Woman's Guide to Hormone Replacement

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About 911BioCare

Our approach to HRT can best be described as "Precision Medicine": each patient deserves a comprehensive evaluation and an individually- tailored treatment regimen that must be continually optimized. We don't subscribe to the "One size fits all" philosophy followed by most physicians when treating hormonal imbalance. Every patient is different and everybody responds differently to the same dosage. We believe the path to optimized health consists of balanced bioidentical hormone replacement, anti-oxidant therapy and proper nutrition & exercise.

The Decline of Hormones with Aging

For more than 50 years women have been receiving estrogen replacement therapy for the abrupt cessation of hormone production known as menopause. Researchers looking for the clues to aging have documented the decline of other important hormones, though such decline is less abrupt and universal than menopause. In the next few sections we will discuss these hormones, their effects, and the rationale behind their use as anti-aging therapies.

What is menopause? Premenopause? Perimenopause? Postmenopause?

The terms describing a woman's transition from having regular periods to none at all can be confusing. You will often see the terms 'premenopausal,' 'menopausal,' and 'postmenopausal' used to denote, respectively, the years before any menstrual irregularities occur, the time when periods have recently stopped for good, and the years after this transition and through the rest of a woman's life. Alternatively, the term 'the climacteric' is used to denote the period when the change in menstruation occurs.

The confusion arises when one looks at the technical definition of menopause: it is the cessation of menses for 12 months. But this is a discrete event that begins and ends on the last day of the twelfth month after a woman's last period. Is a woman postmenopausal on the next day and is she premenopausal the day before? Recent studies have demonstrated that the process of reproductive aging in a woman is more continuous—as are all aging processes—and therefore we prefer a different terminology. But first, how does the menstrual cycle work? In order to understand what happens to a woman's reproductive system as she grows older, it is necessary to review the normal menstrual cycle. The purpose of the menstrual cycle is to prepare the lining of the uterus for implantation of a fertilized egg, the beginning of pregnancy. To accomplish this, the pituitary gland starts to release follicle stimulating hormone (FSH) to stimulate the ovaries to start producing estradiol (the principal estrogen of the menstrual cycle). FSH also recruits one of the remaining immature eggs (called follicles) to mature and become the one that will be ovulated. Estradiol stimulates the cells lining the uterus to proliferate and cause thickening of the uterine wall. In a normal menstrual cycle, this stimulation continues for the next 14 days. Then the increased level of estradiol causes a surge in the pituitary hormone called luteinizing hormone (LH) which causes the release of an egg from an ovary--ovulation. The egg travels down the fallopian tube to the uterine cavity in anticipation of being fertilized. Meanwhile, the part of the ovary from which the egg left (the corpus luteum) starts to produce progesterone which stabilizes the lining of the uterus and readies it for implantation after fertilization. If it is not fertilized, it does not

implant. The corpus luteum stops producing progesterone after about two weeks and without this support, the lining of the uterus sheds. Thus, the cycle ends and the period starts a new cycle.

This normal cycle, however, does not continue unchanged from the first period to the last in a woman's life. There are a number of stages: After menarche, the age at which an adolescent has her first period, there is a time of menstrual irregularities and less than optimal fertility. Over the next few years, her ovulation regularizes and in her late teens and through her twenties a woman has her greatest fertility. As she enters her thirties, and especially after her mid-thirties, a woman's reproductive capacity (her ability to get pregnant and subsequently deliver) starts to decline. She may decrease her production of estrogen slightly on average, and her progesterone production in the second half of the cycle can decrease. During this time, however, she usually continues to ovulate and her menstrual cycle generally remains regular and normal, even though her reproductive capacity has decreased.

Over the next five to ten years, a woman's menstrual cycle can become very disrupted and estrogen levels can swing from very high (above the normal when she was young) to very low (virtually no estrogen as in the menopause). This can result in alternating sensations of enlarged and tender breasts with bloating and irritability when estrogen is dominant; and hot flashes, confused thinking or lack of concentration, memory difficulties and vaginal dryness when the estrogen level plummets. Accompanying these swings can be cycles in which no ovulation occurs and therefore no progesterone is produced to counteract the effects of the estrogen and to regularize your periods. This leads to times when there is no bleeding (often leading to the worry that a pregnancy has occurred or menopause has started), which can then be followed by heavy bleeding (dysfunctional uterine bleeding) accompanied by severe cramps (dysmenorrhea). In the past few years, the term 'perimenopause' has been adopted to denote these symptoms that occur in the 5 to 10 years prior to menopause.

The menopause, as defined above, can only be defined retrospectively, i.e., after a woman has gone twelve months without having a period. At this point, estrogen levels have remained so low that the lining of the uterus is not stimulated to build up enough to shed and therefore periods no longer occur. This continued low level of estrogen is reflected in the lack of fluctuation between heavy bleeding and breast tenderness, and no periods and shrinking breasts. These continued low levels can cause an increase in hot flashes (most women start to experience hot flashes in the perimenopause), difficulty concentrating, and memory problems. The loss of bone accelerates at this point and in the first five years after menopause a woman loses bone at a faster rate than at any time in her life. Other symptoms of the perimenopause may intensify, such as vaginal dryness, decreased libido, dry skin, and decreased mood and energy.

