



Progesterone-3/.3®

NDC # 65448-2175-1



PROTOCOL
No. 71

www.amtrx.com

Lipid Encapsulated Crémé

DESCRIPTION

Progesterone 3/.3® is uniquely formulated to provide a high potency, convenient, quick release form of progesterone that is extremely bio-available as a result of the delivery system utilized. A one ounce (28.4 ml) bottle of Progesterone 3/.3® contains 2 grams of USP Progesterone and 0.2 grams of USP Androstenedione in an easily applied lotion for trans-dermal application. Each drop delivers 3 mg of Progesterone and 0.3 mg Androstenedione.

INGREDIENTS

The active ingredients in Progesterone 3/.3® include all natural 100% USP grade Progesterone and USP grade Androstenedione.

ACTIONS AND PHARMACOLOGY (Function)

Progesterone is a basic steroidal hormone and is a requisite precursor to all other hormone production for proper hormonal balance. Adequate quantities and conversion of progesterone are necessary for the production of different classes of steroid hormones including Glucocorticoids (cortisol, etc.), Mineralcorticoids (aldosterone), DHEA and Sex Hormones (estrogen, androgens, androstenedione, testosterone, etc.).

During the proliferative phase (the first portion of the cycle, also known as the follicular phase), the endometrium thickens while the blood vessels and glandular components proliferate. The cervical mucus becomes thinner, clearer and "stretchy" or "stringy" in appearance in order to facilitate passage of sperm. During this first phase, estrogen is the dominant hormone and the levels of progesterone are relatively low as compared with the second portion of the cycle. The proliferative phase ends upon ovulation.

The secretory phase (the second portion of the cycle, also known as the luteal phase), occurs immediately post ovulation and is when progesterone levels become exceptionally high. The glandular components and blood supply mature and prepare to provide nutrition to the fertilized egg, which is maintained by the increase in progesterone. It is the progesterone that is responsible for causing cervical mucus to become sticky and thick. If the egg is not fertilized, the secretory phase concludes with menstruation.

Menstruation is the final phase and is characterized by progesterone and estrogen levels dropping precipitously, causing blood vessels to constrict and decrease the supply of blood to the glandular components, resulting in the shedding of the entire endometrial lining. Menstruation flow includes not only blood but glandular components and sloughed tissue as well. The typical cramping associated with menstruation results from a lack of progesterone and an increase of prostaglandins within the uterus.

Endogenous progesterone production spikes up to an elevated level at the point of ovulation and remains high, until it precipitously drops approximately 14 days after ovulation, signaling the onset of menses. Exogenous administration of progesterone is utilized to supplement and maintain physiological levels of progesterone. Progesterone also counters the deleterious effects of estrogen on osteoblasts. Because progesterone deficits affect all systems, attaining proper physiological levels affects the positive feed back cycle and production of progesterone as well as other hormones. Progesterone production diminishes with age, affecting all consequential hormonal cascades.

Most steroid hormones are hydrophobic. They easily complex with chaperone peptides and are easily transported hematogenously. Progesterone is hydrophilic and is not easily absorbed unless complexed with other lipid and hydrophobic agents. Upon administration, 66% of ordinary progesterone is carried inside RBC's and 33% is associated with chaperone peptides within the plasma. The difficulty with most trans-dermal delivery systems used for progesterone is that they have been shown to have a substantial portion bound to the subcutaneous tissue, preventing systemic absorption.

If formulated properly, trans-dermal administration is superior to other methods of administration, because the majority of the progesterone is rapidly absorbed directly into the circulatory system, is bioactive, does not elicit an allergic response, and does not enter the portal system. Progesterone 3/.3® is complexed with tocopherols and a structured lipid carrier creating a lipid micro-encapsulation for quick transport across the epidermis. Progesterone 3/.3® has also been shown to have extremely high bio-

availability with over 95% systemic absorption, setting it apart from other trans-dermal progesterones on the market.

Androstenedione, the other ingredient in this trans-dermal formulation, is a precursor in the sex hormone cascade and serves as the precursor for testosterone. Androstenedione also aids in the balance of endogenous Estrone (E1), Estradiol (E2) and Estriol (E3).

INDICATIONS AND USAGE

Progesterone 3/.3® is indicated in female patients that may be experiencing symptoms of estrogen dominance and / or adrenal exhaustion. In addition, patients may benefit from the administration of Progesterone 3/.3® if they are seeking to increase bone mass density, achieve optimum levels of precursors for other hormones, prevent or reduce the symptoms of fibrocystic breast disease and uterine fibroids, reduce the symptoms of PMS, improve and maintain the uterine lining (as is beneficial in endometriosis), improve cellular fluid levels, improve metabolism, stimulate lipolytic pathways, alleviate depression and anxiety, improve thyroid function, improve sex drive, prevent coagulation, and normalize essential mineral levels.

DOSAGE AND ADMINISTRATION

General Information:

The ideal length of a complete cycle is 28 days but can range from 20 to 36 days. Approximately 10% of the females actually have this "ideal" 28 day cycle with most women experiencing a cycle that ranges from 26 days to 32 days. The cycle can have a variation in length occurring at different times of life but generally the change occurs over time. The conventional method is to count the 1st day of active flow as day 1 of the menstrual cycle. Active menstrual flow generally lasts 2 to 7 days but has a wide variance in duration, amount of active flow and pattern of flow.

