A Brief History of Bio-identical Hormones

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(Click on SCIENCE and then HISTORY AND POLITICS OF BIO IDENTICAL HORMONES)

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Bio-identical hormones have been in use for thousands of years. The first record of their use goes back to Ancient China where the aging female nobility routinely ingested dried young women's urine to counteract problems associated with menopause. The reason for this type of therapy was that young women's urine contains the metabolic waste products of estrogen, progesterone, and testosterone. Throughout history you can find references to the use of young women's urine to help older women with problems of aging.

Research and development of synthetic and equine hormones since the 1940s has provided the basis for most references on modern hormone replacement therapy (HRT). Current conventional practice, which is derived from this research, is to prescribe progestins and estrogens that are not molecularly the same as those found in the human body. Even though bio-identical hormones were known to be effective and were available as early as the 1930s, the only way to avert their destruction by the digestive tract was to administer them intramuscularly in a painful oil-based injection. Since pharmaceutical companies could not patent natural substances and the technology was not available to painlessly get bio-identical hormones into the body, researchers came up with an alternative.

Oral conjugated equine estrogens (CEEs) were the first non-bio-identical hormones to be developed. Mass marketing helped make estrogen-only replacement therapy (ERT) popular until the mid-1970s, when ERT was associated with endometrial cancer. The popularity of ERT then plummeted, until scientists observed that endometrial cancer was not a significant occurrence in women whose ovaries produced a proper balance of estrogen and progesterone. A synthetic non-human form of progesterone, called progestin, was developed by the 1980s to balance the non-bio-identical estrogens in commercially available HRT preparations. To add to the confusion in HRT development, the term "progesterone" was used interchangeably with the term "progestin" in medical, nursing and pharmaceutical literature. Prescribers often assumed them to be one in the same, although their effects on the human body were very different.

In the late 1980s, the micronization of bio-identical steroids allowed absorption of progesterone orally, and estradiol, estriol and testosterone in therapeutic amounts via transdermal routes.

Micronized 'human' progesterone became available in Europe in the late 1980s, in Canada in 1995, and was approved by the U.S. FDA in 1998. It has been available from U.S. compounding pharmacists for years, and the active component is bio-identical to endogenous progesterone. Micronization of BHRT enables it to be released slowly and readily absorbed by several routes other than the painful IM injections of the 1930s. However, physicians and affiliated health professionals don't typically learn

about this option in their medical, nursing or pharmaceutical educational programs. They therefore don't consider it unless their patients ask for BHRT.

Despite clinical studies that document benefits of HRT, many women don't take any form of HRT and experience a diminishing quality of life related to peri-menopausal symptoms. On the other hand, female baby boomers are entering menopause at an ever increasing rate and many do not experience total remission of peri-menopausal symptoms with conventional, non-bio-identical, synthetic equine HRT options. By using non-bio-identical hormones, women trade off peri-menopausal symptoms for unwanted medication side effects and incomplete symptom relief.

Several factors can influence how each woman uniquely responds to non-bio-identical HRT. Women who take traditional HRT preparations metabolize then to derivative hormones that bind 2.1 to 3.2 times more firmly to receptor sites than our endogenous hormones. The chemical structure of these non-bio-identical substances is very different from hormones that humans produce. Non-bio-identical estrogens contain animal hormones (e.g. Equilin a true horse estrogen) bind to receptors with two fold to eighteen fold potency, and produces metabolites that contribute to hypertension.

Synthetic progestins tend to increase LDL and decrease HDL cholesterol concentrations, as well as decrease sex hormone-binding globulin (SHBG). This decrease in SHBG can result in an increase in free sex hormone levels and potentially increased androgenicity. Compliance can be an issue due to the varied side effects of conventional non-bio-identical HRT. In fact, only an estimated 10% to 20% of postmenopausal women continue HRT on a long-term basis. Non-bio-identical hormones cannot flow through the steroid pathway and produce moment-to-moment balances in hormone levels as do our endogenous precursor steroids.

Bio-identical HRT

Bio-identical HRT is also referred to as 'natural' HRT and 'human-identical' HRT in the literature. A bio-identical steroid hormone is not human in origin but is identical in organic structure and function to human hormones. Bio-identical hormones are derived from a type of plant oil called diosgenin, which is very similar in chemical structure to our endogenous precursor steroid hormone, cholesterol. Diosgenin is extracted from soybeans and wild yams. These crops can abundantly and inexpensively produce the oil, which is also available in several thousand other plants worldwide. Diosgenin is then chemically altered in a lab to exactly match our human bio-identical steroids. Any allergenicity to these plants is also removed during the conversion process.

There are more than 15 endogenous steroid hormones, each with its own metabolites and an enzyme system that converts them from one steroid to another from moment to moment. This is known as the steroid hormone cascade. Any deficiency in this system will cause symptoms that are unique to certain steroids. Another important concept is that we need an appropriate amount of precursor hormones, such as cholesterol and pregnenolone, which are located at the top of the cascade. The enzymes then convert these on down the cascade into the steroids that are essential to our hormonal balance.