Five years after the menopause, a period often referred to as the 'post menopause,' a woman's body settles into a lower estrogen state, bone loss slows down--but definitely continues—and many women become acclimated to the symptoms. Unfortunately, the damage to the many organ systems that need estrogen continues insidiously. Consequently, cardiovascular disease rates increase; osteoporosis and fracture rates increase; diabetes rates increase; Alzheimer's disease rates increase. So as you can see, the 'pause' in 'menopause' refers only to a discreet point with regard to menstrual periods; the aging of a woman's reproductive system is actually a fairly continuous process that starts in the early thirties. An

anti-aging medicine approach takes this into account and intervenes before the actual menopause to treat the symptoms and long term consequences that result from less-than-optimal hormone levels.

When does an anti-aging approach to reproductive aging start? Which among the various options for hormone replacement does it employ? These questions will be addressed in the following sections.

What is Estrogen?

Many women do not realize that 'estrogen' is not an actual hormone, such as testosterone or progesterone, but is the term used to refer to a class of molecules that have estrogen-like activityin the body. There are many molecules that are estrogens, but the principal bioidentical estrogens in a woman are estradiol, estrone, and estriol. It is important to understand this when you are deciding on a type of estrogen replacement therapy.

What do estrogens do, and how do they do it?

Estrogens circulate throughout the body, and become attached to cells that express the estrogen receptor (ER). Estrogens and the ER function in much the same way as a key and a lock. When the key is placed in a lock the door is opened; when an estrogen locks onto an ER, a series of events occur that mediate the effect that we see in the tissue, such as building up of the lining of the uterus, or keeping the bones from becoming thinner. The difference is that the many different estrogens can lock on to the ER, but each with a different degree of effectiveness and with different effects in different tissues. For example, estradiol is the most potent of the estrogens produced by the ovary. A very small amount circulating in the blood can tightly lock onto the ER and cause potent changes in estrogen responsive tissues. Estrone, a metabolite of estradiol is considerably less potent, and estriol a further metabolite of estradiol, is quite weak.

What is the difference between a 'natural' and a 'synthetic' estrogen?

This is a question often asked by women who are seeking a 'more natural' approach to HRT because they have heard that there are fewer side effects with a natural approach. Unfortunately, natural is equated with herbal or coming from a plant rather than being chemically synthesized. Thus, women choose to take things like yam extract or herbs that are said to have estrogen like activity. But yams have no molecules with any significant estrogen activity. What they contain is a precursor molecule, diosgenin, which can then be chemically converted into many different estrogens. We believe that the important distinction is not between natural and synthetic, but between hormones that are "naturally" found in the human body, which are called bioidentical hormones; and hormones that may have similar activity in some tissues but are not naturally found in the human body—exogenous or foreign hormones.

Estradiol, estrone, and estriol, and all of their metabolites are bioidentical hormones; which are "naturally" found in the body. In contrast, Premarin, the most commonly prescribed estrogen formulation for HRT, is mixture of two human estrogens, estradiol and estrone, and 10 or more horse

estrogens, which are exogenous to humans. The problem with exogenous hormones is that while their activity in some tissues is well studied, we can't be sure of it in other tissues.

Premarin is very natural in that it is derived from pregnant mare urine and is not synthesized, but it is not natural in that it contains many estrogens that are not naturally found in a woman's body. Some of these hormones, such as equilenin, are very potent estrogens, even more so than estradiol. As such, the level of these potent hormones needs to be closely monitored. Unfortunately, there are no readily available blood or saliva tests for monitoring the levels of these foreign hormones (and that also goes for the estrogen substitutes such as raloxifene, known as Evista, and tamoxifen, known as Novaldex). This is particularly important because, as we will see in the next section, how one takes a hormone, especially an estrogen, under certain circumstances dramatically alters the blood level.

Bioidentical is important, but transdermal is even more so. The majority of women take their HRT in pill form by mouth (oral HRT). While very convenient, this results in changes in the metabolism of estrogen that can be harmful. The reason for this is called the "first pass effect." When any substance is ingested, it is absorbed by the intestines and then the whole dose hits the liver immediately. This does not mimic what occurs naturally when the ovaries are releasing estrogen into the circulation gradually all day and then it gradually goes through the liver. When a large amount of estrogen hits the liver at once, the processing of the estrogen changes the metabolism of the liver and results in a number of deleterious effects:

1. Increase in clotting factors, hence the warnings on the box that women who smoke and older women may have an increase in blood clots in the veins of the legs that can then cause a potentially fatal pulmonary embolism.

2. Increase in the carrier molecule of the sex hormones called 'sex hormone binding globulin,' which can result in too-tight binding of testosterone and thus symptoms of a low testosterone level--decreased libido, vaginal dryness, and thinner bones. Dr. Rogerio Lobo, a nationally known researcher in estrogen replacement therapy has said, "The fastest way to make a woman androgen deficient is to put her on oral estrogen replacement therapy."

