant supplements. Treatments with antioxidant supplements may take months of daily intake before achievement of adequate levels of antioxidants. Patients with disease or persons in prolonged stressful conditions often need to continue the treatment by taking the needed antioxidant supplements in order to keep the antioxidant capacity of their body high and to prevent or counter further aggravation of their disease. The approach 'high-quality tests/personalized supplementation' is the most efficient one and the most recommended. It is for many patients not sufficient to merely take a daily multi-antioxidant complex without any knowledge of the body's levels. Some rare studies have shown moderate increases of disease or mortality risk in case of vitamin E and beta-carotene intake, in particular among smokers, which represents sufficient evidence to recommend caution and avoid excesses in any

supplementation. The cost /effectiveness of the available tests are considered by the members of the Consensus Group of Experts of the World Society of Anti-aging Medicine to be good for the best specialized laboratories. In order to treat their patients, we do recommend physicians to search for the highest quality of products as not all brands are equal in composition and availability.

CONSENSUS # 3 on **"TESTS and TREATMENTS of INTESTINAL WALL PERMEABILITY and GUT FLORA"** November 19, 2006

After reviewing the scientific literature and exchanging experiences with physicians from all over the world who are competent in nutritional therapies, we, the Consensus Group of Experts of the World Society of Anti-Aging Medicine, think it is time to re-evaluate the tests for intestinal health. In particular, we are interested in the tests that measure intestinal mucosal permeability and intestinal microfloral composition. We are also concerned with establishing the best corrective treatments and diet modifications to reduce intestinal mucosal leakiness, and, when indicated, to fight the overgrowth of yeast or any other gut pathogens.

Intestinal mucosa should absorb essential micronutrients without allowing macromolecules to penetrate the digestive system. The loss of this barrier function is referred to as *leaky gut syndrome*. The micronutrient functional permeability of the intestinal mucosa can be measured by having a fasting patient ingest two types of sugar. A monomeric sugar, such as mannitol or rhamnose, will test for intestinal absorption, while a dimeric sugar, such as lactulose or lactitol, tests for pathologic permeability of the intestinal mucosa. Dimeric sugars are not normally absorbed by the brush border of the intestinal mucosa. Therefore, no dimeric sugar should be absorbed or leak through the normally sealed tight junctions. These tests have been available for many years in university hospital pediatric units, but are surprisingly rare in gastroenterology units. Now, however, they are performed by laboratories specializing in nutritional and functional testing. A large number of studies have been published in leading mainstream medical journals, where the quality of these tests is recognized in obtaining valuable information on gut permeability, especially for the indications mentioned above.

Leaky gut syndrome can be caused by malnutrition and the lack of specific factors necessary for adequate selective permeability. Whenever this is the case, we recommend treating the excessive intestinal permeability by improving diet and providing nutrients that improve the intestinal barrier such as L-glutamine, butyrate, zinc, vitamin A, vitamin E, folic acid, omega 3 fatty acids, etc.

Leaky gut syndrome can also be caused by an imbalance of intestinal microflora, i.e. yeast or putrefactive bacteria "overgrowths". The term "infection" does not apply in that these micro-organisms are normally present in the human gut, however in much smaller amounts. This pathologic permeability can also be caused by amoeba, flagellates, or helminths. Unwanted organisms in the gut are traditionally detected by microscopic identification or by culturing stools in specific nutritive broths. However, yeast (not necessarily alive when excreted in stool) often cannot produce colonies in a Petrie dish because it cannot adapt and reproduce in an incompatible environment.

We have carefully reviewed the recent scientific publications in which the presence of yeast is detected by measuring specific fungal metabolites (arabinose, arabinitol, citramalate, β-cetoglutarate, furanes) in the host's organic fluids, especially in urine. These metabolites are secreted by the fungus in the patient's intestinal lumen, where they are absorbed and then secreted in urine. They then can be evaluated by classic chromatography. We recommend that physicians do this test, as it avoids many false negatives. It also circumvents the many false positive results obtained from culturing stool, as yeast can be detected in the stools of 80% of healthy subjects. Measuring metabolites provides a quantitative evaluation of yeast overgrowth directly within the host's environment. To treat yeast overgrowth, we recommend the administration of antifungals (medications, herbs and/or essential oils), while simultaneously supporting healthy microflora with probiotics (friendly live bacteria), prebiotics (their nutritive fibers) or both together.

Allergic, inflammatory and autoimmune diseases have all been increasing in the last decades. Every month, new scientific evidence is published showing that an imbalanced intestinal ecosystem and especially an increase in intestinal permeability (intestinal leakiness) may lead to these diseases, and that patients who experience intestinal yeast overgrowth may suffer from irritable bowel syndrome, abdominal bloating, excessive production of gas, headaches, fatigue and much more. Patients suffering from an amoeba infection may complain of diarrhea, arthralgia, lumbalgia and fatigue. Patients affected by helminths may loose weight despite an increase in hunger and food intake. They may also become anemic, fatigued and may suffer from bruxism (unconscious tooth grinding).

In light of this growing body of evidence, we recommend testing intestinal mucosal permeability and intestinal microflora quality in any patient who, based on family or personal history, is suspected of having the above-mentioned diseases, or who shows signs of intestinal dysfunction, or who suffers from unexplained fatigue. We recommend that physicians work with specialized laboratories with a reputation for quality and reliability, which have experience in handling these tests, including sampling and transport. The Consensus Group of Experts of the World Society of Anti-Aging Medicine believes that the tests provided by the best specialized laboratories are very cost effective.

As for treatments of intestinal dysfunction, we recommend that physicians use the highest quality products, as not all brands are equal in composition and availability, especially probiotics, where a new generation of better, more potent and more reliable products have been developed and are preferred.

CONSENSUS # 4 on **"GENETIC TYPING TESTS"** December 4, 2006

After reviewing the scientific literature and exchanging experiences with physicians from all over the world who are competent in genetic typing, we, the Consensus Group of Experts of the World Society of Anti-Aging Medicine, think it is time to provide a consensus on the quality and usefulness of these tests.

Genes are basic working units of hereditary material, the double-stranded DNA (Desoxyribonucleic acid) housed on the chromosomes. A gene is composed of a specific sequence of nucleotides. Genes contain the information for the synthesis of proteins that are at the basis of physical or functional traits. Each gene may have several alternative forms, called alleles, which vary in one or more of their amino acids. Occurrence of more than one allele at the same locus is called **genetic polymorphism**. Different alleles of a gene may be found in different individuals of a population. Variant alleles of a gene may also be expressed in different proportions throughout the body cells in one individual.

Genetic typing tests: Genetic typing tests analyze the genetic polymorphisms. They are performed on the DNA isolated from white blood cells obtained from a blood sample or from epithelial cells obtained from mouth swabs. It is a **fast growing field of medicine:** Everyday, new research on genes and their variants is published. The evidence on links between genetic polymorphisms and various diseases is increasingly growing.

Diseases associated with genetic polymorphisms: Genetic typing tests detect alleles or genetic variants of a gene. A genetic variant may be associated with an increased or reduced relative risk of certain diseases. Up to now, risk variations associated with genetic polymorphisms have been reported in peer-reviewed medical journals for the following multifactorial diseases: obesity , diabetes mellitus, cardiovascular diseases (such as hypercholesterolemia, hypertriglycridemia, hypertension, coronary heart insufficiency, stroke), osteoporosis, Alzheimer's disease, Parkinson disease, breast cysts, polycystic kidney disease, thrombophilia (i. e. Factor Leiden), hemochromatosis, gluten and lactose intolerance, periodontitis, Crohn's disease, different types of allergies, and cancers that may be environmentally-

induced such as breast, prostate, colon and lung cancer, melanoma, and secondarliy, also gastric, larynx and ENT (ear-nose- throat) cancers, etc. Not all studies in genetic analyses have the same value. Meta-analyses and critical review and some major multi-centre studies can be considered as the reference in genetic analysis. For obesity and diabetes type II, large-scale screening programs are currently going on and their results should further increase our knowledge of genetic polymorphism.

Usefulness of genetic typing tests: Genetic tests for prevention purposes allow physicians to detect the modified susceptibility/ sensitivity to unfavourable environmental factors and the genetic predisposition of increased relative risks for disease early in the life of individuals at a presymptomatic stage. In this way they help physicians provide early and personalized health advices to their patients to improve prevention or delay the outbreak of a disease. For some genes ("modifier risk" genes), lifestyle or diet changes, nutritional or hormone replacement therapies may minimize the expression of a disadvantageous genetic polymorphism. For other polymorphisms, the expression of a gene cannot be influenced, but its associated increased relative risk of disease may be attenuated by improving the life style or diet, or by taking medications. Genetic typing may also help a physician make a better choice of a medication ("pharmacogenetics") in order to avoid severe adverse drug reactions (ADR) or treatment failure. For example, with some antihypertensive drugs, anticoagulants and antidepressants, the efficacy and relative risk for ADR depends on the genetic variant of the patient. Similarly, genetic typing may help a physician make a better choice of a nutritional supplementation ("nutrigenetics") or find more efficient therapies to eliminate pollutants ("toxigenetics"). For the World Society of Anti-Aging Medicine, genetic typing is useful as it improves the overall level of healthcare by personalizing more adequately the therapy of a patient, helping mainly in disease prevention. Once a patient is ill, it is likely that genetic typing tests will become increasingly important as aids to better therapy choices in the future.