The amount of Progesterone 3/.3® indicated and used will depend on the various situations as described below. It is important that Progesterone 3/.3® is administered to an area of the body consisting of minimal subcutaneous tissue and a capillary dense region with high vascular supply. Dosages on forearms should be evenly divided and applied to both forearms. Upon application, smooth drops into the skin for complete absorption.

Generally speaking, after the first 3 months of usage, the dose of Progesterone 3/.3® may be reduced to a maintenance dosage once the presenting symptoms have been resolved, gradually decreased to the point where the patient remains symptom free. If used for preventive reasons, as with decreasing bone mass density, the maintenance dose used should be as if the patient were having "moderate" symptoms.

Menopausal Symptoms:

Normal dosage is 18 drops per day, applied in three separate doses at morning, early afternoon and before bedtime. For severe menopausal symptoms, if the suggested dose is not efficacious within 30 days, dosage may be increased incrementally up to 36 drops daily at the discretion of the treating physician.

Menopause Symptoms: No. of drops per day:

Mild:	12
(2 drops on each arm, three times a day)	
Moderate:	18
(3 drops on each arm, three times a day)	
Major:	24
(4 drops on each arm, three times a day)	
Severe:	up to 36
(6 drops on each arm, three times a day)	

Irregular Menstruation:

Progesterone 3/.3® is administered relative to the normal menstrual cycle. During the first two weeks of the cycle (luteal phase), total administration is 6 drops daily (1 drop on each forearm, applied 3 times daily). During post ovulation (follicular phase), the dosage is increased 3 to 4 fold to a dose between 18 to 24 drops daily (3 to 4 drops on each forearm, applied 3 times daily), depending on the irregularity of the menstruation cycle. The more irregular the cycle, the higher the increase in dosage of Progesterone 3/.3®. When due to menstruate, Progesterone 3/.3® is discontinued. It is important to note that if Progesterone 3/.3® is not discontinued when due to menstruate, active flow may not occur. Upon cessation of active flow, the Progesterone 3/.3® is restarted at the original starting dose. It may take up to 3 months before a regular menstruation cycle is re-established.

For example, if a patient is having an irregular menstruation, start of with 18 drops total daily dose (3 drops on each forearm, 3 times a day). Continue until the 28th day of the cycle or

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when due to menstruate and then, discontinue Progesterone 3/.3[□]. This is done for the first month only. Upon cessation of active flow, resume Progesterone 3/.3[□] at one third to one fourth the previous dose or, as in this case, 6 drops total daily dose (1 drop on each forearm, 3 times a day).

If symptoms are more severe, increase the post ovulation dosage as necessary. For example, if a patient is on 24 drops daily during post ovulation (follicular phase), the dose would decrease to one fourth, or 6 drops daily after cessation of active flow. Thus, after cessation of active flow, the dose is always reduced to 6 drops until ovulation. After ovulation, the dose is increased to 18 drops to 24 drops, depending on the level of irregularity of menstruation.

Irregular Menopause Symptoms: No. of drops per day:

Luteal Phase: 6

(1 drop on each arm, three times a day)

Follicular Phase: 18 to 24

(3 to 4 drops on each arm, three times a day)

Active Menstruation Flow: (0

(Progesterone 3/.3[□])

PMS Symptoms:

If the symptoms of PMS are evidenced during the last days of the cycle, administration is started 2 to 3 days before onset of symptoms and discontinued at first day of menstrual flow. For example, if the patient complains that every month, she experiences PMS symptoms 3 days prior to starting her menstruation, then the Progesterone 3/.3[□] should be started 5 to 6 days prior to the onset of expected menstruation and continued until the 28th day of the cycle (expected day of menstruation).

On the 28th day, the Progesterone 3/.3[□] should be discontinued. It is important to note if Progesterone 3/.3[□] is not discontinued on the 28th day of the cycle, the patient will become asynchronous with her natural menstruation cycle and will fail to have a period. This cycle is repeated monthly and may take up to 3 months before stabilization of the cycle is achieved.

CONTRAINDICATIONS

No known sensitivity to active or inactive ingredients.

DRUG INTERACTIONS

No drug interactions have been reported or documented.

OVERDOSE

Exceptionally high doses of 100 mg + can cause very mild euphoria and/or lethargy. Patient should not drive or operate machinery for 30 minutes after use if taking high doses of Progesterone 3/.3[□] above 100 mg daily. Long term adverse effects: none known.

Packaging: 1 oz bottle (30 cc)

Storage: 15-30 deg C (59-86 deg F)

Manufactured exclusively for Balance Dermaceuticals®

Made in U.S.A.

FREQUENTLY ASKED QUESTIONS (FAQS)

What is meant by pre, peri and post menopause?

Pre-Menopause is defined by the interval from the onset of menses with the first menstrual period until the onset of the irregular monthly fluctuations of estrogen, progesterone, LH and FSH causing a deviation from the normal menstrual cycle. The most common problem of Pre-Menopause is commonly called PMS which includes the disruption of neurotransmitters affected by hormone fluctuations. PMS is most commonly treated with stress reduction, diet, exercise, certain herbs/vitamins/minerals, and prescription medications such as NSAIDs.

Peri-Menopause is defined by the interval period between onset of changes in hormonal secretions and the onset of menopause. Peri-Menopause is caused by the fluctuating secretions due to mix of normal and abnormal menstrual cycles, sometimes referred to as periods of "estrogen dominance". Peri-Menopause ends with the cessation of menstruation.