3. The metabolism of fats and protein is changed which results in the loss of lean muscle and increase in fat. These often counter balance each other to cause no change in weight, but an undesirable body composition.

4. When a woman drinks the equivalent of even just one glass of wine or other alcohol a day and takes estrogen orally, her level of estrogen can increase 300% above when she is not drinking. This can cause levels of estrogen that are higher than are ever experienced in a normal menstrual cycle. This may be one of the causes of an increased risk of breast cancer with oral HRT. In contrast, transdermal estrogen results in only a 30% increase in estrogen level with alcohol consumption.

5. An increase in the incidence of gall stones which can lead to the need for gall bladder removal.

6. An increase in triglycerides, a form of cholesterol that is a known risk factor for heart disease. None of these "side effects" occur with transdermal (through the skin) ERT because the daily dose is released gradually into the general circulation, just as when the ovaries are functioning naturally.

So why aren't all women taking their ERT transdermally?

Some of the reasons why more women are not taking transdermal ERT are:

1. Inertia: Transdermal therapy has not been available nearly as long as oral therapy, and once a pill-a-day therapy takes hold, it is hard to change the preferences of both physicians and women. Furthermore, most physicians are not trained in prescribing precision amounts of multiple hormones and optimizing them through lab test analysis and dosage modification. Physicians are most often educated about treatment options by pharmaceutical companies, who have nothing to gain by developing and marketing a product that is not patentable.

2. Convenience / Availability: Most women don't want to wear a patch. This problem is solved with transdermal creams that exhibit excellent absorption and provide steady estrogen levels. However, the pharmaceutical companies have chosen not to market these forms of ERT because they can't protect their investments with patents. Women must resort to a specialized class of pharmacies that perform compounding, the art of combining several ingredients in customized amounts.

3. Oral ERT raises HDL (the good cholesterol) higher than transdermal ERT. This argument is often the sole reason put forth by gynecologists and internists when asked why they persist in prescribing oral ERT in the face of the six reasons against it listed above. The reasoning here is flawed in most cases. While it is true that HDL is raised considerably more with oral therapy, the majority of women have an HDL in a very good range even off ERT so raising them from 60 to 80 mg/dl does not confer enough benefit to outweigh the above negatives. Moreover, it has been shown that only about 30 to 40 percent of the heart disease reduction benefit of ERT comes from the changes in the cholesterol profile, which further mitigates the marginal benefit of raising HDL in a woman with a good baseline level. This is not to say that in some cases, e.g., when a woman's HDL is less than 30, oral therapy on balance is preferable, but certainly not in the majority of cases.

Bioidentical Progesterone vs. Provera

To protect the uterine lining from continuous stimulation by estrogen, most physicians prescribing standard ERT combine it with Provera. If you ask them if it is progesterone, they'll probably even tell you it is—it is not. It is medroxyprogesterone acetate, which is natural progesterone altered by the addition of a molecule to make it patentable and more orally absorbable. This molecule alters Provera's effect on tissues other than the uterus.

Many women discontinue ERT because they don't like the way it makes them feel—irritable and often depressed. In contrast, bioidentical micronized progesterone is often called the feel-good hormone because it elevates mood and is calming. Women who have experienced mood swings and migraine headaches on Provera often notice complete resolution of these symptoms when switched to

bioidentical progesterone. In addition, bioidentical progesterone was found to have the best effect on HDL cholesterol in the PEPI trial. This trial is the largest to date to include bioidentical micronized progesterone. Unfortunately, the WHI did not include an arm with progesterone, only Provera. If it had, we think the results would have been very different. Bioidentical progesterone can also act as a natural diuretic, in contrast to Provera which often causes fluid retention and bloating.

There is, however, an even more compelling reason to avoid using Provera. It comes from recent studies by a number of different researchers, and thus is unlikely to be disproved. These researchers showed that Provera can reverse by 50% the coronary artery-dilating effect of estrogens and that progesterone does not have this negative effect. This may explain the results of the HERS trial that is often quoted in the press as showing that estrogen does not protect the heart as was thought. In this large, prospective trial, the progestin used was Provera, not progesterone. The early slight increase in heart attacks in women with established cardiovascular disease could have resulted from the negative effect of Provera on the coronary arteries. (The other probable reason for the increase in heart attacks in the first year of therapy is that the oral estrogen caused a greater propensity to clotting and in women with arteries already narrowed from atherosclerosis this can cause coronary clots--heart attacks.)

Testosterone – Not just for men anymore

When we think about the growing body of scientific evidence demonstrating the important role testosterone plays in maintaining a woman's health and the fact that there is so little awareness of this information.

Do you have symptoms of a low testosterone level? Take this test before reading on:

1. Do you have decreased sexual desire or a lack of sexual fantasy thoughts and dreams?

2. Have you noted a decreased sensitivity to stimulation of your nipples or clitoris?

3. Have noted a loss of optimism and energy?

4. Has the quality of your orgasm or ability to get aroused sexually diminished?

5. Have you noted a loss of muscle tone, thinning pubic hair, or decreased fullness of

your vaginal tissues?