Quality of genetic typing tests: The quality of the genetic tests done by experienced laboratories that are accredited and participate to external quality assessment programs, can be considered as good. Some studies have shown possible faults in the tests, namely sample mismatching, cross contamination and interpretation errors. Overall, the number of false positive or false negative tests does not exceed the average percentage found in other laboratory assays. We recommend physicians to send samples to certified laboratories which frequently process such tests, as they have the largest experience in doing them.

Genetic testing procedure: According to the basic international documents of the UNESCO (Universal Declaration of Human Genome and Human Rights), the WHO (International Guidelines on Ethical Issues in Medical Genetics and the Provision of Genetic Services) and the Council of Europe (Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine), genetic testing for personalized prevention measures can be performed for any person, who is considered as major (> 18 years old). Any genetic testing should be confidential and performed on the voluntary basis and only for the health purposes. Any form of discrimination against a person on grounds of his or her genetic heritage is prohibited. .

Conclusion: in the light of the current evidence, the quality and usefulness of genetic typing tests is high enough for the World Society of Anti-Aging Medicine Consensus group of Experts to recommend

International Hormone Society

www.intlhormonesociety.org

IHS statement

IHS statement on Bio-identical Hormones
December 5, 2006

After a literature review and discussions with physicians from all over the world who are well versed in treating patients with endocrine abnormalities, we, the members of the International Hormone Society, think the time is right to release a statement on the use and delivery of bio-identical hormones.

A "bio-identical hormone" has exactly the same chemical structure as a hormone produced by the human body. The term "bio-identical" is generally used for preparations containing sex hormones such as estradiol, estrone, estriol, progesterone and testosterone. The alternatives are non-bio-identical hormone preparations such as those widely commercialized in most birth-control pills and in post-menopausal hormone treatments. The prevailing concept is that bio-identical hormones may be safer to use than non-bio-identical hormones because they fit the body, in particular when a safer route of administration is used such as transdermal delivery.

The members of the International Hormone Society were concerned about product safety long before the publication of studies such as Women's Health Initiative [WHI] in 2002 and the British One Million Women study in 2003 that found an increase in the incidence of breast cancer in postmenopausal women using non-bio-identical hormones as compared to placebo or nonusers. In the WHI study, the use of non-bio-identical female hormones was also associated with an increased risk of cardiovascular and cerebrovascular diseases.

In accordance with the recommendations of a growing number of medical societies, the International Hormone Society, in a consensus on **"Estrogen and Progesterone Treatment of Pre- and Postmenopausal Women"** issued on December 11, 2005, **did not and still does not recommend the use of non-bio-identical estrogens and progestogens for the treatment of ovarian deficiencies**. However, the use of synthetically modified female hormones used for birth control may be considered for a limited time if no other contraceptive alternative exists. The consensus is based on an extensive review of the literature on the use of bio-identical and non-bio-identical estrogens and progestogens. Greater potential toxicity and risks were found in the non-bio-identical compounds.

On the other hand, **the International Hormone Society did and still does recommend in the consensus the use of bio-identical estrogens, in particular estradiol and estriol, and also bio-identical progesterone,** for the correction of ovarian deficiencies. In contrast with the recent Endocrine Society's position (October 2006) and the American Medical Association's resolution (November 2006) that state that "little or no scientific and medical evidence exists to support the claims that bio-identical hormones may be safer", a review of the literature contradicts this statement. There currently is sufficient evidence confirming the greater safety of bio-identical sex hormones compared to the non-bio-identical ones, in particular when the transdermal, nasal or intramuscular routes are used instead of the oral route.

Critics object to bio-identical hormones sold by compounding pharmacies due to the lack of oversight by the Food and Drug Administration (FDA), and assume that there is no guarantee of dosage, purity, efficacy and safety. We share with the American Medical Association, the Endocrine Society, the American College of Obstetricians and Gynecologists, and the American Academy of Family Practitioners the concern that patients should be offered the best products at all times, and that all products must be as consistent as possible in dosage, and as pure, efficient and safe as possible.

The physicians of the International Hormone Society think they can provide a valuable, decisive opinion in this debate for two reasons. First, many of them have broad experience in the use of bio-identical hormones compounded by compounding pharmacies, experience which does not seem to be shared by the writers of the various positions and resolutions of the aforementioned societies. Second, the opinion of the International Hormone Society members is independent of any pressure from advertisers, sponsoring pharmaceutical firms, or compounding pharmacies.

The physicians of the International Hormone Society wish to stress the following points:

1) **Control of compounding pharmacies:** The production of bio-identical hormone preparations by compounding pharmacies is under control of the pharmacy state board in each state. This control has sufficiently warranted high quality products, in dosage, purity, efficacy and safety, to satisfy physicians. Better control may be acceptable as long as it does not restrict physicians from exercising their therapeutic freedom to prescribe compounded preparations for the full benefit of patients.

2) **Major advantage of compounded preparations:** Compounded preparations of bio-identical hormones offer a major, indispensable advantage over standardized preparations, namely that the dosage and formulation of the product can be tailored to each patient. Concentration and composition, including solvents or fillers, can be individualized to what the patient needs or is able to tolerate. We think personalized treatments such as those offered by compounding pharmacies offer the best prospect for optimal health care.

3) **Production and distribution of bio-identical hormones is not limited to compounding pharmacies:** The FDA approval of "bio-identical" hormones already exists in the form of patches and mass-produced estrogen gel and cream. Compounding pharmacies are merely making a cream or gel that better suits the individual patient.

4) **Conjugated estrogens, an example of widely sold non-bio-identical hormones:** The form of estrogen, conjugated estrogen, which initiated this entire debate, is actually an estrogen waste product found in the urine of pregnant mares. Many of the estrogens in horse urine cannot be considered "bio-identical" to the human body because they are structured differently than human estrogens. Although some of the estrogens are equivalent to human estrogen, they have been altered biochemically by conjugation. Conjugation takes place in the liver of horses and humans in order to excrete unwanted estrogen. Therefore, conjugated estrogen medications are not bio-identical because they are waste product forms of estrogen marked for removal by a horse liver.

5) **Use of the term "bio-identical" hormones.** The AMA's request to the Food and Drug Administration to prohibit use of the commonly employed term "bio-identical hormones," unless the preparation has been approved by the FDA, contradicts the first amendment rights of the Constitution of the United States, denying the freedom of speech ensured by the amendment, and unacceptably interferes with the rights of medical doctors currently prescribing compounded preparations of bio-identical hormones. Section §503A of the FDA *Modernization Act of 1997* attempted to restrict the first amendment rights of compounding pharmacies, stipulating "that they refrain from advertising or promoting particular compounded drugs." However, the Supreme Court, in a 2002 decision, found that restriction unconstitutional. In the words of the FDA itself: "The Supreme Court affirmed the 9th Circuit Court of Appeals decision that found section 503A of the Act invalid in its entirety because it contained unconstitutional restrictions on commercial speech." This Supreme Court decision should firmly establish for all parties that first amendment speech applies to compounding pharmacies as to all Americans, and that first amendment speech does not require approval from anyone, including the FDA.

6) **Testing:** Most physicians who work with bio-identical hormones from compounding pharmacies use traditional blood tests, not saliva tests, as incorrectly stated by the American Medical Association (resolution of November 2006) and the Endocrine Society (position statement of October 2006).

7) **Safety:** As previously stated, there is currently sufficient evidence confirming the greater safety of bio-identical sex hormones as compared to non-bio-identical ones, particularly when administered transdermally, nasally or intramuscularly instead of orally.

8) **Research:** We recommend future research in this area, and, in particular, we support independent research on the potential risks and benefits of bio-identical and non-bio-identical hormones.

In conclusion, we urgently advise the American Medical Association to revise its position and the Food and Drug Administration to take all points of the International Hormone Society's statement into consideration and to preserve physicians' rights to prescribe the best possible products for their patients, including compounded preparations of bio-identical hormones.

IHS consensus

Consensus # 1 on **"Thyroid Hormone Therapy of Hypothyroidism**
September 29, 2005**"**

After having reviewed the scientific literature and exchanged experiences between physicians from all over the world who are competent in hormone therapies, we, members of the Consensus Group of Experts of the International Hormone Society, think the time is ripe to reconsider current concepts on thyroid treatment of hypothyroidism.

The view that hypothyroidism is best treated by thyroxin alone is not based on solid scientific evidence. The studies comparing the efficacy of thyroxin alone versus that of combination thyroxin and triiodothyronine medications have in general **not shown superiority of thyroxin alone** above the combination of thyroxin with a smaller dose of triiodothyronine. On the contrary**, a few studies** have shown a **significantly greater efficacy of combined thyroxin-triiodothyronine medications** compared to the use of thyroxin alone in humans on such divergent parameters as serum cholesterol, mental and physical symptoms, and in animals on goitre formation and intracellular triiodothyronine(T3)-euthyroidism, just to name some of the greater benefits. The facts that T3 is the major intracellular thyroid hormone, and that a low serum level of T3 is more often than a low serum T4 (thyroxin) or a high TSH, the critical parameter in mortality studies, especially cardiovascular, and that the absorption of T3 is much more efficient and stable than that of T4, give credibility to the view that a combination of thyroxin with triiodothyronine may be better for the hypothyroid patient.

The evidence is sufficient to guarantee the physician a **freedom of choice in thyroid medication: either thyroxin alone or thyroxin and triiodothyronine**.