Menopause is defined as the interval period between the termination of the menstrual cycle with onset defined as having missed 12 consecutive menstrual cycles until cessation of symptoms of hormonal imbalance. It is important to note that not all women experience problems going through menopause.

Post-Menopause is defined as the years after cessation of menstruation when hormone replacement may be necessary to maintain the optimal function and health of the heart,

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lipids, bone mass, etc., as well as to help alleviate the symptoms associated with menopause. These symptoms are often the same symptoms noted with hormonal imbalances as previously discussed.

But menopause is natural, so why should I try and replace my hormones?

Some women do not want to take supplements because they feel that menopause is a natural part of life. This is a true statement and every woman will experience menopause if they live beyond the age capable of reproduction. But our lifestyles today are anything but natural. Over the past few decades our society has drastically changed the way we live. Most of these changes have been detrimental to our health. We now live in a polluted environment, eat processed and synthetic foods and get very little exercise.

Consequently, menopause is starting to occur earlier in life than in previous decades. We often accept the idea of taking medication to correct other natural processes associated with aging, such as heart disease and arthritis. These medications are often very unnatural and are not without risks. Taking natural hormones to minimize the negative effects of menopause is extremely safe. For any woman wanting optimal health, keeping the body's hormones in balance is just as important as diet and exercise.

What does hormone replacement really offer me?

The key issue to address for patients with hormonal problems is the issue of "balance". Hormone replacement has profound and immediate effects on menopausal symptoms. It restores vaginal lubrication, alleviates night sweats and hot flashes and has antidepressant effects. Given the average age of menopause at 50 years, a woman can expect to live approximately 30 years beyond menopause when on hormone replacement. The hormonal balance in the body will be restored and the risks of heart disease, osteoporosis, and memory loss decreased as well as resolution of menopausal symptoms. The primary hormone responsible for these improvements is progesterone.

What are the symptoms of hormonal imbalance?

Symptoms of hormonal imbalance include

anxiety, depression, forgetfulness, inability to concentrate, insomnia, irritability, lethargy, mood swings, dry hair, eyes, and mouth, headaches, increase in facial hair, lowering of voice, wrinkled skin, breast soreness, chest pain, night sweats, heart palpitations, back pain, muscle soreness, bloated abdomen, constipation, dry vagina, irregular periods, loss of bladder control, loss of libido, painful intercourse, urgent or frequent urination, aches and pains, pins and needles, stiff joints, swollen joints.

Why is progesterone important?

Women often think they do not need progesterone if they no longer have a uterus. This is not true. Your body still has progesterone receptors in other areas that need progesterone to produce several critical functions. The progesterone used in natural hormone therapy is prepared from soybeans or wild yam. It is chemically and biologically identical to your own body's progesterone and therefore functions in the same way.

What are the functions of natural progesterone?

Progesterone is a naturally occurring female hormone that is produced in the ovaries. Some functions of progesterone are as follows: Promotes bone formation; Precursor to other hormones; Balances estrogen; Maintains the lining of the uterus; Protects against fibrocystic breast disease; Stabilizes cell fluid levels; Improves the body's fat burning ability; Antidepressant effects; Aids in thyroid function; Maintains sex drive; Normalizes blood clotting; Normalizes zinc and copper levels.

What are the different types of progesterone and is the difference really that important?

Progesterone is available in two forms (natural and synthetic) and the choice is critical. Natural progesterone is produced from yams and soybeans—plants rich in compounds known as phytoestrogens, which have hormone-like properties. Once extracted and prepared, it is an exact chemical copy of the progesterone produced by your body. In addition, natural progesterone is known as a precursor hormone to estrogen, leutinizing hormone and testosterone, among others. This means that to an extent, progesterone controls the production of these other hormones. It can help balance any deficiencies

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or excesses of them in your body.

Progestin is a synthetic chemical analog similar to progesterone, but different enough to have some dramatic negative effects. Progestin can lower our own body's innate production of endogenous progesterone, which can further exacerbate a hormone imbalance and lead to mood swings, headaches, fluid retention, and weight gain. Other more serious side effects, including blood clots as well as uterine and breast cancer, have been linked to progestin supplementation. Synthetic progestin, however, is unable to synthesize into other hormones or help our body produce the other hormones needed to function at full potential.

How is natural progesterone most commonly administered?

Natural progesterone can be administered in a number of ways—orally (powdered or oil-based product), vaginally or rectally (with capsules or suppositories), by way of injection (usually intramuscularly), or in creams or gels. Natural progesterone is much weaker than synthetic progestin—up to several hundred times less potent. A comparison of progestin versus natural progesterone doses would be in the range of 5mg versus 50-500mg. Usually, a dose between 100mg and 200mg per day of oral natural progesterone is recommended. Unfortunately, more often than not, despite the dosage being appropriate, due to the delivery mechanism, the progesterone is often not optimally utilized by the body and the problems persist.

This is where the uniqueness of Progesterone 3/3[®] becomes evident. The delivery mechanism utilized in Progesterone 3/3[®] allows for greater than 95% delivery to the active receptor sites, unlike other progesterone creams which leave much of the active ingredients bound to the subcutaneous tissue. As a result of higher systemic utilization with Progesterone 3/3[®], a lesser amount is necessary with most severe symptoms resolving with less than 75 mg daily.

What is natural hormone replacement therapy (natural HRT)?