6. Has your hair, facial skin, or scalp become drier lately?

7. Has your muscle tone decreased?

If you answered 'yes' to any of these questions, then you may have a testosterone level that is below the lower level of normal for a young woman and could benefit from testosterone replacement therapy. The greater number of questions you answered positively, the more likely you are to have a low testosterone level. Evidence is accumulating that just as for men, testosterone is important for maintaining lean muscle mass, assertiveness, and bone density. It is also important for warding off

depression, increasing libido, and maintaining the health and sensitivity of the vaginal tissues. The difference is that women only need about a tenth of the circulating testosterone as do men.

Where is testosterone produced in women and how is it replaced?

Approximately 30 percent of a woman's testosterone is produced in the ovaries; the other 70 percent is derived from the transformation of adrenal androgen precursors such as DHEA and androstenedione, both of which decline inexorably with age. So, as a woman ages, she will have a decline in her testosterone level. It is not a precipitous decline as with estradiol at menopause, but is more gradual reflecting the DHEA decline. Interestingly, the ovarian production of testosterone decreases with age and menopause as well, but less so than the adrenal precursor source. After menopause, therefore, the percentage of total circulating testosterone produced by the ovary rises to more than 50%. This fact is important when we consider the idea—promulgated by many gynecologic surgeons— that the postmenopausal ovary is a useless organ and can be lopped out during a hysterectomy "because it no longer serves any purpose and is a cancer risk." This practice leaves a woman with an abrupt drop in her testosterone production that she feels acutely, and it probably accounts for the often observed drop off in libido and sense of well being, as well as the weight gain that many women experience after having their ovaries removed as part of a total hysterectomy. These women often say, "I just don't feel the same as I used to," even when they are on adequate estrogen replacement therapy.

We check testosterone levels—here, as with men, the free testosterone level is most important, and in a woman with intact ovaries, restoring DHEAS to youthful levels often will adequately restore the testosterone levels. If not, we will then add bioidentical testosterone to a woman's ERT cream which will always bring it right into the desired range. In a woman who has had her ovaries surgically removed, it is usually necessary to start directly with bioidentical testosterone replacement. The importance of replacing testosterone in these women is underscored by the fact that even with ERT, they often will continue to be osteoporotic. Most physicians confronted with this situation will add Fosamax or increase the estrogen dose to the point of side effects. But a number of recent studies have shown a normalization of bone density in these patients with the addition of testosterone. This is another proof of the principle that when one replaces all the hormones that decline with age, many of the diseases of aging can be avoided.

What about side effects and cancer risk?

Many women are reluctant to start HRT —even when they are aware of all the benefits—because they are worried about side-effects and breast cancer risk. Side effects can be virtually eliminated by breaking from traditional HRT and taking only youthful levels of bioidentical estradiol and progesterone, by administering them transdermally, and by monitoring blood levels closely. Two of the basic tenets of our hormone replacement program are to put into the body only the same hormones it produces on its own, and only at levels the body has known before (physiological levels). Furthermore, commercially available blood tests cannot accurately measure blood levels of horse hormones in humans. This becomes important when one considers what recent studies by Dr. Elizabeth Ginsberg show us about what happens to estrogen blood levels when estrogens are taken orally and even a small

amount of alcohol is consumed: the level can be increased by 300%--considerably above even the peak levels experienced during the menstrual cycle of a normal young woman. This may account for the excessive vaginal bleeding and breast tenderness that women often experience on standard dose oral ERT.

Whereas extensive large-scale clinical trials of transdermal bioidentical HRT have not yet been completed, we can say that having treated more than 1,000 patients since 1997, the side effects are minimal, manageable, and reversible. The most commonly reported side effects from ERT are breast tenderness and vaginal bleeding; these are often dose-related and can be eliminated or mitigated by reducing the dose. If a woman has a tendency to have hair growth in unwanted areas or acne as a teenager, this can be worsened with testosterone replacement therapy. Prolonged exposure to high levels of testosterone can cause enlargement of the clitoris and a deepening of the voice, both of which decrease with reduction of the levels. In summary, when hormone levels are restored back to youthful levels but not above them (what doctors call supraphysiological levels), side effects are easily managed. The main impediment that long-term HRT presents to the majority of women is the fear of breast cancer. Let us be very clear on our position: the lay press has overstated the risk of breast cancer. The oft quoted "one in eight women" figure is understood by women to mean that a woman has greater than a twelve percent chance of getting breast cancer at any age; in reality this is only true if she reaches the age of 85. The increased risk of breast cancer for a 65 year old woman who has been on ERT for 10 years increases from approximately 4.5 percent to 5.6 percent—a small increase in comparison to the benefits. But even this increase may be avoidable by taking bioidentical ERT in the transdermal form as mentioned above.