The steroid family is classified in five major categories including the estrogens (estradiol, estriol, estrone), progesterone, androgens (DHEA, testosterone, androstenedione), glucocorticoids (cortisol, cortisone) and mineralcorticoids (aldosterone).5,6,11 The human female body produces three estrogens with very specific roles. Estrone (E1) is a proliferative estrogen that comprises about 10% of the total estrogens premenopausally. Estradiol (E2) is a proliferative estrogen and the most potent estrogen premenopausally comprising another 10% to 20% of the total. Estriol (E3) is the very weak non-proliferative estrogen dominant in pregnancy E1 and E3 are made in the body from E2. All estrogen hormones (estrone, estradiol, and estriol) bind to the same receptor sites with different affinity. Estradiol is the most potent and is converted to the weaker estrone, and then to estriol under the influence of progesterone.

BHRT can be compounded to replace any of several types of deficient steroids in amounts individualized to the unique needs of each woman. Compounding pharmacists, who work closely with prescribers, have hundreds of individualized formulations in their databases that are representative of the unique needs of their clients. Compounding pharmacists who are specifically trained comply with specific, well-researched guidelines to produce pure, standardized formulations. These compounding pharmacists obtain pharmaceutical-grade hormones, researched formulas, guidelines and technical support from their professional organization to provide the highest quality product to consumers. As compounded BHRT becomes more popular, prescribers need to familiarize themselves with pharmacists who are members of their professional compounding organization. The International Academy of Compounding Pharmacists (IACP) will refer patients and prescribers to IACP members in their areas.

Over the past few years, a handful of bio-identical hormones have become available among commercially prepared HRT options. Pharmaceutical companies have avoided the restriction on patenting natural substances by patenting the delivery systems of the bio-identical hormones. Allergic skin reactions to the patented glue in the estradiol patches and allergies to the patented peanut oil release mechanism in oral progesterone capsules are examples of limitations with commercial bio-identical preparations.

Evaluating the Need for BHRT

Candidates for BHRT include women who have had hysterectomies, who have personal or family histories of cardiovascular disease, osteoporosis or Alzheimer's, and women with peri-menopausal symptoms that affect their quality of life.

The most commonly reported symptoms of menopause are hot flashes, night sweats, fatigue, vaginal dryness, mood swings, tender breasts, fluid retention, memory lapses, sleep disturbances and decreased libido.

Patients experience very few, if any, side effects while taking Bio-identical HRT that is prescribed in physiologic doses. Oral progesterone can cause drowsiness in about 2% to 5% of women who use it, an outcome of how it is metabolized by their hepatic systems. It is therefore usually taken orally at bedtime. Bio-identical hormones prescribed in non-physiologic doses can cause minor symptoms related

to excessive supply, such as increased breast tenderness and headaches with too much estrogen or reversible mild acne of hair growth with too much testosterone.

The advantages of BHRT are that it is individualized, well-tolerated and produces exceptional symptom reversal in most cases. The only possible disadvantage of compounded BHRT is that prescribers must commit themselves to a new level of learning and creative problem-solving as they step beyond the basics taught in medical school.

Fast Forward to the Politics of our Times

In the late 1960s, Wyeth-Ayerst Pharmaceuticals introduced Premarin in the U.S., a patented hormone replacement made from pregnant mare's urine. Using young women's urine, although available and cheap, was not a marketing option for Wyeth because women's urine cannot be patented. In the 1960s, getting a patent became the major driving force for drug production in the United States. The marketing of patented drugs proved to be the best way to make money. As the drug companies went public, the only thing that mattered was the bottom line. (An interesting aside is that in the 1970s human insulin came to the market and changed management of diabetes for the better. Perhaps women in menopause aren't as important).

For 30 years, Premarin (and subsequently Provera) was marketed to millions of women as the best way to eliminate symptoms of menopause and even prevent cancer, heart disease and osteoporosis. In the early 1990s, while believing their own marketing data, Wyeth Pharmaceuticals (then treating more than one million women a year with Premarin and Provera) decided to partner with the National Institutes of Health to conduct a national study to evaluate the long term effects of Premarin and Provera in post menopausal women. The study was conducted in hundreds of academic centers around the country. Oddly, the premise for the study was based on assumptions that had no proof!

The NIH proceeded with the study with extensive financial support and free Premarin from Wyeth. The unspoken goal of the study (from Wyeth's point of view) was to prove that aging women needed Premarin to protect them from diseases of aging. In 2002 the study was abruptly stopped because after almost eight years too much data accumulated against Premarin, suggesting it increased the incidence of heart attacks and certain types of cancers and strokes in the study participants.

Based on the Results of the Women's Health Initiative the Following Happened

Extensive media coverage of the abrupt discontinuation of the study created mass confusion among millions of women who were taking the drugs and the doctors who were prescribing them.