As hypothyroidism has serious adverse consequences on the quality of life and health of patients, we recommend that physicians, in light of the solid evidence here collected, should **first** try to treat hypothyroid patients with **a combined thyroxin and triiodothyronine preparation.**

As the combination treatment contains the immediately active triiodothyronine, we recommend that physicians **follow some safety guidelines,** in addition to the obvious one of avoiding overdoses when they administer thyroxin and triiodothyronine medications. Following the measures listed below increases the safety and tolerance of the treatment:

1. The **first** guideline is to start the treatment at very low doses and then to slowly and gradually increase the dose until clinical eu-thyroidism is reached.
2. The **second** guideline is to tell the patient to avoid all caffeinated and similar stimulating drinks that may increase the orthosympathic activity.
3. The **third** guideline is to regularly follow-up the patient with a good clinical interview and examination and laboratory tests every two to twelve months depending on the patient's needs.
4. The **fourth** guideline is to carefully screen for adrenal deficiency in hypothyroid patients, as some patients with low or borderline low cortisol levels may poorly tolerate any type of thyroid medication, and in particular thyroxin-triiodothyronine combinations. The intolerance may come from over-activity of the orthosympathic nervous system that often accompanies states of low Cortisol, and an excessive and rapid conversion of thyroxin to triiodothyronine that puts these patients easily into a state of excess T3 and thus hyperthyroidism, and further increases the orthosympathic activity. In patients with Cortisol deficiency, we recommend the physician to treat the low cortisol state prior to or simultaneously with the thyroid treatment. If not, thyroxin alone may be the better treatment of hypothyroidism in the presence of an untreated cortisol deficiency. In most other instances, thyroxin and triiodothyronine remains the first, but not exclusive, choice for treatment of hypothyroidism for the International Hormone Society's Consensus Group.

Concerning the debate about which combination treatment works best: **synthetic T3-T4 or desiccated thyroid**, the Consensus Group states the following:

Reports of patients feeling better on desiccated thyroid may have scientific evidence as these preparations contain along with T3 and T4 a number of other substances that may have some thyroid activity as diiodo-and monoiodo-thyronines. In addition, the binding of much of the thyroid hormones to the bigger thyroglobulin molecule allows a slower intestinal absorption and, later, once arrived in the bloodstream, a slower release of thyroid hormones in the blood, thereby insuring a more persistent action and a better tolerance by spreading the action over a longer period of time. Thus, desiccated thyroid may work better.

The view that the potency of thyroid preparations of animal origin may have more fluctuations has arguments. For this reason, preference is given to preparations that are officially registered and well-controlled. It must be said that the frequent FDA-recalls of poorly reliable, less potent than announced thyroxin preparations of various pharmaceutical firms in the USA, makes thyroxin not a better alternative. In the light of the Mad Cow's Disease, the International Hormone Society does not recommend the use of desiccated thyroid of beef origin. For these reasons, the position adopted by the Consensus Group members of The International Hormone Society is that both type of T3 -T4 preparations have their pros and cons, and the freedom of choice between these two should be left over to the physician."

Consensus # 2: Estrogen And Progesterone Treatment of Pre- and Postmenopausal Women
December 11, 2005

After a literature review and discussions with physicians from all over the world who are well-versed in treating patients with endocrine abnormalities, we, the members of the Consensus Group of Experts of the International Hormone Society, think the time is ripe to reconsider current concepts on correction of female hormone deficiency.

We acknowledge the present controversy on the use of female hormone replacement since the American Woman's Health initiative (WHI) study published in 2002 and the British One Million Women study published in 2003. In both of these studies, the use of female hormone supplementation was associated with an increased breast cancer incidence compared to placebo or nonusers. In the WHI study the use of female hormones was correlated with an increased risk of cardio- and cerebrovascular diseases.

For the members of the consensus group of the International Hormone Society, the main bias of these studies is that none of the participants took progesterone. Of the women who did take a progestogen, it

was a synthetic that is structurally different from the body's endogenous progesterone. Similarly, the estrogen administered in the WHI study was not bio-identical and structurally different from the body's endogenous estradiol. This is also true for the majority of women in the One Million Women study who took a non bio-identical estrogen. We have reviewed the literature on the use of non bio-identical estrogens and found other studies that confirm the potential toxicity and increase in risk of these compounds for the female body. Therefore, In accordance with the recommendations of an increasingly growing number of medical societies, **we do not recommend the use of non bio-identical estrogens and progestogens for treatment of ovarian deficiencies**, except when no other possibility exists such as for the use in birth-control where contraceptive pills with synthetically modified female hormones are often the only alternative. This is also true for the treatment of menorraghia where synthetic progestogens may have a better effect.

If the use of the compounds that are structurally different from the body's own hormones is not recommended, then what is the alternative? In contrast to recommendations of some other societies not to use female hormones in postmenopausal women, or to use them for a limited time (a maximum of five years after menopause), **we recommend the use of female hormones before and after menopause for as long as necessary,** as long as the patients remain deficient in these hormones and no new events occur that would contraindicate their use.

However, **we recommend the use of bio-identical hormones, estrogens, in particular estradiol and estriol, and of bio-identical progesterone** for the correction of ovarian deficiencies, except for specific cases as those mentioned above, where for limited periods the use of non bio-identical hormones may work better. The scientific literature we reviewed on bio-identical hormones is clearly more reassuring than that on non bio-identical ones. The route of administration is also of considerable importance. The transdermal route is safer for estradiol administration than the oral route. No increase of the incidence of breast cancer has to our knowledge be found with the use of transdermal gel of estradiol, while the addition of bio-identical progesterone may reduce the incidence as reported in at least two studies. In the One Million Women study the use of transdermal estradiol nonsignificantly increased the incidence of breast cancer, but the increase concerned only a very small subgroup (about 300 women out of a total of more than one million participants). Moreover, nearly all these women were using transdermal patches of estradiol, a delivery system that may be far from optimal as it provides fluctuating serum levels of estradiol levels that make it difficult to correctly balance the estradiol with progesterone.
In one Australian study the increased risk of breast cancer found in women who used non bio-identical hormones such as those in the WHI and One Million Women study disappeared in women who received testosterone combined to estrogen-progestogen preparations. The observation needs confirmation, but it does give some support to physicians who opt to correct ay androgen deficiency in female patients who take female hormone replacement therapy.

May women who have had breast cancer, take estrogens and progesterone? The general trend nowadays is to avoid administering female hormones to women who have had breast cancer. The recommendation may not be justified for women with total surgical removal of the cancer. In all studies, except one, we reviewed on breast cancer patients treated with female hormones, no increase in risk was reported. On the contrary, female hormone replacement generally was associated with a considerable reduction of the risk of breast cancer recurrence and mortality in most studies or with no significant difference in some studies. However, it is still too soon to recommend the intake of female hormones by all women with breast cancer and ovarian deficiency. It is perhaps too soon yet to recommend the treatment for women who had their tumor surgically and totally removed and who seem to be cured. We recommend that large-scaled controlled studies should be urgently undertaken, in order to check safety and find for which women who had breast cancer, sex hormone therapy is best indicated.

Whatever the choice of female hormones, we recommend the physicians to **carefully and regularly follow-up** all female patients undergoing female hormone therapy**, including submitting them to regular cancer screening**.

In conclusion, we recommend pohysicians to **correct any female hormone deficiency in female patients with preferably transdermal estradiol and oral, or even better vaginal, progesterone** under the condition the female patient is carefully and regularly followed, including cancer screening.

Consensus # 3 : Cortisol Replacement Therapy in Milder Forms of Adrenal Deficiency in Adults

December 9, 2005

After a literature review and discussions with physicians from all over the world who are well-versed in treating patients with endocrine abnormalities, we, the members of the Consensus Group of Experts of the International Hormone Society, think the time is ripe to reconsider current concepts on glucocorticoid treatment of adrenal deficiency, and in particular to consider treating cortisol deficiency in adults, not only those affected by severe deficiencies, but also those that suffer from milder forms.

We acknowledge and approve **the worldwide consensus** that has been reached on **glucocorticoid treatment of adults suffering from severe cortisol deficiency**. Generally, in such conditions there is a total or near total cortisol deficiency due to a total or near total removal or inactivation of the adrenal glands, the endocrine glands that secrete cortisol.

We think that the amount of supporting data on cortisol's beneficial effects and the data on eventual side-effects are now sufficient to **extend** the recommendation of cortisol treatment to patients with **milder forms of cortisol deficiency.** Among the milder deficiencies, those forms that may appear in adults during the aging process, due to a progressive deterioration of the pituitary-adrenal axis, are included.

The evidence is that cortisol is not only essential for survival of severely cortisol depleted patients, but also **essential for the mental and physical health of all adults**, including the elderly. An adequate amount of cortisol is essential for multiple organ systems: the brain, skin, joints, muscles, the digestive tract, the immune system, and the cardiovascular system. Cortisol deficiency is often associated with fatigue, poor stress tolerance, confusion and malaise, summarized as a diminished quality of life with severe impairment in patients who are more sensitive to the deficiency. Glucocorticoid treatment has, on the other hand, been reported to improve the quality of life, the mind and mood of patients. Adverse physical consequences of cortisol deficiency range from feeling weak to the often debilitating effects of inflammatory diseases (rheumatoid disorders, gastro-enteritis, colitis, immune disorders, allergies, etc.) and even to the increase in mortality of high-risk conditions such as septic shock. The milder forms of a cortisol deficiency can still be harmful and can pose more serious health issues than previously thought.