The same research that demonstrated a tripling of a woman's estradiol level when her ERT is taken orally and she consumes even one glass of wine a day may explain an intriguing finding by Dr. Susan Gapstur and her colleagues regarding ERT and breast cancer risk. When she analyzed the data from the Iowa Women's Health Initiative she found that the preponderance of the increase in breast cancer risk was in the group of women taking estrogen (virtually all taking it orally) and drinking the equivalent of at least a glass of wine a day. This probably results from the higher than normal levels of estrogen found in the Ginsberg study of the effect of alcohol intake on blood levels of estradiol in women taking oral ERT. This does not, however, mean that a woman needs to completely abstain from alcohol. With bioidentical transdermal estradiol, the increase in estradiol level with alcohol consumption is only about 30 percent; this small increase can be adjusted for when dosing transdermal creams which allow for an infinite number of individualized doses.

DHEA

There has been a great deal written about DHEA in the lay press. Much is true, even more is false. You no doubt have heard it referred to as a "fountain of youth in a pill" in health magazines, or read that it can cause prostate or breast cancer. The truth is that it is just one of the important hormones in an overall hormone replacement therapy program; that its blood level declines continuously and sharply from adolescence to old age; that this decline has been correlated with an increased risk of

cardiovascular disease in men, decreased immune system function in both sexes, decreased insulin sensitivity, and decreased IGF-I levels.

Human studies in which the level of DHEAS (the form found circulating in the blood) was replaced back to the levels of a 20 year old have shown impressive results in older adults and in various disease states in which the level is lower than expected for the age group. Yen and Morales administered 50 mg of DHEA for six months to 13 men and 17 women aged 40 to 70 years. These patients experienced an increase in lean muscle mass and a decrease in fat mass, although the latter only in the men. In addition, they had a remarkable increase in their perception of their psychological and physical well being.

These same researchers did a similar study to assess the effect of DHEA on immune function and found that there was an increase in natural killer cell function, the white blood cell responsible for killing viruses and tumor cells before they grow into cancers. Many other studies have been done documenting the beneficial effect of bringing the DHEAS level back to younger adult levels in lupus, diabetes, heart disease, obesity, and prior to vaccination.

We check our patients' DHEA-S level and supplement it with a dose of DHEA designed to bring it back to the level of a 20 year old; this level is rechecked once a patient is on therapy and is monitored regularly thereafter.

DHEA is so safe and relatively free of side effects that the FDA does not require a prescription for its sale. There is no evidence that its use causes an increased risk of breast or prostate cancer, but if one already has either of these cancers it can cause increased growth of the tumor. Because of this we screen for breast cancer with a mammogram and a breast exam prior to starting therapy. The only side effects of DHEA in the doses we use are a slight increase in acne in patients predisposed to it and in some women increased hair growth.

Thyroid Hormones

Thyroid hormones (TSH, T3 and T4) stimulate and maintain metabolic processes by modulating the synthesis and degradation of proteins and fatty acids in many tissues. Thyroid hormone replacement therapy is one of the unabashed successes of modern clinical medicine. It is standard medical therapy to replace thyroid hormone in anyone exhibiting fatigue, thickened skin, constipation, decreased reflexes, and weight gain if he or she has low thyroid hormone levels as well. Hashimoto's disease, the most common cause of low thyroid levels, is an autoimmune disorder in which the immune system attacks the thyroid gland making it unable to produce adequate levels of thyroid hormones. This is a very common disorder (you probably know someone with it), which can occur at any age, but its incidence increases with age. It is estimated that as many as 10 % of adults over 65 have the disorder. We routinely check blood levels of thyroid hormones in all our patients and treat as necessary. Treatment consists of a combination of T3 and T4, individually tailored to each patient's needs based on thyroid function tests.

Melatonin

If there is a "biological clock" that governs the decline in hormone production, then melatonin is the leading candidate. Melatonin is produced in the pineal gland at the center of the brain. This gland receives direct input from the eyes so that it knows what the day and night cycles are. Melatonin is released in spurts at night to initiate sleep; because of this by taking it in a pill at bedtime it can be effective in resetting the clock of a person who changes time zones, thereby alleviating "jet lag."

To test the theory that the pineal gland controls aging and the rhythms of our lives, Walter Pierpaoli, MD, PhD, in Italy transplanted the pineal glands of old mice into young mice and caused them to age much faster. When he did the reverse experiment, he caused rejuvenation of old mice. Finally, he has shown that by supplementing their diet with melatonin, mice can live up to 25 % longer.

It is well documented that humans produce less and less melatonin as they age. By age 60, most people produce less than 50 % of the melatonin they did at 20. Melatonin is also a strong anti- oxidant and cancer fighter (it has been shown that solid tumors partially regress with melatonin treatment). Because of these benefits and its safety in even very high doses, we recommend that patients take melatonin regularly at bedtime starting at age 40 and increasing the dose as they get older.

Growth Hormone

Before we discuss the story of human growth hormone (hGH) as an anti-aging therapy, we think it would be helpful to review some physiology. hGH is produced in the pituitary gland by the somatotroph cells (hGH's medical name is somatotropin). Under the influence of the hypothalamus (the part of the brain concerned with the more primitive bodily functions), hGH is released in four or five short spurts, predominantly at night during the third and fourth stages of deep sleep. As it circulates through the blood, hGH stimulates the liver to produce "insulin-like growth factor I" (IGF-I). Because it is released in spurts, hGH is difficult to measure except in a research setting where blood can be drawn every 10 minutes. The blood level of IGF-I, in contrast, is more constant, and therefore, except under certain circumstances, it serves as a reliable surrogate measure of hGH production.