Any woman entering peri-menopause, menopause, or post-menopause should consider natural hormone replacement therapy (NHRT) to relieve symptoms associated with menopause and for its many

physiological benefits, which include: prevention of osteoporosis and restoration of bone strength, protection against heart disease and stroke, improvement of cholesterol levels, reduction of hot flashes, improvement in vaginal moisture, improvement of muscle strength, decreased risk of depression, improved sleep and mood, improved memory and concentration, decreased urinary tract infection risk, and improved sex drive. Natural hormone therapy is not the same as taking the commercially available prescription hormone medications.

Natural hormones match your own hormones exactly and are not associated with the many side effects and risks of conventional prescription hormone replacement therapy. Although the usage of natural estrogens is also considered a part of natural HRT, the use of all estrogens regardless of being natural or synthetic is felt to NOT be beneficial due to the over abundance of phytoestrogens, xenoestrogens and synthetic estrogens. Clinically, with the use of Progesterone 3/3[®] the use of natural estrogens is not necessary since progesterone is the natural precursor of estrogen and in sufficiently high doses, will bind to the estrogen receptor sites. Heavy metal toxicity may however prevent the conversion of progesterone to estrogen, leading to the loss of effectiveness of Progesterone 3/3[®].

What exactly are natural hormones?

The term natural can be confusing when referring to hormones. Natural means that the exact chemical structure is identical to the hormone that your body made prior to menopause. The term natural does not mean that it is readily available in the health food store. Specialty compounding pharmacists use pharmaceutical grade hormones prepared from plant sources to compound your individual natural hormone replacement medications. These natural hormones are medications, and do require a prescription. Most medications used to treat menopausal symptoms in the past have used synthetic hormones. A synthetic hormone has a chemical structure similar to your own hormones, but is not identical. Synthetic hormones will act differently in your body, often causing troubling side effects and health risks. Natural and synthetic hormones should not be considered interchangeable. The two

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most important components of natural hormonal therapy recommended are Progesterone 3/.3® and Trans-D Tropin®.

Are natural hormones FDA approved?

The Food and Drug Administration does not approve or disapprove natural substances and does not test medications itself. Drug manufacturers submit the results of tests of their new medications to the FDA for review and approval. The FDA then decides if these new substances referred to as medications are safe. The FDA however does not compare these new medications to others to determine the most ideal therapy or medication for a particular condition. In the specific case of Progesterone 3/.3® and Trans-D Tropin®, the FDA has reviewed both products and both are registered with the FDA. In fact, all Balance Pharmaceuticals® trans-dermal products are registered with the FDA and have been issued NDC numbers (National Drug Code numbers) which indicates that the substances and constituents of the product have been registered and evaluated by the FDA and are categorized as GRAS (Generally Regarded As Safe) and considered to be without any potential risks or side effects for public use.

What is the role of Testosterone in hormonal replacement?

Testosterone is a hormone that most women think is only for men. Testosterone is an androgen, a hormone produced in both men and women. The normal ovary makes testosterone in small amounts, even after menopause. If the ovaries are removed or stop producing testosterone, a deficiency will result, causing a loss of sex drive, decrease in energy levels, decrease in bone and muscle strength, breast tenderness and hot flashes. A balance of estrogen, progesterone, and testosterone is necessary to prevent unwanted and unhealthy changes in your body after menopause.

Testosterone is also commonly used for increasing libido in males and females. Decreased libido is a common factor in the aging process and usually occurs secondary to decreasing testosterone levels. Natural testosterone is available only at specialty compounding pharmacies. Progesterone 3/.3® includes androstenedione, a precursor of testosterone, as one of the main active ingredients and virtually eliminates the need

for using additional testosterone.

What is the Estrogen-Cancer Connection?

There have been numerous studies published that link cancer with estrogen use and as a result, much of the public is frightened with this hormone. And they should be. But there is more to this issue that meets the eye. Estrogen medications available in our market do NOT mimic the body's ratio of the 3 natural estrogens. Often, they are much more potent and are in different forms than the body's forms of estrogens. But the most important aspect to remember here is that progesterone is a precursor of natural estrogens. In other words, if progesterone is supplied in sufficient doses, it will be converted by the body into the endogenous estrogens the body needs. In addition, progesterone will bind to estrogen receptor sites if delivered in adequate amounts.

Should I try and balance my estrogen with progesterone?

Natural estrogen in the body does not function by itself. Progesterone primarily, in addition to many other hormones, interacts with and mediates estrogen. The problem is that in our society, so many substances act as estrogens, from the xenoestrogens found in the plastic bottles from which most of us drink to the phytoestrogens found in various food substances we consume on a daily basis. Estrogen is also a sympathetomimetic, meaning it induces a sympathetic response in the body, resulting in the flight-fight response. Our modern society makes it virtually impossible not to be inundated with substances that have an estrogenic effect.

It is unopposed estrogen (estrogen dominance) that promotes unbridled endometrial growth and increases the risk of endometrial or uterine cancer. Estrogens taken alone, especially in excessive amounts, can cause the cells of the uterus to become malformed. Progesterone is used to control this effect and protect an individual from endometrial abnormalities. Also, progesterone helps in the building of bone and the alleviation of menopausal symptoms. Proper supplementation with the right form of progesterone delivered to maximize assimilability will help reestablish natural hormonal balance. Progesterone 3/.3® offers one of the most effective methods available

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Further Editorial Information of Interest

To understand the significance and importance of Progesterone, the reader is asked to take a few minutes and read the following background information.