As cortisol and other glucocorticoids have been associated with serious side effects, we do, however, recommend that physicians treat patients for cortisol deficiency by observing safety guidelines. Immune system suppression, osteoporosis, an increase in bruising, weight gain, skin atrophy, high blood pressure, excessive adrenal suppression, and a Cushingoid physical appearance, are some of the possible adverse consequences. We estimate that in general the adverse consequences attributed to glucocorticoids are due to excessive doses and treatments that are not well-balanced with other hormones, in particular the anabolic ones. Anabolic hormones can block the disproportionate tissue breakdown caused by excessive amounts of glucocorticoids. In some cases of cortisol deficiency, in particular for the patients with an extreme deficit such as Addison's disease, the use of synthetic derivatives of cortisol may be less effective (and associated with side effects) than the use of cortisol that is identical chemically to our endogenous cortisol (hydrocortisone).

Diagnosis of cortisol deficiency

1. Laboratory Testing – *At least two of the below-mentioned tests should be ordered based on the type of adrenal deficiency suspected.*
Blood tests:

- Serum total cortisol and (calculated) free cortisol, and transcortin (CBG) in the morning and late afternoon.
- Serum ACTH
- ACTH stimulation test with a dilute formulation of 1.0 micrograms rather than 250 micrograms.

24-hour Urine Test:

- Urinary cortisol and its metabolites, 17-hydroxysteroids using gas chromatography.

It is helpful to test for levels of anabolic hormones such as

- DHEA sulphate

Other blood tests:

- Serum Estradiol, SHBG, androstanediol glucoronide, IGF-1, IGF-BP-3, freeT3, freeT4 (as cortisol may lower the conversion of T4 to T3, and cortisol deficiency does exactly the opposite); urinary 17-ketosteroids (gas chromatography), aldosterone, 6-sulfatoxy-melatonin, growth hormone,
- Sodium and potassium (checking the mineral corticoid effects of cortisol)

2. Interpretation of laboratory tests

A certain number of patients may show clinical signs and symptoms of cortisol deficiency, and test values that are in one or more tests borderline low for cortisol, close to the lower reference value (2 standard deviations from the mean of a laboratory designated population). In such borderline patients, a therapeutic test may be warranted. The patient can be given cortisol in a combination with a safe anabolic hormone, at least DHEA (Dehydroepiandrosterone) to assure a correct catabolic-anabolic balance. The same balance is also needed in the patients with a more severe cortisol deficiency.

Treatment: Daily doses:

1. Milder cortisol deficiencies: should be treated with

- 15 to 30 mg of hydrocortisone (or 2.5 to 7. mg of prednisolone, or 2 to 6 mg of methylprednisolone) per day in women
- 20 to 40 mg of hydrocortisone (or 2.5 to 7. mg of prednisolone, or 2 to 6 mg of methylprednisolone) per day in men

2. More severe cases: need generally 30 % higher doses than the maximum useful for milder deficiencies.

Tips: Men need higher doses because their adrenal glands secrete approximately 50 % more cortisol than those of women. Only about half of the doses are absorbed through the intestinal tract. For stress related conditions, such as infections, surgery, severe emotional distress, etc., the doses should be temporarily increased.

Precautions: as glucocorticoid treatment may further aggravate any existing deficiency in thyroid hormones, aldosterone, and adrenal androgens (such as DHEA), we recommend that the physician correct any of these deficiencies.

In conclusion, no convincing data have been found against the use of cortisol or other glucocorticoids in adults suffering from mild cortisol deficiency. On the contrary, reports of maintaining cortisol deficiency in patients results in adverse effects on their health that can be avoided by treating with physiologic doses of cortisol.

Therefore we recommend treating patients **with low cortisol level and/or low 17-hydroxysteroid levels. Cortisol or other glucocorticoid treatments should be restricted to physiological amounts and in most cases balanced with anabolic hormone supplements** (if these levels are low), and be monitored carefully by regular check-ups.

Consensus # 4 on **"DHEA Therapy of Adrenal Androgen Deficiency in Adults**"
December 11, 2005

After a literature review and discussions with physicians from all over the world who are well-versed in treating patients with endocrine abnormalities, we, the members of the Consensus Group of Experts of the International Hormone Society, think the time is ripe to consider treating DHEA deficiency in adults.

Up to now, no international society has officially acknowledged the need and value of treating deficiencies in adrenal androgens with DHEA. Some, rare, national institutions in the world have published reports with prudent and reserved opinions on DHEA treatment. In general, these reports concluded that the time was not yet ripe to supplement patients with DHEA. They were of the opinion that the scientific literature on DHEA was too scarce and its efficacy was uncertain. They also expressed a concern that DHEA supplementation might be harmful to humans with the potential of reducing HDL cholesterol and increasing the incidence of genital cancer.

We have carefully reviewed the literature on DHEA, and read and discussed the negative institutional reports, and have not found solid scientific evidence to support the view that DHEA would present a significant danger.

We acknowledge and approve the undertaking of an increasing number of studies where men and women with severe adrenal deficiency are being treated with DHEA in addition to glucocorticoids. In these studies on severely DHEA deficient patients, DHEA supplementation significantly increases mental and physical health. In adults with a less severe DHEA deficiency such as "normal" elderly persons, the effects of DHEA have not always been as evident. In some reports only moderate effects, of borderline significance, were observed with DHEA supplementation, and in some rare studies no improvements were noted.

The fact that no improvement or only a moderate improvement was seen with the addition of physiological doses of DHEA in patients with mild deficiency in some studies, does not imply that DHEA treatment is worthless or dangerous. Indeed, the duration of treatment of many of the "no significant effect of DHEA"- studies was often too short to show any effects (several negative studies on DHEA's effect on memory were of two weeks or less duration for example). Besides the minority of negative studies, a greater number of positive studies with significant beneficial results with the use of DHEA in humans can be found. In addition, the overall conclusion of the positive studies is that DHEA, the most abundant hormone in our blood, is one of the safest of all hormones. Controlled studies of DHEA treatment concluded that no harmful side effects were seen with physiologic doses and that if any side effects were found, they generally were due to excessive doses. The most typical signs of DHEA were signs of excess androgens such as oily skin and hair.

In many studies with DHEA treatment significant beneficial effects were obtained on bones, skin, the immune system, as well as on serum glucose, insulin and lipid levels, etc. Positive effects were also noted on mental and emotional issues such as quality of life, fatigue, and depression. In animal and some human studies the effects of DHEA treatments included, among others, a beneficial effect on cardiovascular diseases, diabetes, obesity, and osteoporosis and even in animal studies agaInst cancer .

In the opinion of the members of the IHS's consensus group, the following arguments support DHEA treatment of deficient adults:

- DHEA is natural to humans and in fact is our most abundant hormone. DHEA is fully adapted for our bodies and under stressful conditions it is greatly increased.
- DHEA has several significantly beneficial effects on mental and physical health parameters, and against the development of age-related diseases.
- DHEA is relatively safe.
- Pharmaceutical grade-DHEA can be purchased in pharmacies in many countries.
- DHEA is relatively inexpensive.

Therefore, we estimate that DHEA treatment of adults, who have low DHEA sulphate levels, is justified.

To increase the safety of DHEA treatment, we recommend that physicians do a **regular check-up** of their patients, including a good clinical interview and examination, and laboratory tests every six to twelve months depending on the patients' needs. The Consensus Group of Experts of the International Hormone Society concludes that it is essential to do a regular cancer screening, including breast and prostate examination, every six months to once a year, including an ultrasound examination or mammography when necessary. Although DHEA has not been shown in a valid human study to promote prostate cancer, there are two studies where a high serum DHEA sulphate level was found too be significantly and positively associated with an increased risk of breast cancer in postmenopausal women, while in premenopausal women a "safe" inverse relationship is found. For this reason, the IHS consensus group proposes the avoidance of DHEA treatment in postmenopausal women without safe female hormone replacement therapy.

In our experience, the best method to diagnose a DHEA deficiency is to **check the serum levels of DHEA sulphate and the urinary excretion of the 17-ketosteroid DHEA metabolites** (measured by gas chromatography). Safe doses for DHEA treatment are the physiological doses, namely between **20 and 60 mg per day for men**, and between **5 and 30 mg per day in women**.

In conclusion, we have found no convincing evidence against the use of DHEA in adults presenting with low DHEA levels, except in cases of postmenopausal women who are not taking female HRT. On the contrary, enough beneficial effects have been reported to recommend the use of physiological doses of DHEA to correct well–diagnosed DHEA deficiencies in adults in a program with regular follow-ups.

The addition of a physiological dose of DHEA may be particularly justified when glucocorticoids are used in order to safely neutralize any excessive catabolic effects of glucocorticoids as shown in animal studies.

Consensus # 5 on **"Growth Hormone Therapy of Milder Forms of Growth Hormone Deficiency in Adults**"
September 29, 2005

After having reviewed the scientific literature and exchanged experiences between physicians from all over the world and who are competent in hormone therapies, we, members of the Consensus Group of Experts of the International Hormone Society, think the time is ripe to consider treating growth hormone deficiency in adults, not only severe, but also milder forms.