Interestingly, the use of growth hormone as an anti-aging therapy resulted from research on its use in two disease states. Lack of hGH causes dwarfism or short-stature in children. In 1957, hGH isolated from human cadavers was injected into these children and normal growth ensued without significant side effects. However, when these children reached normal adult height, the hGH was discontinued because of its expense and scarcity (it took many human pituitary glands to make a few drops of the substance).

The other cause of hGH deficiency occurs when a person has had damage to his pituitary gland, either from surgery for a tumor of the gland or trauma. If this occurs when he is young, the patient will be growth retarded just as the children mentioned above. If it occurs when he is past adolescence, he will have already grown to normal height, but usually will have other endocrine abnormalities such as cortisone, thyroid hormone, and sex steroid deficiencies. These latter hormones routinely have been replaced because their deficiencies can be immediately life threatening or at least decrease the quality of life in the short term; but since hGH was not thought to have any important physiologic role, other than causing growth in children, it was not routinely replaced.

In 1986, the advent of recombinant DNA technology (gene cloning) enabled scientists to produce large quantities of pure, uncontaminated human growth hormone from bacteria. This development set in motion renewed interest in the other physiologic roles of hGH because of its availability for clinical research.

When researchers looked back at records of adults who had been treated with hGH as children or those who had become growth hormone deficient as a result of trauma or tumors, they found that they were not doing very well. They had two times the rate of death from cardiovascular disease compared with age-matched controls; increased abdominal fat; decreased muscle mass and strength; increased fatigue, social isolation and depression; and poor performance at work. These patients appeared to be suffering from premature aging. Bengt Bengtsson, MD and his group in Sweden decided to study the effect of the now more available recombinant hGH on these patients. He found that virtually all of these aspects of premature aging were reversed with one year of treatment, and that they returned to baseline with cessation of therapy. This research led to the FDA approval of hGH replacement therapy in growth hormone deficient adults (GHDA) in August of 1996.

At about the same time, Daniel Rudman, MD, at the University of Wisconsin, was approaching this from a slightly different angle. He had documented the continuous decline in growth hormone secretion beginning in the third decade of life and wondered if it was responsible for the well-known body composition changes associated with aging such as decreased muscle tone, increased abdominal fat, and thinning skin. In 1990, he published a seminal article in The New England Journal of Medicine in which he reported the spectacular age reversing effects of hGH replacement in 21 men between the ages of 61 and 81. After six months of therapy, these men had gained on average 8.8% lean body mass and lost 14% fat mass, predominately around the waist; had increased their skin thickness by 7% (your skin is thicker and more elastic when you're young); had increased bone density 1.4%; and felt a greater sense of well-being. In the conclusion, Rudman wrote that these changes in body composition are "equivalent in magnitude to the changes incurred during 10 to 20 years of aging."

The results of this study triggered immense interest in hGH as an anti-aging therapy. The National Institutes on Aging (NIA), a branch of the National Institutes of Health, initiated nine large clinical trials to test the effect of hormone replacement with hGH and sex steroids on healthy adults 65 and older. This is likely because they recognize that fully 40 % of adults over 60 have IGF-I levels the same as growth stunted children or individuals suffering from pituitary damage. The studies began in 1992 and ended in June of 1997. The preliminary results were presented at the June 1999 annual international meeting of endocrinologists called ENDO '99. During our discussions with the principal investigators of the studies, it became clear that the beneficial results of Dr. Rudman's study were confirmed and many more benefits with regard to psychological well-being have been published since then.

What to Expect from hGH Therapy

The amount of hGH we prescribe and the benefits you can expect depend on your starting level of IGF-I. Most people over the age of 35 will have a level less than the optimal level of 350 to 400 ng/ml and therefore will benefit from supplementation.

Once on therapy, the benefits you can expect are as follows:

- Decreased fat mass, 10 to 14 percent after approximately 6 months, predominantly around the waist, without change in diet and exercise
- Increased lean muscle mass of approximately 7 to 10 percent in the first six months of therapy
- Improved bone density after one year of therapy, percentage increase depending on how deficient it was to start with
- Improved cardiac and lung function, lowered blood pressure
- Increased physical and mental energy level
- Increased hydration of the skin with reduced propensity to develop wrinkles
- Accelerated wound healing
- Increased immune system functioning, including re-growth of the thymus (the gland important in the function of T-cells)
- Decreased total and LDL cholesterol levels, and increased HDL levels
- Improved sleep
- Improved vision
- Improved mood

The degree to which you see these improvements will depend on your level of growth hormone deficiency as measured by your IGF-I level and clinical exam. If your level is below 100 ng/ml, you will likely see significant changes in body composition in the first six months. If you have a higher level, the effect of the supplementation will be to prevent these age-related changes from occurring.