NIEHS Reports Adds Estrogen To List Of Known Human Carcinogens

The following report, NIEHS Report Adds Estrogens to List of Known Human Carcinogens, was reprinted here from the source: Tenth Report on Carcinogens, National Institute of Environmental Health Sciences, National Institutes of Health; <http://ntp-server.niehs.nih.gov>.

SUMMARY: The tenth edition of the federal government's biennial Report on Carcinogens added steroidal estrogens used in estrogen replacement therapy and oral contraceptives to its official list of "known" human carcinogens. This and 15 other new listings bring the total of substances in the report "known" or "reasonably anticipated" to pose a cancer risk to 228. The report was released by the Department and Health and Human Services (HHS) and prepared by the National Toxicology Program, an arm of the HHS at the National Institute of Environmental Health Sciences (NIEHS), one of the National Institutes of Health.

A number of the individual steroidal estrogens were already listed as "reasonably anticipated carcinogens" in past editions of the report, but this is the first to list all these hormones

as a group. Also newly listed as "known" causes of cancer in humans are broad spectrum ultraviolet radiation, whether generated by the sun or by artificial sources; wood dust created in cutting and shaping wood; nickel compounds and beryllium and its compounds commonly used in industry.

As with all the other medications listed, the Report on Carcinogens does not address or attempt to balance potential benefits of use of these products, nor does it assess the magnitude of the carcinogenic risk. (Listing in the report does not establish that such substance presents a risk to persons in their daily lives. Such formal risk assessments are the responsibility of federal, state, and local health regulatory agencies.)

Background

The Report on Carcinogens is prepared by the National Toxicology Program to identify substances, mixtures of chemicals, or exposure circumstances associated with technological processes that cause or might cause cancer and to which a significant number of persons in the U.S. are exposed. Listed in the report is a wide range of substances, including metals, pesticides, drugs, and natural and synthetic chemicals. The reports are informational, scientific, and public health documents. The U.S. Congress mandated the preparation of the report in 1978 to respond to the recognition that many cancers apparently were induced by environmental agents and to educate both the public and health professionals.

Definition

Agents, substances, or exposure circumstances are listed as either a "known to be human carcinogen" or a "reasonably anticipated to be human carcinogen." The category "known to be human carcinogen" is reserved for those substances for which there is sufficient evidence of carcinogenicity from studies in humans that indicate a causal relationship between exposure to the agent, substance, or mixture and human cancer. The second category, "reasonably anticipated to be human carcinogen," includes those substances for which there is limited evidence of carcinogenicity in humans and/or sufficient evidence of carcinogenicity in experimental

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animals. Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information.

Steroidal estrogens: Overview

The report cites steroidal estrogens commonly used in estrogen replacement therapy to treat symptoms of menopause and in oral contraceptives. Data from human epidemiology studies show an association between estrogen replacement therapy and a consistent increase in the risk of endometrial cancer (cancer of the endometrial lining of the uterus) and a less consistent increase in the risk of breast cancer. The report also says the evidence suggests estrogen-containing oral contraceptives may be associated with an increased risk of breast cancer but may protect against ovarian and endometrial cancers.

Steroidal estrogens: Carcinogenicity

The tenth report's listing of steroidal estrogens supersedes the previous listing of specific estrogens (in the Fourth Annual Report on Carcinogens in 1985) and applies to all chemicals of this steroid class.

The International Agency for Research on Cancer (IARC, 1999) evaluated the carcinogenic effects of hormone replacement therapy (HRT) used to relieve symptoms of menopause and reported that an increased risk of endometrial cancer was associated with increasing duration of HRT, as well as a small increased risk of breast cancer. Most of the studies reviewed by IARC did not distinguish between the effects of estrogen-only or estrogen-progestin combination HRT. Four studies published since the IARC (1999) review reported increased risk of endometrial cancer with estrogen replacement therapy (Gushing et al. 1998, Shapiro et al. 1998, Persson et al. 1999, Weiderpass et al. 1999); most of these studies reported strong positive associations between estrogen replacement therapy and risk of endometrial cancer with increased length of estrogen use. Three recent cohort studies of women taking HRT have shown an association with breast cancer (Persson et al. 1999, Gapstur et al. 1999, Schairer et al. 2000). Two of four recent case-control studies found that estrogen-only replacement therapy was associated with an

increased risk of breast cancer (Heinrich et al. 1998, Magnusson et al. 1999), whereas Brinton et al. (1998) reported a slight reduction in breast cancer risk among women receiving estrogen replacement therapy, and Titus-Ernstoff et al. (1998) found no association of breast cancer risk with HRT. One recent study (Purdie et al. 1999) found that estrogen therapy was associated with ovarian cancer.

Numerous case-control and cohort studies have addressed the risks of various cancers associated with the use of oral contraceptives (IARC 1999). Most of these studies have involved estrogen-progestin combinations, in general, oral contraceptive use was associated with a small increased risk of breast cancer. Three recent case-control studies (Titus-Ernstoff et al. 1998, Brinton et al. 1998, Rohan and Miller 1999) do not support the increased risk of breast cancer with oral contraceptive use suggested by the earlier studies reviewed by IARC (1999). Recent published reports indicate that oral contraceptive use may decrease the risk of ovarian and endometrial cancer (Salazar-Martinez et al. 1999), confirming the results of studies reviewed by IARC (1999).

