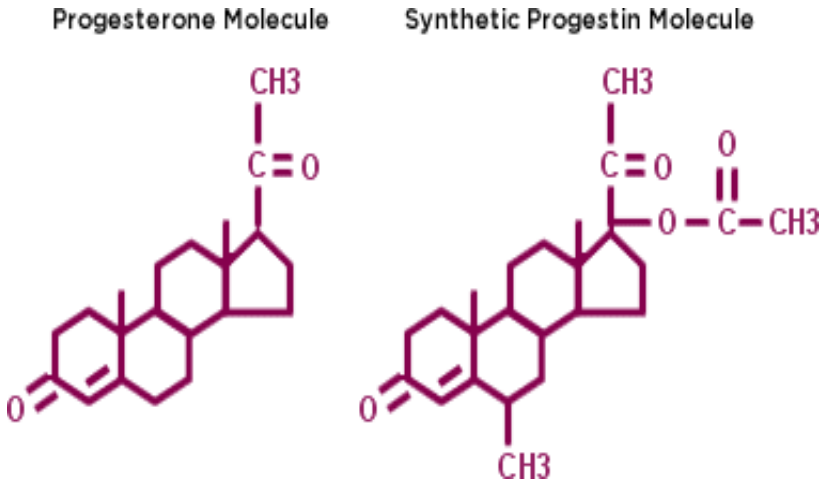
*A Traditional Naturopathic Perspective and Discussion on*

# Bio-Identical Hormones

## Part 1

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## *Introduction*

The subject of hormone therapy is a big one in our modern times. In fact, the endocrine system, which governs the world of hormones, provides many challenges for both the conventional and naturopathic communities. It's nature as a system in constant flux – one that is both setting the stage for health and responding to it can be tricky. One treatment therapy that has emerged as a more "natural" treatment for the ups and downs of the endocrine system is "Bio-Identical Hormone Therapy". The term Bio-identical is not a marketing term, it is a descriptive term. It describes the biologically identical molecular formula born by Bio-identical hormones. It is a term that makes the important distinction between Bio-identical hormones and non-biologically identical or synthetic hormones. Their popularity in use came about somewhat as a response to the dangers of conventional Hormone replacement therapy or HRT. Bio-Identical Hormone replacement therapy or BHRT has been hailed as a "VERY SAFE" and "NATURAL" alternative to conventional HRT since the composition of the hormones are chemically the same as human hormones. But what exactly is BHRT, where did it come from, and what is it's safety profile? As traditional Naturopathic practitioners, this realm of therapies does not fall under our jurisdiction in terms of prescribing the compounded forms of BHRT - but knowledge of these products is vital. Especially since a few, somewhat standardized Bio-identical hormones are available over-the-counter. These products carry the term "natural" in their descriptions, and because of this, much of our client

base may be encouraged to try them as an alternative to conventional HRT. There are two parts to this research work:

- Part 1 reviews the endocrine system, goes into detail about the history of hormonal products, provides an overview on the production and preparation of Bio-identical hormones, and answers the simple questions of "What are Bio-identical hormones and Are they safe?
- Part 2 goes into detail about the production of Bio-identical hormones, how to suggest them based on current products available, how to assess inputs of diet, herbal alternatives, and discusses how to obtain laboratory tests for hormones using blood, urine, and saliva.

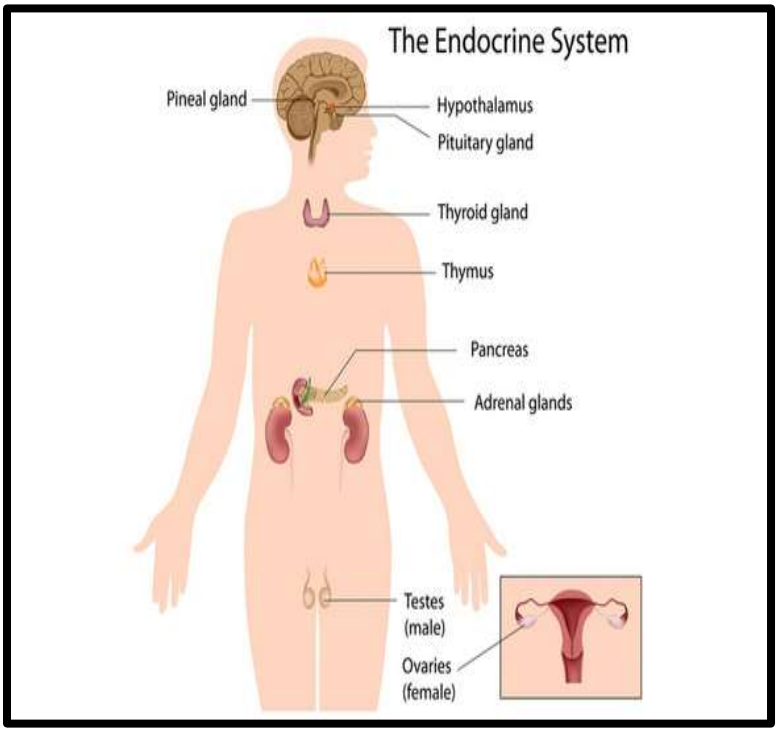
With careful client observation and guide, a Traditional Naturopathic practitioner could work with a client using these natural forms of hormones along with diet, exercise - whatever would be needed for a client. It is imperative that naturopathic practitioners have a working knowledge of the endocrine system - plus these products – to know what pitfalls to look for. The sheer number of hormonal products that exist and the detail and scrutiny needed to assess what is available stands as reason alone to gain a better understanding of efficacy. Bio-identical hormones need to be examined for ingredient source, side effect profile, and effects from long term use. Though they are a "natural product", problems can arise from obtaining a low-quality product! If the product quality is especially low, it is possible no result could be obtained and it amounts to money wasted. Intimate knowledge of BHRT is important because