Safety of hGH Replacement Therapy

There is ample evidence to support the safety of growth hormone replacement therapy in growth hormone deficient adults (GHDA). In fact, Dr. Bengtsson has said, "When one does not abuse or overdose human growth hormone, there is simply NO evidence suggesting that human growth hormone replacement therapy causes ANY LONG TERM side effects." (Hormone Research, 43,p 93-99, 1995, emphasis added) Therefore, in August of 1996, the FDA approved the use of hGH in growth hormone deficient adults. Because the body composition changes and IGF-I levels are similar in a GHDA and an older adult, we believe that the same safety profile pertains. Moreover, none of the NIA long-term studies of growth hormone replacement in older adults were stopped because of adverse effects. Finally, data was presented at the ENDO '99 meeting showing no adverse effects in a small number of growth hormone deficient adults on therapy for 10 years.

Oxidative Stress: The Rust of Mother Nature

Free radicals are very reactive by-products of normal metabolism that are constantly being produced by your cells. A major cause of age-related decline, free radicals can damage the DNA in cells and cause cancer as well as abnormal function. Diet, lifestyle, and inheritance can affect your levels of free radical production. For example, some people inherit a propensity to produce high levels of homocysteine. Abnormally high levels of this amino acid are as much a risk factor for heart disease as are smoking and high cholesterol.

In addition to restoring your key hormone levels to a youthful level, we analyze the degree to which your body is susceptible to damage from free radicals. For instance, after detecting a high homocysteine level in a patient, we add specific antioxidant supplements that reduce the homocysteine level and thus greatly reduce the likelihood of a heart attack. Antioxidants such as vitamins B & C are very effective molecules in your body for neutralizing these free radicals before they can do you harm. Other antioxidants that we assess & replenish are vitamin E, coenzyme Q10, glutathione, etc., all of which can help to reduce stiffening of the arteries and heart while decreasing wrinkling of the skin.

The Importance of Nutrition and Exercise

Research in nutrition and medicine over the past few decades increasingly has born out the truth of the old adage, "You are what you eat." We strongly believe that there is now enough scientific evidence to prescribe a youth-preserving and disease-fighting diet. Much research shows a link between diet and key hormones such as insulin and anti-oxidants such as glutathione. For these reasons, we closely monitor your dietary habits and prescribe changes to optimize body composition and energy levels. Our on-staff nutritionist is available for an in-depth consultation at your request.

We encourage our patients to exercise regularly. This promotes enhanced effects of the hormones and possibly to decreased doses necessary to achieve optimal effects. For example, short bouts of high intensity exercise cause release of growth hormone from the pituitary gland, further intensifying the fat-dissolving effects of externally administered GH. It is also well- documented that weight-bearing exercise helps to maintain good bone density.

When should I start thinking about bioidentical hormones?

My doctor wants me to wait until I reach menopause. The menopause is defined as a single day--12 months after your last period. Your physician's suggestion that you wait until you have passed this milestone reflects an antiquated view of a woman's transition from the premenopause to menopause. The majority of women experience their severest symptoms in the months to years leading up to this milestone. To wait for this single day would be to subject women to a year or more of unnecessary hot flushes, night sweats, mental fogginess, and bone loss. Our approach is to start addressing these symptoms as soon as they appear. They often begin a year or two before the final menstrual period, a

time called the perimenopause. By so doing, we can avoid all the havoc that fluctuating hormone levels can wreak on a woman. Our approach is to smooth the transition from normal cycling through the menopause rather than to wait for a somewhat arbitrarily defined date.

What are the side-effects?

Side-effects are often minimal and manageable when restoring hormones to physiological levels (levels your body has seen before). Some patients report breast tenderness or swollen joints when first starting bioidentical hormone replacement therapy; these and other adverse reactions can be remedied by reducing the dosage until symptoms resolve, then gradually resuming.

Will I continue to get my period?

The answer to the question of whether to cycle or not to cycle when undergoing bioidentical HRT (bHRT) is complex and depends upon many factors specific to each woman. It also entails a long discussion of the evidence for and against it at this time. Briefly, our current interpretation of available data is that while cycling may turn out to have benefits with regard to breast cancer risk, there is not enough clinical trial data to mandate it for all patients, particularly those with a low risk of breast cancer and who have difficulty tolerating the fluctuation of hormones that cycling entails.

How long do I need to stay on the program?

You should continue treatment as long as you wish to see results.

What happens if I stop the program? Will my body stop producing hormones on its own? Will my hormone levels decrease? Will I lose my gains?

In general, supplementation by exogenous (external) hormones will result in decreased endogenous (internal) production. However, the body tends to restore hormones to pre-treatment levels after cessation of treatment. If your own hormone production was low before treatment, it will most likely return to the same levels after treatment. As a result, most of the physical changes enabled by the program will gradually revert back to "normal".

Have you had any success in treating fibromyalgia?

We are treating several patients with fibromyalgia and/or chronic fatigue, all with significant improvement in energy, level of pain, and frequency of exacerbation of symptoms. None have

encountered a negative response. This does not assure similar response in all patients with fibromyalgia, but to date the response to therapy has been more effective than prior therapies. Although our program is not specifically designed to attack the underlying cause of fibromyalgia, it does restore function and strength of the immune system, restore efficiency of mitochondrial production of energy with cells, and improves the body's natural anti-inflammatory capacity. If you are interested in pursuing treatment, contact the office to schedule a set of laboratory blood tests prior to coming in for consultation. With the test results we will be better able to discuss possible benefits of our treatment specific to your current condition.