The evidence for carcinogenicity of steroidal estrogens in humans is supported by experimental animal studies, which have shown that steroidal estrogens induce benign and malignant neoplasms, as well as preneoplastic lesions, in a variety of organs, including the mammary gland and female reproductive tract. The strength of evidence in animals differs for different estrogenic compounds. Estrogen compounds generally cause endometrial, cervical, and mammary tumors in mice; mammary and pituitary neoplasms in rats; and cancer of the kidney in hamsters.

Source: *Tenth Report on Carcinogens*, National Institute of Environmental Health Sciences, National Institutes of Health; <http://ntp-server.niehs.nih.gov>

The following article, **HRT Fails Again in Two Secondary Prevention Studies**, was taken from OBGYN.net at the web site www.obgyn.net.

HRT Fails Again in Two Secondary Prevention Studies – Findings show worsening of preexisting heart disease or no cardiac benefit. ‘Perhaps estrogen is more effective when it is used earlier,’ when vascular walls are still responsive.

CHICAGO –The results of two more studies of estrogen therapy in postmenopausal women with coronary artery disease continued the losing streak of this once-promising approach.

Both studies involved relatively small numbers of women, and both tested whether estrogen replacement could slow the progression of preexisting coronary-artery stenotic lesions as measured by quantitative, digital angiography. The results failed to show any benefit of estrogen over placebo, and in the larger of the two studies there actually was more disease progression and worse clinical outcome among the women treated with estrogen, researchers reported at the annual scientific sessions of the American Heart Association.

The finding from the smaller trial also stood in sharp contrast with the results from a parallel study published in 2001. In the earlier report, estrogen treatment led to significant slowing of atherosclerotic progression, compared with placebo in postmenopausal women without coronary artery disease. Because the current study was limited to women with documented coronary disease, they tended to be older, on average about 18 years beyond menopause, said Dr. Howard N. Hodis, director of the atherosclerosis research unit at the University of Southern California in Los Angeles.

“Perhaps estrogen is more effective when it is used earlier, when a woman’s vascular walls are still responsive to estrogen,” he said.

His study involved 226 women who had at least one coronary artery lesion that was at least 30% stenotic; the average age of the women was 63.4 years. They were randomized to treatment with 1 mg/day of

micronized, 17- β estradiol or placebo. Women with an intact uterus who received estrogen also received 5 mg/day of medroxyprogesterone acetate for 12 days each month.

After an average follow-up of 3 years, angiography showed that the extent of atherosclerotic progression was roughly comparable for all three treatment groups.

The second, larger study involved 423 postmenopausal women with at least one coronary stenosis of 15%-75%; their average age was about 65. The women were randomized to treatment with either 0.625 mg/day of conjugated equine estrogen or placebo. Women with an intact uterus who received estrogen also received 21.5 mg/day of medroxyprogesterone acetate.

After an average follow-up of 2.8 years, coronary artery disease progression was worse in the women treated with estrogen, although the difference was not statistically significant, reported Dr. David D. Waters, professor of medicine at the university of California, San Francisco.

However, when the women who died or had a myocardial infarction were factored into the outcome—the study was designed so that these women were presumed to have substantial atherosclerotic progression—the women on estrogen had a statistically significant worse outcome than those who received placebo. These results were published the same day that Dr. Waters reported them at the meeting (JAMA 288P[19]:2432-40, 2002).

Although clinical outcomes were not the primary end point for the study, these showed a striking effect from estrogen. During the entire study, 26 women in the estrogen group died or had a nonfatal myocardial infarction or stroke, compared with 15 women in the placebo group, a difference that just missed statistical significance. During the first year of follow-up, 12 women in the estrogen group died or had a myocardial infarction or stroke, compared with 6 women in the control group.

Written by Mitchel L. Zoler (Philadelphia Bureau) for OBGYN.net.

The following segments have been reprinted here from the foreword and chapter 13 of a book by Dr. John Lee, entitled **Natural Progesterone: The Multiple Roles of a Remarkable Hormone**. BLL Publishing, Sebastopol, CA 1989.

Discovery, it is said, favors the prepared mind. Such preparedness may occur as a result of intentional study or may be accident and/or serendipitous. In my case I credit serendipity. Some twenty-five years ago I was editor of our local medical society bulletin and responsible for a monthly editorial. Always casting about for topics of interest, I was facing a December editorial without any idea of a seasonally pertinent topic. During the week before the editorial due date, two intriguing articles crossed my desk. One was a Harvard Alumni journal article on the mystery of the Christmas mistletoe custom, i.e., a license to kiss any lady standing under a sprig of mistletoe, a custom apparently originating with the Celts for reasons unknown. The other was a JAMA story of a doctor recently retired from a career at the NIH who had visited his boyhood hometown in Texas and, in conversation with the local gypsy lady renowned for her successful "morning after" treatment for pregnancy prevention, discovered that her success involved the use of European mistletoe berries. The NewWorld mistletoe lacked the essential ingredient for this effect. His subsequent analysis of the European mistletoe berry found an unexpected high concentration of progesterone, as well as other sterols and glycosides, including digitalis.

Here was a mystery to be solved. Did the progesterone in mistletoe berries have anything to do with the Celts' use of them and what connection could it have with the Christmas holiday? Consulting Frazer's "The Golden Bough" and other references I've long since forgotten, it is clear that our knowledge of the Celts comes primarily from the Roman historian, Pliny. European Celts, called Gauls by the Romans, revered oak-grown mistletoe (a saprophyte) for its multiple medicinal benefits (their name for it being "All Heal"), as well as for its presumed sacred role, being sent by god as a sign of Life over Death. During the long frozen

winters, the non-deciduous oaks, its mistletoe, and the evergreens are the only green and growing plants among the leafless trees of the vast snow-covered forests; and only mistletoe produces its berries in the dead of winter.