We acknowledge and approve **the consensus** that has been reached in many countries for **growth hormone treatment of adults suffering from severe growth hormone deficiency** after severe head injury, surgery or radiation of tumours in the pituitary region. Generally, in such conditions there is a history of removal or severe inactivation of the pituitary gland, the endocrine gland that secretes growth hormone.

We think that the amount of supporting data on growth hormone's beneficial effects is now sufficient to **extend** the recommendation of growth hormone treatment to patients with **milder forms of growth hormone deficiency** such as those that gradually appear in adults of increasing age, because of the progressive age-related decline of the pituitary gland.

The evidence is that growth hormone is not only essential for the growth of children, but also **essential for mental and physical** (in particular bone, muscular and cardiovascular) **health of adults**, including elderly persons. Growth hormone deficiency is often accompanied by fatigue, anxiety and depression, evidenced by a poor quality of life and is often severe in persons whose growth hormone deficiency started in late adulthood, as confirmed in many studies. On the other hand, growth hormone treatment has been reported to considerably improve the quality of life, moods and sleep.

Not treating the milder forms of growth hormone deficiency in elderly persons may, much more seriously than thought before, adversely affect human health. The increased atherosclerosis and mortality, especially cardiovascular, that are found in individuals who suffer from severe growth hormone deficiency, and that are partially or totally reversed with growth hormone correction, make it likely that such problems also occur to some degree in patients with more moderate deficiencies, and may likewise be improved by growth hormone injections.

We recommend that physicians do a **regular check-up** of any patient treated with growth hormone. This includes doing a good clinical interview and examination, and laboratory tests every two to twelve months depending on the patient's needs. A regular cancer screening, including breast and prostate examination, every six months or once a year eventually completed by ultrasound examination, and whenever necessary mammography, is essential to the Consensus Group of Experts of the International Hormone Society.

Concerning an eventual increase in risk of certain cancers with growth hormone, the data is conflicting. In some investigations protective effects against cancer are reported, while in other studies increases of risks for patients with high serum IGF-1 and low serum IGF-BP-3 were found. The most serious study done on patients treated with growth hormone compared to a group of untreated growth hormone-deficient adults, showed an approximate 50% decrease in cancer incidence and cancer mortality. Actually, there is **no convincing evidence to believe there is an increase in cancer risk in most individuals treated with growth hormone**. Nonetheless, we recommend that physicians administer only physiological doses that correct the deficiency, thereby carefully avoiding over treatment. By following this principle, the physician further increases the safety of the treatment.

After thoroughly reviewing the report of two studies where **critically-ill patients** encountered a doubling of the mortality rate with growth hormone compared to a similar group of critically-ill patients without growth hormone, we can say the following: This "negative" report forms an exception. The critically ill patients clearly received supra-physiological doses: 10 to 50 times higher than physiological. At physiological doses a 20 to 40% reduction of cortisol serum levels and urinary 17-hydroxy-steroids, the cortisol metabolites, has been observed. At supra-physiological doses the cortisol-reducing effect of growth hormone, that in normal people is a way to prevent any excess in cortisol, more than probably weakens the critically-ill patient who crucially needs high doses of cortisol for his survival. The increased mortality of the treated patients was due to infections and poly-organ failure, conditions typical of severe adrenal failure. The results of the study are probably due to over treatment and possibly also overlooking of glucocorticoid supplementation, not to growth hormone per se. The use of physiological doses of growth hormone and more than probably glucocorticoid supplementation in the critically-ill patients would have been much safer and might have reduced mortality rather than increase it.

In conclusion, no convincing data against the use of growth hormone in adults suffering from low growth hormone or IGF-1 levels have been found. On the contrary, **adverse symptoms of persisting low growth hormone levels** have been abundantly reported, as has their improvement or disappearance with growth hormone treatment.

We therefore recommend treating with **growth hormone in cancer-free adults with low growth hormone and IGF-1 levels. Growth hormone treatment should be restricted to physiological doses and be** accompanied by careful and regular check-ups.

Consensus # 6 on **"Melatonin Treatment of Melatonin Deficiency**"
December 13, 2005

After a literature review and discussions with physicians from all over the world who are well-versed in treating patients with endocrine abnormalities, we, the members of the Consensus Group of Experts of the International Hormone Society, think the time is ripe to consider treating Melatonin deficiency in adults.

Up to now, no international society has officially acknowledged the need and value of treating pineal gland deficiencies with melatonin. In some countries melatonin is not readily available, not even by prescription, because of government restrictions or lack of attention and in other countries melatonin can be bought easily, over the counter. Controversy exists about melatonin's efficacy. For some, it is an essential hormone with major effects, for others it is a useless placebo. In striking contrast with this controversy is the almost complete **unanimity on melatonin's safety** among researchers and physicians who are experienced with melatonin in animals and humans. Melatonin appears to be so safe that has not been possible so far to determine a lethal dose for melatonin. Even extremely high doses do not kill animals, nor do they cause dangerous effects.

We have carefully reviewed the literature on melatonin, and read and discussed the negative, as well as the positive reports, and observe that in the majority of studies, treatment with melatonin appears to produce significant beneficial effects. Studies on melatonin's inefficacy are rare, in particular on melatonin's sleep-inducing effects. The evidence is significant for the beneficial effects of melatonin on sleep, free-radical scavenging, glucose metabolism, bones, the cardio- and cerebrovascular systems (including the positive effects on serum lipids), several circadian rhythms (from the sleep-wake cycle to various hormone rhythms), and the benefit of limiting jet lag.

The controversy on melatonin's sleep efficacy may be due to a misunderstanding. We reviewed nearly 200 studies on the relationship between melatonin and sleep (including a little less than 100 placebo-controlled studies). In the vast majority of the studies significant beneficial effects on sleep were found. Rarely have there been reports on significant beneficial effects of melatonin on the essential sleep stages (slow wave sleep and rapid eye movement). Melatonin appears to work differently. It induces sleep, shortening the time it takes to fall asleep, with a faster onset of deep sleep (slow wave sleep) and REM sleep. Furthermore, melatonin relaxes the muscles and nerves by stimulating the parasympathic system. This facilitates sleep, improves sleep quality and enhances recovery.

The members of the consensus group of the International Hormone Society (IHS) find no scientific or medical reason to ban or excessively restrict the use of melatonin. Even though, this is the case in some countries. The relative safety of melatonin should reassure authorities to accept **the use of melatonin, at least under doctors' prescription and supervision**. Arguments do exist that validate the sale of melatonin over-the-counter without a doctor's prescription, in particular its usefulness, great safety and ubiquity in nature (it is found in every living being analyzed up to now for the presence of melatonin: from bacteria to plants and animals). If melatonin is authorized over-the-counter, we do recommend that small doses be mandatory. Most preparations now on the market are sold in tablets or capsules containing pharmacological doses, apparently useful to combat diseases such as cancer or acute ischemia. Tablets or capsules of 0.1 to 0.3 mg per day provide melatonin levels in the physiological range. Physiological doses and concentrations may be better adapted to treat a simple melatonin deficiency such as the one that is found in aging adults.
As melatonin may reduce cortisol activity, we recommend starting melatonin supplementation at a low dose (0.1 to 0.3 mg sublingual melatonin per day before bedtime, sometimes lower).

In the opinion of the members of the IHS's consensus group, the following arguments support melatonin treatment of deficient adults:

- Melatonin is natural to humans and is a dominant hormone at night. Melatonin is fully adapted for our bodies.
- Melatonin has several significantly beneficial effects on mental and physical health parameters, and against the development of age-related diseases.
- Melatonin is relatively safe.
- Pharmaceutical grade-melatonin can be purchased in pharmacies in many countries.
- Melatonin is relatively inexpensive.

Therefore, we believe that melatonin treatment of patients with low urinary 6-sulfatoxy-melatonin levels or salivary nighttime melatonin, is justified.

In our experience, the best method to diagnose a melatonin deficiency is to **check the urinary excretion of the 6-sulfatoxy-melatonin,** the principal metabolite of melatonin, or, eventually, nocturnal saliva levels of melatonin.

In conclusion, we have found no convincing evidence against the use of melatonin in patients with low melatonin levels and with complaints of the symptoms of a melatonin deficiency (difficulties in sleep onset, tensed muscles at night, etc.). On the contrary, considerab**le evidence supports the beneficial effects of the use of physiological doses of melatonin in patients with melatonin deficiency i**n a program with regular monitoring.

Consensus # 7 on **"Testosterone Therapy of Partial Androgen Deficiency in Men"**
December 5, 2006

After a careful literature review and discussions with physicians from all over the world who are experienced in treating endocrine disorders, we, the members of the Consensus Group of Experts of the International Hormone Society, think it is time to treat **testosterone deficiency** in aging men.

Since the chemical structure of testosterone and a method to synthesize it were discovered in the 1930's, a significant number of studies have shown testosterone and other androgens to be essential hormones for optimum male health. The level of bio-available testosterone, along with levels of other androgens, declines as men age. Androgens decrease gradually and their decline is associated with various signs and symptoms such as fatigue, depressed mood, loss of sexual desire, impotency, loss of muscle mass, increase in fat mass, and many other manifestations generally attributed to aging. Persistent androgen deficiency may increase the risk of age-related conditions such as obesity, diabetes and cardiovascular disease. Although this age-related androgen decline does not affect men as brutally as menopause impacts women, it may nonetheless impair a man's quality of life, his health, and perhaps his lifespan. The age-related decrease of androgen activity in men is variously known as andropause, male climacteric, PADAM (partial androgen deficiency in aging men), ADAM (androgen deficiency in aging men), age-related hypogonadism, male menopause, and penopause.