How To Begin Your Treatment Program

Step 1: Contact 911BioCare at (855) 901-0911 to schedule an appointment and laboratory evaluation

Before you visit our offices, we will prepare a requisition that you can take to any draw site to undergo the following tests:

Hormones of aging

- Insulin-like growth factor-I (IGF-I)
- Insulin-like growth factor binding protein-3 (IGFBP-3)
- Free and total testosterone
- Estradiol and estrone
- Sex hormone binding globulin (SHBG)
- Progesterone
- Fasting insulin
- DHEA-S
- TSH, free T3, & T4

Step 2: Initial Consultation

Before your initial consultation you will fill out a questionnaire designed to detect any underlying conditions that need to be addressed. This will also establish a baseline of aging against which to compare your progress. You will then meet with your physician to discuss your medical history and undergo a physical exam. Your laboratory results, history, and exam will be used to design a precision-tailored program specifically for you. You will discuss the expected benefits and risks of your program as

well as its administration. The physician will write you a pharmacy prescription to take with you when you leave the consultation.

Consultation Fees

Precision Medicine involves frequent assessment and adjustment of hormone levels until a stable regimen is achieved. This methodology requires lab tests and subsequent follow-up visits 2-3 times during the first year, then twice-a-year thereafter. For patients who are not able to visit the office, telephone consultations are available. The fee for the initial evaluation and consultation is $499 and $199 for follow-up consultations every 60 to 90 days. Whereas we do not accept insurance for payment, we will provide you with properly coded invoices that you may submit to your insurance provider for reimbursement. Office visits are generally covered by indemnity insurance plans according to your out-of-network provider schedule.

FREQUENTLY ASKED QUESTIONS

How do I begin? What does the program involve?

STEP 1: Contact Us

Contact 911BioCare at (855) 901-0911 to schedule an appointment.

STEP 2: Blood Test

You are required to get a blood test before your visit. We will send you a lab requisition that you can take to any draw lab. No appointment is necessary for your lab test. You must be fasting for 8-12 hours before the test is performed - nothing to eat or drink except water. Most labs open before 8AM. The results will be sent to our office 3 days later.

STEP 3: Treatment

At the end of your initial consultation, you and your physician will determine the course of treatment. A prescription for custom-compounded medications will be written for you by the physician.

STEP 5: Follow-Up

After 6 weeks of treatment, you will have your first follow-up consultation with your physician. You will need to get a follow-up blood test 7 days before your consultation. Your physician will discuss the effects of the program and adjust your dosages accordingly. You will repeat this process after 2-3 months and again every 6 months thereafter, depending on the situation.

What are the costs involved?

The fee for the initial consultation and is $499. New patients will need two or three follow-ups during the first year of treatment while the proper dosages are determined. Follow-up visits are $199.

Does your office accept health insurance?

Our office does not accept insurance for payment. However, this does not rule out the possibility of reimbursement by your insurance provider. We will be glad to provide you with properly coded invoices that you may submit for reimbursement. Many insurance plans will cover the cost of office visits according to their out-of-network provider schedule. You may be subject to an annual deductible and a co-pay, depending on your coverage. Please contact your provider for more details on coverage.

Will my insurance cover the cost of prescriptions?

Most insurance companies do not cover the cost of compounded medications. For this reason 911BioCare does not accept insurance for direct payment. However, we will provide you with properly coded invoices that you may submit to your insurance carrier for reimbursement.

Will my insurance cover the cost of lab tests?

Insurance plans will sometimes cover the cost of lab tests. Speak with your insurance carrier for more details.

Will my FSA cover your treatment?

Many employers offer a Flexible Spending Account (FSA) to their employees. These arrangements permit the employee to stow a portion of their pre-tax earnings in a special account for use on health-related expenses NOT covered by primary health insurance. Depending on the type of FSA, these arrangements may cover the portion of your treatment not covered by your primary health insurance, including medications, office visits, co-pays, program fees, vitamins & supplements

Can I use my own pharmacy?

We are better able to manage your hormone levels with precise accuracy if all medications come from the same pharmacy. Bioidentical hormone modulation is very different from prescribing "one-size-fits-all" drugs like Premarin. Every treatment regimen is custom-tailored to the individual based on the results of blood tests, medical history, physical exam, and symptoms presented. With compounded medications, hormone powders are mixed with a cream base or loaded into capsules. There are many variables such as the absorption level of the cream base or the particle size of the powder. By standardizing with one pharmacy, we are better able to predict a patient's response to a certain dosage and properly adjust the dosage in response to symptoms. If a patient obtains their hormones or supplements elsewhere, we can never be sure exactly what they are taking. Consequently, this makes it much harder for your physician to keep your hormones at optimal levels. We may charge an additional fee to compensate for the commensurate clinical burden associated with the use of another pharmacy.