it may provide needed overlap with our own suggestions for treatment in regard to hormone balancing. The vast majority of hormone imbalance that both men and women experience can be addressed with diet and lifestyle changes if the client is willing to do the work needed. Often though, this work is not of interest to clients. BHRT does provide fairly quick results and can often boost a client's health program exponentially. If a client is using BHRT, it is crucial to understand what changes the client may experience, if the product is working well, how to wean off it once balance is established, and some good referral information should a client want to source the product. This research work (part 1) will provide a brief history of HRT and BHRT, will cover the mechanisms involved with BHRT, give clear and concise definitions for terminology a practitioner would encounter with BHRT, and provide an answer to the question of safety and efficacy as it relates to BHRT. Part 2 of this research work will provide suggestions, product examples, considerations, and dosing guidelines for Naturopathic practitioners so work can be done proactively and intelligently to restore health and balance.

## *THE ENDOCRINE SYSTEM*

The endocrine system is made up of a network of glands. These glands secrete hormones to regulate many bodily functions, including growth and metabolism. The glands are also involved with tissue function, sexual function, reproduction, sleep, mood, and a host of other body processes. The glands are controlled directly by stimulation from the nervous system as well as by chemical receptors in the blood and hormones produced by other glands.

By regulating the functions of organs in the body, these glands help to maintain the body's homeostasis. The primary glands of the endocrine system include the Hypothalamus, Pituitary, Pineal, Thyroid, Parathyroid, Adrenal, Pancreas, Gonads, and the Thymus. In addition to the glands of the endocrine system, many other non-glandular organs and tissues in the body produce hormones. An example of a non-glandular organ producing a hormone can be found in the cardiac muscle tissue of the heart. This tissue is capable of producing the hormone atrial natriuretic peptide (ANP) in response to high blood pressure levels. ANP works to reduce blood pressure by triggering vasodilation to provide more space for the blood to travel through. ANP also reduces blood volume and pressure by causing water and salt to be excreted out of the blood by the kidneys. The kidneys, digestive system, placenta, damaged tissues, and even adipose tissue or fat produce hormones when necessary. In many ways, the entire body could be considered part of the endocrine system.

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The hypothalamus is a part of the brain located superior and anterior to the brain stem and inferior to the thalamus. It serves many different functions in the nervous system and is also responsible for the direct control of the endocrine system through the pituitary gland. The hypothalamus contains special cells called neurosecretory cells—neurons that secrete hormones:

- Thyrotropin-releasing hormone (TRH)
- Growth hormone-releasing hormone (GHRH)
- Growth hormone-inhibiting hormone (GHIH)
- Gonadotropin-releasing hormone (GnRH)
- Corticotropin-releasing hormone (CRH)
- Oxytocin
- Antidiuretic hormone (ADH)

All of the releasing and inhibiting hormones affect the function of the anterior pituitary gland.

The pituitary, also known as the hypophysis, is a small pea-sized lump of tissue connected to the inferior portion of the hypothalamus of the brain. Many blood vessels surround the pituitary gland to carry the hormones it releases throughout the body. Situated in a small depression in the sphenoid bone called the sella turcica, the pituitary gland is actually made of 2 completely separate structures: the posterior and anterior pituitary glands. The posterior pituitary gland is actually not glandular tissue at all, but nervous tissue instead. The posterior pituitary is a small extension of the hypothalamus through which the axons of some of the neurosecretory cells of the hypothalamus extend. These neurosecretory cells create 2 hormones in the hypothalamus that are stored and released by the posterior pituitary:

- Oxytocin triggers uterine contractions during childbirth and the release of milk during breastfeeding.
- Antidiuretic hormone (ADH) prevents water loss in the body by increasing the re-uptake of water in the kidneys and reducing blood flow to sweat glands.