Men are treated much less frequently for testosterone deficiency than postmenopausal women are treated with female hormones for ovarian deficiency. Men endure a pre-andropause progressing to andropause, just as women undergo perimenopause, followed by menopause. This concept of a male equivalent to ovarian deficiency and failure is currently not fully accepted, yet we see no valid reason for the distinction.

Opponents of treating age-related androgen decline cite rare, conflicting, and often weak studies. Some of these studies show no significant difference in androgen levels of young and old men, others suggest that testosterone might increase the proliferation of prostate cancer (at least in vitro), and others suggest that testosterone replacement at low doses does not have significant effects. These atypical studies are generally contradicted by a larger number of studies that show the opposite, and, in particular, a neutral or protective effect of testosterone against prostate cancer.

A global review of the literature does not provide any conclusive evidence that treatment with testosterone or its derivatives increases the risk of prostate cancer in vivo. On the contrary, men with low testosterone levels appear to have a higher risk of more aggressive prostate cancer, atherosclerosis and poor quality of life. Moreover, prostate cancer patients whose androgen levels are drastically lowered by anti-androgen therapy, which does not appear to increase the survival in these men.

IHS recommendation for Diagnosis of Partial Testosterone Deficiency in men: To diagnose a mild to moderate testosterone insufficiency, physicians should do a thorough clinical evaluation noting all the suggestive signs and symptoms. These include a loss of libido in varying degrees, impotence, fatigue, depression, sarcopenia, abdominal obesity and gynaecomastia. Laboratory tests are also essential. We recommend testing the patient for total and free testosterone, SHBG (sex hormone binding globulin), dihydrotestosterone or androstanediol glucuronide (the major metabolite of dihydrotestosterone), FSH

and LH. It is also important to test for serum estradiol and possibly estrone because high levels of estrogen can block androgen activity. Testing for prolactin is indicated when hyperprolactinemia is suspected, as this may block the action of male hormones.

IHS recommendation for Treatment of Partial Testosterone Deficiency in men: Because of its adverse impact on health, we recommend that physicians treat any persistent testosterone deficiency, even if moderate, with androgens, preferably testosterone or a close derivative, unless there is a contraindication. All men who live long enough can expect to need supplemental testosterone. Significant declines usually occur between the ages of 30 and 50, although there are exceptions in which supplementation may be needed earlier or later.

Only physiological doses of testosterone or another suitable androgen should be given, in doses that bring testosterone levels into the reference range of 21-30, or perhaps 31-40, year old men. The best routes of testosterone delivery appear to be via a transdermal gel or intramuscular injections.

Caution: Testosterone can convert into estradiol, high levels of which have adverse effects in men. These include gynecomastia, benign prostatic hypertrophy (in particular prostate stromal hyperplasia), and possibly myocardial infarction. Therefore, we recommend that physicians avoid excess serum estrogen levels during testosterone treatment. Dietary measures, such as avoiding daily alcohol and caffeine intake, can help keep estrogens low. Avoiding obesity is also important because fat tissue, rich in the enzyme aromatase, catalyzes the conversion of testosterone to estradiol. When these measures are not adequate, the use of an aromatase inhibitor or progesterone may be indicated. Progesterone enhances the conversion of estradiol, the most potent estrogen, into estrone, a weak estrogen.

Contra-indication: Prostate cancer may constitute a major contra-indication. However, there appears to be very little solid supporting evidence, despite the body of research on this issue. Some studies support the conclusion that patients with prostate cancer, who also suffer from a severe androgen deficiency that impairs their health and quality of life, may have benefits from low dose testosterone treatment that outweigh the potential risk of stimulating the prostate cancer.

In **conclusion**, we have found no compelling evidence against the use of physiological doses of testosterone in adult men presenting with borderline to overtly low androgen levels, particularly testosterone. On the contrary, as such replacement therapy may offer significant beneficial effects, we **recommend the use of physiological doses of testosterone,** or one of its close derivatives, to **correct well–diagnosed testosterone deficiencies in men** in a program where they are regularly followed.

Consensus # 8 on **"Testosterone Therapy of Testosterone Deficiency in Women**"
December 5, 2006

After a literature review and discussions with physicians from all over the world who are well-versed in treating patients with endocrine disorders, we, the members of the Consensus Group of Experts of the International Hormone Society, think the time is ripe to consider **treating testosterone deficiency in aging women**.

Studies: Since the 1940's reports have been published on testosterone treatment of women. In early smaller, often anecdotal case studies, testosterone had been reported to exert progesterone-like activity on the endometrium (reduction of menorrhagia), fluid retention (decreased swelling, including of breast tenderness) and on the nervous system (stimulation of the parasympathic system, calming down the sympathic system that can be excessively activated by estrogens). Beneficial actions in a wide variety of conditions such as loss of libido and sexual sensitivity, vulvar sclerosis, enuresis, sarcopenia and breast cancer (testosterone was shown to counter the development of malignant breast tumors) have been published. Testosterone was even used as a last chance treatment of severe depression in postmenopausal women. In the earliest reports excessive doses were a little too often administered allowing some virilizing side effects to be reported. Nowadays, better structured and larger observational studies and more credible double blind placebo studies have confirmed the positive effects of low doses of testosterone therapy in women, in particular on the mood, quality of life, sexuality, bone density, muscle mass. In several studies higher levels of testosterone and related androgens have been associated with lower degrees of atherosclerosis. One Australian study showed that postmenopausal women had no significant increase in risk of breast cancer if they took testosterone treatment in addition to therapy with female hormones similar to those used in the Women's Health Initiative study (the well-known double –blind placebo-controlled study where (female) hormone replacement therapy was shown to increase the risk of breast cancer). Thus, well-balanced testosterone therapy may have many beneficial effects on women.

Age-related decline: The serum levels of testosterone generally decrease with age in women. In one study the mean level of testosterone in women of an average age of 40 years was more less than half of that of women of an average age of 21 years. The decline of the serum level of testosterone occurs in women at a faster speed than in men, because most of a woman's testosterone is derived from DHEA (dehydroepiandrosterone), the major adrenal androgen, which's level quickly decline after age 30. Consequently, the chances that a women suffers from a testosterone deficiency that requires treatment, quickly increases with advancing age.

Current state of evidence: For the International Hormone Society, the current state of evidence is sufficient to recommend testosterone treatment of testosterone deficiency in women.

IHS recommendation for Diagnosis of Testosterone Deficiency in women:

Interpretation of laboratory tests: When does a woman have a testosterone deficiency? For the consensus group of the International Hormone Society, a testosterone deficiency occurs when women experience signs and symptoms of testosterone deficiency, and have lower levels of testosterone and one or more of its metabolites. What are low levels? Low testosterone levels are borderline low (low, but still inside the reference range) or overtly low levels of testosterone (values beneath the lower reference values of the laboratory) in female patients who clinically suffer from an androgen deficiency syndrome with signs and symptoms of testosterone deficiency. What are the best androgen reference ranges for women? For the International Hormone Society, as most elderly persons have more or less the same body size, weight and volume as when they were young, the best reference range is that of young adults, 18 to 30 years, ages where a woman's body fully develops and adapts to "optimal" levels of hormones.

Diagnose of testosterone deficiency: The IHS recommends physicians to make an adequate clinical evaluation and collect the symptoms and signs suggestive of testosterone deficiency (such as complaints of loss of sexual appetite, anorgasm, fatigue, depression, sarcopenia, abdominal obesity, osteoporosis, etc.) to diagnose mild to severer degrees of testosterone deficiency in women. The diagnosis is then confirmed by laboratory tests. We recommend to test the female patient for total (and free) testosterone, SHBG (sex hormone binding globulin, the major plasma transporting protein of testosterone and dihhydrotestosterone), dihydrotestosterone or preferably androstanediol glucuronide (its major metabolite), LH (luteinizing hormone), and also, as high levels of estrogens may block androgen activity, serum estradiol, and possibly estrone. Checking the levels of DHEA sulfate, the main provider of testosterone, is also valuable. 24-hour urine analyses of testosterone or its two 17-ketosteroids, androsterone and etiocholanolone (by gas chromatography), may provide additional information.

IHS recommendation for Treatment of Testosterone Deficiency in women: Because of the discomfort and adverse health consequences of testosterone deficiency, we recommend physicians to treat with **testosterone** or one of its close derivatives any persistent testosterone deficiency in adult female patients, even moderate degrees, if no contra-indication is found. Basically, all women who live long enough may expect to be in need of testosterone supplementation. .

Only small physiological doses of testosterone or of another suitable androgen should be administered, doses that bring the testosterone levels back into the reference range of 21-30 or perhaps 31-40-year olds. In general, the doses of testosterone that are given to women are approximately 20 to 30 times lower than what is given to testosterone-deficient men as the levels and production of testosterone are 20 to 30 times higher. The best routes of administration of testosterone in women are the transdermal route (by means of a gel) and more rarely intramuscular (by injection) route. Some oral preparations ma

be justified in certain cases, but physicians should know that oral micronized testosterone e.g. is greatly broken down by the liver after intestinal absorption and works only at very high doses.

IMPORTANT CAUTION: In almost all cases, **testosterone** should **solely** be given **to women** who **simultaneously** receive **estrogen and progesterone treatment in adequate doses**, otherwise virilization signs may occur, even at physiological doses.