The government was concerned the results of the study might expose their intimate involvement with Wyeth, the manufacturer of Premarin. Consequently, a federal decision was made to distance the NIH from Wyeth by making a public statement to the media that all hormones are bad. Nevertheless, Premarin and Provera were not removed from the market.

Little productive has happened since the summer of 2002. Grumblings against synthetic hormones and anecdotal reports in favor of bio-identical hormones could be heard around the country, but not much

more. Initially doctors were recommended to stop writing prescriptions for Premarin and Provera. In time though, Wyeth renewed its marketing efforts with low dose Premarin and Provera and recommended their use for "short a period of time as possible". No other research or options for women in menopause appeared available.

Women around the country started learning about bio-identical hormone options from a growing cadre of compounding pharmacists and "alternative" medicine doctors. At the academic centers, no one talked of hormones if they could help it. Drug company grants are vital to most academic medical research institutions. Books for the public were published on bio-identical hormones but nothing filtered through to academic institutions. In 2004 a book by Suzanne Somers called The Sexy Years brought the option of bio-identical hormone therapies to the general public. What had been a grass roots movement started to gain some steam.

By 2005, bio-identical hormones had reached millions. Wyeth had lost billions of dollars in revenue and decided to retaliate. First, they petitioned the FDA in October 2005. Wyeth submitted a Citizens' Petition to the FDA asking for stronger regulation and federal supervision of compounding pharmacies that produced bio-identical hormone preparations. Keep in mind that the practice of pharmacy and medicine are legislated at the state level. In reality, Wyeth was asking the federal government to step in and protect their corporate financial interests.

Without any publicity, tens of thousands of women sent in letters and e-mails to the FDA asking for the Wyeth petition to be rejected. The word was out "Please let me keep getting my bio-identical hormones from the compounding pharmacies". Women were asking to keep this viable option for treatment available. Media attention to the Wyeth petition precipitated a swift reaction from the drug manufacturer. Website information on menopause promoted the use of Premarin and used paid medical experts to bash bio-identical hormones as a marketing term. This resulted in even more confusion.

Finally, in October 2006, a controversial new book by Suzanne Somers pushed the envelope even further. While Ms. Somers is an avid proponent of bio-identical hormones, her new book served to push bio-identicals further into the fire. Wyeth and the North American Menopause Society (an association sponsored by Wyeth) retaliate through the AMA. While everyone was arguing in 2006, the AMA passed a resolution in support of Wyeth asking for more regulation from the FDA in the area of compounded bio-identical hormones. Fortunately, the United Sates Congress, in a display of wisdom, summarily rejected the FDA's submitted regulation as requested by Wyeth. The facts below speak for themselves.

1. Bio-identical hormones are medications, they are not natural products. They are manufactured by drug companies from soy and yam oils. The only natural thing about them is their molecular formula which is identical to the molecular formula of hormones our bodies make. The difference between equine and bio-identical hormones is crucial information that most medical schools have not taught their students.

2. The term bio-identical is not a marketing term, it is a descriptive term. It describes the biologically identical molecular structure of bio-identical hormones. It is a term that makes the important distinction between bio-identical hormones and non-biologically identical hormones.

3. Bio-identical estradiol, progesterone and testosterone are FDA approved. Estradiol and testosterone can only be obtained by prescription through a licensed medical practitioner (some states allow nurse practitioners to write prescriptions while others do not). Estriol is not FDA approved.

4. Progesterone is the only bio-identical hormone available without prescription in low doses, 50 mg or less per unit dose.

5. Bio-identical hormones are commercially available from pharmaceutical companies in formulations in which they can patent the transport system such as in troches, gels, patches, and creams. Examples include but are not limited to the following: Vivelle patch, Climara, Estraderm, Estrace, Prometrium, Androgel. These commercially available bio-identical hormones cannot have the dose adjusted. They are standardized to specific doses. Also, the hormones are not delivered in a steady state manner, but have peaks in valleys in blood levels as well as varying rates absorption through the skin due to skin environmental factors at the time of application (dryness, moistness, flakiness, etc.)

6. To circumvent this dosing problem compounding is another viable option for the use of bio-identical hormones. Compounding pharmacies provide individualized preparations of bio-identical hormones in gels, creams, capsules, sublingual troches, and subdermal pellets.

7. Bio-identical hormone pellet insertion offers a sustained release and high compliance way to regulate blood hormone levels at a steady state. They also avoid the problem of hepatic degradation to active metabolites (via the portal system) as seen when oral ingestion of testosterone and estradiol are attempted.

What is Needed for the Future

Today, we are standing in the midst of a crisis between science, politics, and the corporate profit motive. Men and Women's health is at stake. We need university studies that are funded by non-profits and the government to follow up on the potential of better health through bio-identicals. The savings in terms of human suffering and health costs could be huge.

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