The physician-priest leaders of the Celts, the Druids, had for many centuries held a mid-winter celebration timed to coincide with the winter solstice, starting on December 22-23 by our modern calendar. The event, lasting a week, was meant to celebrate the promise that the sun would not disappear entirely and that the world would not die but would be rejuvenated by the return of the sun and the coming of Spring. Debts were paid in full, gifts exchanged, fears were laid out, and a sacred concoction of hot mead laced with the revered berries, cut and collected in white cloth so as not to touch the ground, was plentifully supplied. We now know, of course, that progesterone stimulates libido and it is not difficult to imagine what whatever proscriptions there were against sexual license were relaxed considerably under the influence of the warm alcohol and progesterone drink. We also know that menstrual shedding is the result of an abrupt fall in progesterone levels, which undoubtedly occurred when the week's carousing was over. Thus, any conception that occurred during the week of unrestricted sex would be lost with the induced menstrual flow, re-enforcing the perception that festival sex without subsequent responsibility was merely another gift of the gods. When the midwinter week-long celebration was over, the leaders proclaimed the start of a new year and life among the Celts returned to normal.

The medicinal benefits of mistletoe were highly regarded throughout a number of different cultures of what is now Europe and elsewhere, even among the Aino of northern Japan. Concoctions of mistletoe were used to assist conception in humans and domesticated animals; to restore a zest of life; to cure epilepsy; to heal ulcers; and many other ailments. In a parallel to recent FDA pronouncements that deserves more attention, authorities of "modern" times earlier this century declared that mistletoe had no medicinal

value and was, in fact, dangerously poisonous. One might argue that the real message is that items of healing and health must be kept out of the hands of ordinary folk and left strictly to the authorities and their professional guilds.

So it was that I wrote my Christmas editorial a quarter century ago on the subject of mistletoe, pointing out that the seasonal license to kiss any woman standing under a twig of mistletoe was merely a pale reminder of the sexual license enjoyed by the Celts during their winter solstice celebration, a gift of the natural progesterone, if not the gods, found in the mistletoe berry. As one might expect, I heard from a number of readers, some licensed that I had implied a non-Christian, perhaps again, relic appearing in the celebration of Christ's birth (but offering no other explanation for the custom); but others pointed out to me that this business of hormones in plants was not at all unusual in that over 5000 plants contain progesterone-like substances. The word phyto-hormone was not yet in vogue. A number of surprisingly tolerant responses came from theological school sources, also, asking for further references.

Some years later, in 1978 when I heard Dr. Ray Peat lecture on the subject of natural progesterone derived from wild yam root, the concept was not at all strange to me. I had been in practice long enough to realize that estrogen along with calcium and vitamin D was not the complete answer to osteoporosis. Neither did I doubt that progesterone was absorbable transdermally. The fact that osteoporosis accelerated at the time of menopause strongly implicated the gonadal hormones. If estrogen alone wasn't the answer, perhaps progesterone was also involved in keeping bones strong. Faced with menopausal osteoporotic patients unable to use estrogen by reason of prior breast or uterine cancer or other contraindications, it seemed entirely reasonable to me to offer them the option of using a progesterone skin cream moisturizer (Cielo) readily available over-the-counter.

In a further incidence of serendipity, Dr.

Malcolm Powell had just recently opened a facility offering relatively low cost dual photon absorptiometry (DPA), thus making accurate evaluation of bone mineral density a reality for those of us in clinical practice. To my considerable surprise, serial lumbar DPA tests showed actual *increase*, rather than mere delayed loss, in these patients. With that as encouragement, I broadened the scope of progesterone therapy to include patients already on estrogen and found the same results. As if that were not enough, the patients reported improvement in other areas as well—increased alertness and energy, relief of breast fibrocysts and related mastodynia, recovery from mild hypothyroidism, decreased need of aspirin or anti-inflammatory drugs, normal blood pressure in those previously with mild hypertension, and, most unexpected of all, a return of normal libido. The icing on the cake was the fact of no hint of side effects.

As patient after patient showed the same pattern of benefits from transdermal natural progesterone, it did not take long to accumulate data to share with my colleagues. It was here, however, that another unexpected dimension of progesterone therapy arose: my colleagues applauded my presentations but, almost uniformly, chose not to apply the treatment to their patients. Their reasons were weak and self-serving, it seemed to me, invoking the fear of mal-practice, their liability if perchance one of their patients developed cancer, their concern about what colleagues might think, and the fact that no pharmaceutical company had undertaken to sponsor the treatment. Several, of course, called to inquire about details of my treatment plan since they wanted to use natural progesterone to treat their wives, mothers, or mothers-in-law. Over-riding all, however, was (1) their reliance on some official sanction before using natural progesterone instead of some synthetic progestin, and (2) their rather remarkable ignorance of hormone physiology. Given all the distractions of clinical practice, going "by the book" requires much less effort (and is perceived a whole lot safer) than thinking for oneself, regardless of the potential benefit it might provide to the patient.

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In the fifteen years since then, I have seen the consistent benefits and the safety of natural progesterone therapy. I have learned a great deal and obviously there is still more to learn. I have an urge to share what I have learned. You may call it mundane, but this is the simple reason I have written this book. I hope you enjoy reading it; you may even learn something from it and, in the process, re-enforce the confidence and will power to act in the best tradition of being a physician scientist and a strong advocate for your patients.