Contra-indications:

- Severe hirsutism
- Absence of estrogen-progesterone treatment
- Pregnancy

Conclusion: We have found no convincing evidence against the use of physiological doses of testosterone in adult women presenting borderline or overtly low androgen levels, and in particular low testosterone levels. On the contrary, sufficient significant beneficial effects have been reported to **recommend the use of physiological doses of testosterone** or one of its close derivatives to **correct well–diagnosed testosterone deficiency in women** in a program with regular follow-ups. Testosterone treatment should be reserved to women who take at the same time a well-balanced estrogen and progesterone therapy in order to avoid virilism.

Consensus # 9 on **"The treatment of clinically hypothyroid, but biochemically euthyroid patients"**
April 12, 2007

After an extensive literature review and discussions with physicians from all over the world who are well versed in treating patients with endocrine abnormalities, we, the Consensus Group of Experts of the International Hormone Society (IHS), think there is enough clinical and theoretical evidence to expand the application of thyroid treatment beyond the current conventional parameters.

Is the diagnosis of hypothyroidism based on biochemical evaluation or clinical evidence?

There is a controversy between groups of physicians. One group essentially diagnoses hypothyroidism solely with laboratory tests, while the other relies more on clinical factors. Solid scientific evidence does not support the idea that the diagnosis of hypothyroidism can or should only be based on laboratory tests. This would imply that hypothyroidism only exists in patients with a serum TSH beyond the actual upper reference range, and serum thyroxine (T4) and triiodothyronine (T3) levels below the lower reference range, and neglects the clinical signs and symptoms.

The IHS's position is intermediate. The decision to initiate (thyroid) therapy should be based on both clinical and laboratory findings, and not solely on the results of a single test, exactly as expressed in the medical journals *JAMA* and *Thyroid* presenting the American Thyroid Association's guidelines for use of laboratory tests in thyroid disorders[1]. The diagnosis of hypothyroidism is further substantiated when treatment results in the relief of clinical signs and symptoms and the laboratory tests are improved.

Clinical information is essential in diagnosing a hormone deficiency. The clinical data needed to make a diagnosis of hypothyroidism include the physical and emotional complaints of patients, physical signs, personal and familial medical histories suggestive of a thyroid deficiency and the existence of a thyroid gland abnormality (nodule or goiter) and/or autoimmune thyroiditis.

The following evidence supports the existence of patients who are **clinically hypothyroid, but mistakenly considered biochemically euthyroid,** and who may benefit from thyroid treatment:

1) **The normal reference ranges for thyroid tests are too broad and ignore specific individual reference ranges.**

- **Excessively broad reference ranges:** Large reference intervals may include serum levels of T3, T4 and TSH that are compatible with thyroid dysfunction, in particular, with various degrees of mild thyroid failure. The experts on the consensus panel did not find any studies proving that the normal thyroid test reference ranges discriminate adequately between hypo-, eu- and hyperthyroidism. On the contrary, we found studies whose data questioned the usefulness of these reference ranges, in particular, for serum TSH, T3 and T4. The data from these studies support the use of narrower ranges for these serum tests. The broader reference ranges include levels that may be consistent with thyroid dysfunction, especially in its milder forms. This is not surprising, as the reference ranges of a test are not values indicative of health, but merely values found in 95% of a population, generally the population of patients going to the laboratory. Levels compatible with both health and (thyroid) disease may be included.

- **The TSH reference range:** The difference between the upper and lower ends of the reference range is more than 20-fold (0.2-4.1 mIU per liter).

    - In several studies, a serum TSH above 1.5 or 2 mIU per liter has been linked with increased hypothyroid-associated lipid and inflammatory pathologies (such as higher serum levels of homocysteine, cholesterol and highly sensitive CRP). These higher TSH levels have also been linked with coronary and vascular abnormalities (such as higher coronary artery diseases scores, increased risk of multi-vessel disease, increased arterial stiffness), lower birth weight, premature birth of children from mothers with TSH above 2, and an increased risk of progression from mild to overt hypothyroidism. Depending on the study, at TSH levels above 0.4 or 0.9 mIU per liter there is an increased risk of thyroid malignancy in patients with morphological abnormalities of the thyroid. The increased risk may be reversed by treatment with thyroid medication. Other disorders have been observed in patients with a serum TSH within the reference range but above the 25th percentile such as a higher risk of severe depression, a poorer response to antidepressants, an increased incidence of somatic disease, a higher body mass index, an increased waist circumference, higher systolic and diastolic blood pressures, and higher serum glucose and triglycerides. Medicating these patients who are apparently in mild thyroid failure and have a high risk of becoming overtly hypothyroid may prevent the important sequellae associated with the progression of hypothyroidism.

    - Other data support the need for improved serum TSH reference ranges. If the serum TSH reference range is based upon a cohort of truly normal individuals, for example, with no personal or family history of thyroid dysfunction, no visible or palpable goiter, no medication use, no thyroid peroxidase antibodies – and with fasting blood samples taken in the morning (6–10 AM) – then the TSH reference range would be 0.4–2.5 mIU per liter. The data support the acceptance of a value below 3 as an upper limit for the TSH reference range. When data for subjects with positive thyroid peroxidase antibodies or a family history of autoimmune thyroid disease are excluded, the normal reference interval becomes much tighter, i.e. 0.4–2.0 mIU per liter.

    - Moreover, the results of several investigations indicate a mean serum TSH of 1.5 mIU per liter for an iodine-sufficient population, demonstrating that the reference range of 0.1 – 5.1 mIU per liter is far too broad.

    - Ethnic differences should also be taken into account: A study has shown the mean TSH level in African-Americans to be 1.18 mU/liter, in contrast to a mean of 1.40 mU/liter in Caucasians, due to the greater frequency of autoimmune thyroid disease in whites. This may have skewed the upper end of the TSH curve (NHANES data). For African-Americans, the TSH reference range is possibly lower than in whites.

- The American Association of Clinical Endocrinologists in 2002 therefore narrowed the serum TSH reference range to 0.3-3.0 mIU/L, lowering the upper reference end to 3. The National Academy of Clinical Biochemistry reduced the upper end of the reference range from 5.5 to 4.1 mIU per liter in 2003. The latter group also stated that "more than 95% of healthy, euthyroid subjects have a serum TSH between 0.4 - 2.5 mIU per liter" and that "patients with a serum TSH above 2.5 mIU per liter, when confirmed by repeat TSH measurement made after three to four weeks, may be in the early stages of thyroid failure, especially if thyroid peroxidase antibodies are detected." In 2003, the consensus panel (Endocrine Society, American Association of Clinical Endocrinologists, and American Thyroid Association) recommended a target TSH range of 1.0 to 1.5 mIU per liter in patients already receiving thyroxine therapy.

- **Erroneously low TSH:** Some patients may suffer from centralized hypothyroidism and will have a low TSH even with a low T4 and a low T3. TSH is currently the primary thyroid screening test recommended. In this population of patients, a hypothyroid disorder will be missed if the low TSH is not followed up by testing free T3 and free T4.

- **Serum free T3 and T4 reference ranges:** The difference between the upper and lower reference ends is more than two-fold (1.8-3.7 ng per liter for free T3 and 0.8-1.8 ng per deciliter for free T4). Although the size of the reference range of free, unbound thyroid hormones is less impressive than that of serum TSH, a patient whose thyroid hormones are borderline high (while still within the normal reference range) may have twice the amount of thyroid hormones in his/her blood than a patient who is borderline low (but also in the reference range of euthyroid patients). If one of these patients is clinically well, then the other probably has a thyroid dysfunction. Patients with a serum T3 in the lower third of the reference range have been documented to undergo more inflammatory processes, to have an increased risk of breast cancer and increased severity of coronary heart disease. Cardiac function has been observed to be decreased in patients with serum T3 in the lower quintile (20%) of the reference range. Studies can be found where lower serum free or total T3 levels within the reference range are correlated with increased severity of illness and/or worse prognosis of a disease, including an increased mortality rate. This is particularly true in cases of myocardial infarction, chronic heart failure and stroke. For serum T4 values within the lower half of the normal reference range in children, there are reports that maximal intellectual development has been impaired, while in the same lower half of the serum T4 range, the rate of depression in patients with Alzheimer's disease appears to be significantly higher. Moreover, a serum T4 in the lower third of the reference range has been associated with increased insulin resistance, premature atherosclerosis (with significantly higher levels of CRP), increased memory loss, and increased mortality. There is enough data to support the need for a profound revision of thyroid hormone reference ranges, where narrower reference ranges with higher lower ends would provide more useful, truly healthy, reference ranges.

- **Need for narrower reference ranges for thyroid tests:** In light of the above data and considerations, the IHS consensus panel of experts stresses the importance of undertaking studies to establish more accurate and narrower reference ranges that reflect true euthyroidism. Narrower reference ranges allow more patients with mild thyroid failure or excess to be detected and treated. Mild thyroid failure is reflected by borderline low serum T3 and T4 and/or borderline high serum TSH. The panel is aware of at least one study in which the treatment of clinically hypothyroid, but biochemically euthyroid, patients was done using thyroxine with no beneficial result. Possibly, the dose or the type of thyroid treatment, namely thyroxine alone, was insufficient to obtain beneficial clinical results. A higher dose or a combined thyroxine-triiodothyronine medication might have been more appropriate. In one study of patients with coronary heart disease, for example, the progression of coronary atherosclerosis over one year was apparent in all patients taking 100 micrograms or less of thyroxine per day, while only one sixth of patients taking 150 micrograms or more had disease progression. Earlier studies have shown significantly better efficacy of combined thyroxin-triiodothyronine medications, compared to thyroxine alone. Improvement was found in such divergent parameters as serum cholesterol, mental and physical symptoms, and, in animals, goiter formation and intracellular triiodothyronine (T3) euthyroidism, to name a few of the possible increased benefits.