Chapter 13 - Progesterone and the Medical-Industrial Complex

If natural progesterone is so wonderful, why isn't it used by [all] doctor[s]? This is the question I am most frequently asked. My answer is that it is not favored by the medical-industrial complex. The reasons for my answer derive not from a systematic study of the problem but from personal experience of over thirty years of active clinical practice and observing the various ways, some subtle and some not so subtle, medical malpractice is influenced.

The medical-industrial complex refers to the close-knit association of organized medicine with pharmaceutical manufacturers and governmental medical regulatory agencies. The connections between these groups is, of course, a web of money, power, and prestige. The system taken together is neither necessarily corrupt nor evil but, like any human agency, is subject to the frailties and faults of humankind. Selling medical drugs is very big business. Medical research is dependent on the \$billions of grants from the National Institutes of Health (NIH) and the private pharmaceutical industry. The two are closely interlocked; managers in one tend to have come from success in the other with many examples of interchangeable personnel.

Any given pharmaceutical company, like any private enterprise, must make a profit to stay alive. Profit comes from sales of patented medicines. The "system" is not interested in natural (non-patentable) medicines, regardless of their potential health benefits. Thus, the flow of research funding does not extend to products

which can not be patented. Experts in research, therefore, tend to have experience only with patented drugs and little or none with natural products or non-patentable procedures. When an NIH or industry-supported academic "expert" speaks on the subject of a natural product or, say, acupuncture, you can be sure that he has had very little, if any, experience using it; or, if he speaks from the literature, you can be sure it is the literature of the medical-industrial establishment. The recent widely-advertised open-mindedness of the NIH to alternative therapies is not sufficiently funded to more than lightly touch on a few items of the wide field that actually exists.

Few people know that the definition of malpractice hinges on whether or not the practice is common among one's medical peers and has little (usually nothing) to do with whether the practice is beneficial or not. A doctor willing to study, to learn the ins and outs of an alternative medical therapy, and to put what he has learned into practice in helping patients is potentially exposing himself to serious charges of malpractice. And he can expect no help from organized and what passes as "organized medicine" is merely a handmaiden to the powers of health agencies and the pharmaceutical industry. The great majority of academic physicians, for instance, do not bother to belong to the AMA. Why should they, when all money and career advances come from the mercy of the funding agencies?

But what has all this to do with natural progesterone? The answer is quite simple, really. Ample medical research regarding progesterone was carried on in the 1940's through the 1960's, and amply reported in mainline, recognized medical literature. Since the early 1970's, however, medical research has become much more expensive and the grants subsidizing progesterone (or any unpatentable medicine or treatment technique) research have dried up and been blown away by the contemporary trade winds of synthetic drugs, particularly the progestins. The potential market for patentable progestins is vast—contraceptive pills, irregular menses, osteoporosis, prevention of endometrial

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cancer—literally every woman through every age from puberty on is a target for a sale. Do you think the prevailing powers wish to see this lucrative market be left to a natural product.....in the hands of physician prescribers and not controlled by the pharmaceutical industry?

Licensed doctors are easy to control. All practicing US physicians must accumulate a given number of hours of “continuing medical education” or CME. Sounds like a good idea, doesn’t it? But where does he acquire his CME credits? From authorized CME seminars, that’s where. And who authorizes which seminar for CME credits? Organized medicine, that’s who. And who sponsors and who provides the speakers for CME-credited seminars? The pharmaceutical industry and its grant –funded corps of academic researchers, that’s who. US physicians are the captive audience for pharmaceutical advertising. They learn which drugs to prescribe. They do not learn of alternative and perhaps better ways of treating illness. If one were to seek this information for himself, he finds himself outside the realm and benevolence of his professional guild. Further, he is reluctant to be perceived as practicing in a manner different than his peers not only because of his fraternal associations with them but also because of the threat of malpractice charges, however unfounded. Thus, when he hears of the uses of natural progesterone, he wonders why none of his associates know about it. If it is not commonly known, it must in some way be false and/or unapproved. Having given the lectures on the role and medical uses of natural progesterone, I have observed numerous instances wherein perfectly fine physicians will inquire about obtaining the product for use by their wives or mother-in-law but not for their patients. What can account for such behavior by professionals? I suspect it is fear of alienation from the flock that is paramount in their minds.

How can this be changed? It will be changed when intelligent, motivated and assertive patients insist on this form of care. If progestins were the equivalent of natural progesterone in effect and safety, the argument would be moot. But

progestins are *not* the equivalent of natural progesterone and never will be. It is extremely unlikely that man can synthesize a hormone better than the one Nature derived from eons of natural selection.

Patients are aware that they can not leave their health care solely in the hands of the doctor. They must assume the responsibility for their own health. They must become knowledgeable and seek informed opinion from various sources. They know that the same medicine is not necessarily the best medicine for every individual. They want their medical advisors to join with them in a partnership for health; they will no longer put up with the present condescending child-parent relationship. Their empowerment must come through knowledge. This is the purpose of this book – to share the knowledge that I and others have accumulated over the past two to three decades of study, particularly as it pertains to progesterone, a natural hormone too remarkable to remain neglected.

Natural Progesterone: The Multiple Roles of a Remarkable Hormone. BLL Publishing, Sebastopol, CA 1989, by Dr. John Lee.

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