- **Specific individual reference ranges:** The optimal reference ranges for an individual can be different from the population reference ranges used by laboratories. Individual reference ranges are usually narrower (for example, 0.5 to 1.5 mIU per liter of serum TSH, rather than 0.2-4.1). Moreover, specific cut-off points between eu- and hypothyroidism may differ from one individual to another. One person may be euthyroid at a serum TSH of 0.5 and hypothyroid at 0.6, while another may be euthyroid at a TSH of 2 and hypothyroid at 2.1. Because of such inter-subject variations, when the results of thyroid tests don't match the clinical picture of thyroid dysfunction, the clinical impression of the experienced physician who has examined the patient should prevail and, if the patient is clinically hypothyroid, a therapeutic trial of thyroid hormones administered, starting at low doses.

- **Tertiles, quartiles or quintiles of insufficiency may have to be considered to diagnosis hypothyroidism, rather than values below or above the reference range.** Serum levels of thyroid hormones in the lower tertile, quartile or quintile, and serum levels of TSH in the upper half of the reference range, have been associated with increased disease and mortality rates, as mentioned above.

2) **Excessive fluctuations of serum levels of T3, T4 and TSH:** Differences up to three-fold in serum TSH and serum T4 have been found within the same individual during a single day. Such dramatic variations put the reliability of thyroid tests in question. At the time of the blood draw a person may be at his/her lowest TSH level, which is well under the upper reference range and looks reassuringly normal, while at other times s/he may be clearly above the upper reference range with a value consistent with subclinical or even overt hypothyroidism.

3) **Thyroid dysfunction at the cellular level, undetectable by classical laboratory tests.** A lack of thyroid activity may also be caused by a decline in the number, availability or affinity of thyroid nuclear cell receptors, in particular of T3. It is known from animal experiments that thyroid (T3) nuclear cell receptors decrease with age. This has also been observed in some human hormone deficiencies such as Addison's disease. A decline in cell receptors cannot be confirmed by classical thyroid tests, as tests for T3 nuclear cell receptors are not currently available in conventional laboratories. The only way to detect insufficient thyroid cell receptors is to evaluate the psychological and somatic effects of thyroid hormones on the body. This must be done through physical examination and interview, checking for hypothyroid signs and symptoms. Useful information might be deduced by testing the peripheral effects of thyroid hormones on serum parameters that increase in proportion to thyroid activity, such as serum SHBG (sex hormone binding globulin), alcalin phosphatase or osteocalcin, and/or that decrease with increasing thyroid function, such as serum total cholesterol. Alternatively, we could test for direct metabolites of T3, namely the T2's (diiodothyronines), but these tests are not yet available. Furthermore, even if thyroid hormone serum levels and receptors are optimal, vitamins, trace elements, minerals or amino acids necessary for enzyme production or function could be deficient, thereby reducing the efficacy of metabolic reactions under control of thyroid hormones.

Thyroid treatment of clinically hypothyroid, though biochemical euthyroid, patients:

If a patient is clinically hypothyroid, presenting with several signs and symptoms of hypothyroidism, but is considered biochemically euthyroid, with low normal laboratory levels of serum T3 and/or T4, and/or high normal serum TSH according to the actual reference range, **a trial of thyroid therapy** may be started to see if the patient's signs and symptoms regress under therapy. Thyroid hormone levels may be considered low normal when in the lower third or half of the reference range, while the serum TSH may be considered high normal when in the upper third or half of the actual TSH reference range (0.2-4.1 mU per liter). In these zones, the patient may be hypothyroid, as demonstrated by several studies in which hypothyroidism is reflected by upcoming disorders such as lipid, vascular, cardiac, insulin and mental disturbances, and cancer and mortality risks, and sharp increases in risk of progression to overt

hypothyroidism, as discussed above. These pathologies suggest mild thyroid failure that may regress under therapy.

We recommend that physicians be careful to exclude, before thyroid intervention, other pathologies that may explain the symptoms. A trial of thyroid hormones should be started at low doses that are progressively increased, and progress should be carefully evaluated, taking care that the patient is not overdosed.

Is there any danger in treating thyroid dysfunction? The most common adverse effect is iatrogenic hyperthyroidism. This is caused either by overdose or intolerance. Intolerance with peaks of T3-hyperthyroidism can be caused by excess conversion of thyroxine (T4) into triiodothyronine (T3), thus accelerating thyroid activity, and is more likely to occur with other hormone deficiencies, such as an adrenal insufficiency (cortisol), a lack of estrogens, and other hormone inadequacies that stimulate the conversion of T4 to T3. Safety can be increased by starting at low doses.

Follow-up on thyroid treatment of clinically hypothyroid, though biochemical euthyroid, patients:

Under treatment, most initially **clinically hypothyroid** (though mistakenly considered biochemically euthyroid) **patients, should have normal lab values (with levels of T3, T4 and TSH inside the reference range when the tests are done more than 9 hours after taking** thyroid medication). They should become *clinically* euthyroid. However, peak serum levels of T4 and T3 may be found that are not representative of the patient's real thyroid activity during the first 9 hours after intake of thyroid medication, and some studies suggest that between 36 and 47 % of patients clinically euthyroid under thyroid therapy have an undetectable serum TSH.

Conclusion: Clinically hypothyroid, though biochemically euthyroid, patients may have a mild degree of thyroid failure. Such patients may benefit from a trial with thyroid hormones starting at low doses that are progressively increased. Before commencing the trial, other pathologies that may be causing the clinical signs and symptoms should be excluded. Careful monitoring is recommended.

[1] *JAMA 1993, 269:2736, Thyroid, 1993; 3 (4): 353-54*

Consensus # 10 on **"The application of hormone therapy by multiple medical specialties"**
April 24, 2007

After an extensive literature review and discussions with physicians from all over the world who are well versed in treating patients with endocrine abnormalities, we, the Consensus Group of Experts of the International Hormone Society, think there is enough clinical and theoretical evidence to expand the use of hormone treatments to other medical specialties than endocrinology.

The medical specialties that should utilize hormone therapies in the treatment of patients

There is no scientific evidence to support the position that endocrine treatments should be exclusively or mainly provided by sanctioned endocrinologists. In fact, limiting hormone treatments to certified endocrinologists may adversely affect the health of patients. As hormones are crucial for the functioning of all cells, tissues and organ systems, treating patients with hormones should be the domain of all disciplines including general medicine, surgery, psychiatry and even ophthalmology.

Additionally, due to the limited number of endocrinologists and the prediction of further shortages, the long wait to see an endocrinologist will be exacerbated. This makes it even more imperative that all physicians be competent and empowered to treat patients with hormone therapies.

Requirements for treating hormone deficiencies or excesses outside the field of endocrinology

1. The patient must have at least one hormone deficiency or excess that necessitates treatment.
2. The physician must be competent and experienced in hormone therapy treatments**.**

The assessment of physician competence in hormone therapy treatments can be determined by several of the following methods:

1) Additional training in treating hormone deficiencies with qualified physicians, via a preceptorship or fellowship, verified by a certificate, diploma or written acknowledgement.
2) Attendance at seminars and conferences on hormone therapy treatments, verified by certificates, CME credits, etc.
3) Several years of experience in treating patients with hormone therapies, verified by examining the medical records of the patients treated
4) Having successfully passed a written or oral exam in endocrinology/hormone therapies
5) Experience as a lecturer or speaker at several conferences and seminars
6) Having publications in the field of endocrinology

Physician competence should be demonstrated in more than one of the above-mentioned ways. Inadequately trained physicians should not attempt to treat hormone-related conditions.

The position of traditional endocrinologists: Most endocrinologists specialize in the management of diabetes and at times thyroid and adrenal problems. As a rule, endocrinologists do not have extensive experience utilizing other hormone therapies. Gynecologists and primary care physicians will generally initiate female hormone replacement, while urologists or primary care physicians treat testosterone deficiencies in men. Even though it is limited, the use of hormone interventions by other specialties is already a reality. Besides expanding the use of hormone therapies to include other medical disciplines, we recommend that endocrinologists receive additional training in providing hormone treatments that are less familiar to them. In this way they would be able to assist physicians from other disciplines in providing more effective treatments of hormone deficiencies. The actual role of an endocrinologist should be enriched to extend beyond the management of diabetes and thyroid/adrenal issues to the role of being an expert advisor on all hormone therapies.

Conclusion: As hormone deficiencies or excesses often have serious adverse effects on patients' quality of life, health, and possibly lifespan, they should be treated as soon as possible, yet as safely as possible. To ensure treatment, patients should have the option of being treated by the physicians they consult, assuming the physicians are competent in treating the patients' conditions. Thus, all medical specialties should include relevant hormone therapies in their training and in the services offered. To ensure safety and competence, evidence-based seminars, training, preceptorships, fellowships and internet education should be organized by medical societies and universities, along with the publication of modified textbooks and hormone therapy handbooks.