The anterior pituitary gland is the true glandular part of the pituitary gland. The function of the anterior pituitary gland is controlled by the releasing and inhibiting hormones of the hypothalamus. The anterior pituitary produces 6 important hormones:

- Thyroid stimulating hormone (TSH), as its name suggests, is a tropic hormone responsible for the stimulation of the thyroid gland.
- Adrenocorticotropic hormone (ACTH) stimulates the adrenal cortex, the outer part of the adrenal gland, to produce its hormones.
- Follicle stimulating hormone (FSH) stimulates the follicle cells of the gonads to produce gametes—ova in females and sperm in males.
- Luteinizing hormone (LH) stimulates the gonads to produce the sex hormones—estrogens in females and testosterone in males.
- Human growth hormone (HGH) affects many target cells throughout the body by stimulating their growth, repair, and reproduction.
- Prolactin (PRL) has many effects on the body, chief of which is that it stimulates the mammary glands of the breast to produce milk.

The pineal gland is a small pinecone-shaped mass of glandular tissue found just posterior to the thalamus of the brain. The pineal gland produces the hormone melatonin that helps to regulate the human sleep-wake cycle known as the circadian rhythm. The activity of the pineal gland is inhibited by stimulation from the photoreceptors of the retina. This light sensitivity causes melatonin to be produced only in low light or darkness. Increased melatonin production causes humans to feel drowsy at nighttime when the pineal gland is active.

The thyroid gland is a butterfly-shaped gland located at the base of the neck and wrapped around the lateral sides of the trachea. The thyroid gland produces 3 major hormones: Calcitonin, Triiodothyronine (T3), Thyroxine (T4).

The parathyroid glands are 4 small masses of glandular tissue found on the posterior side of the thyroid gland. The parathyroid glands produce the hormone parathyroid hormone (PTH),which is involved in calcium ion homeostasis.

The adrenal glands are a pair of roughly triangular glands found immediately superior to the kidneys. The adrenal glands are each made of 2 distinct layers, each with their own unique functions: the outer adrenal cortex and inner adrenal medulla. The adrenal cortex produces many cortical hormones in 3 classes: glucocorticoids, mineralocorticoids, and androgens.

- Glucocorticoids have many diverse functions, including the breakdown of proteins and lipids to produce glucose. Glucocorticoids also function to reduce inflammation and immune response.
- Mineralocorticoids, as their name suggests, are a group of hormones that help to regulate the concentration of mineral ions in the body.
- Androgens, such as testosterone, are produced at low levels in the adrenal cortex to regulate the growth and activity of cells that are receptive to male hormones.

The adrenal medulla produces the hormones Epinephrine and Norepinephrine under stimulation by the sympathetic division of the autonomic nervous system. Both of these hormones help to increase the flow of blood to the brain and muscles to improve the “fight-or-flight” response to stress. These hormones also work to increase heart rate, breathing rate,

and blood pressure while decreasing the flow of blood to and function of organs that are not involved in responding to emergencies.

The pancreas is a large gland located in the abdominal cavity just inferior and posterior to the stomach. The pancreas is considered to be a heterocrine gland as it contains both endocrine and exocrine tissue. The endocrine cells of the pancreas make up just about 1% of the total mass of the pancreas and are found in small groups throughout the pancreas called islets of Langerhans. Within these islets are 2 types of cells—alpha and beta cells. The alpha cells produce the hormone Glucagon, which is responsible for raising blood glucose levels. Glucagon triggers muscle and liver cells to break down the polysaccharide glycogen to release glucose into the bloodstream. The beta cells produce the hormone Insulin, which is responsible for lowering blood glucose levels after a meal. Insulin triggers the absorption of glucose from the blood into cells, where it is added to glycogen molecules for storage.

The gonads—ovaries in females and testes in males—are responsible for producing the sex hormones of the body. These sex hormones determine the secondary sex characteristics of adult females and adult males. The testes are a pair of ellipsoid organs found in the scrotum of males that produce the androgen Testosterone in males after the start of puberty. Testosterone has effects on many parts of the body, including the muscles, bones, sex organs, and hair follicles. This hormone causes growth and increases in strength of the bones and muscles, including the accelerated growth of long bones during adolescence. The ovaries are a

pair of almond-shaped glands located in the pelvic body cavity lateral and superior to the uterus in females. The ovaries produce the female sex hormones Progesterone and Estrogens. Progesterone is most active in females during ovulation and pregnancy where it maintains appropriate conditions in the human body to support a developing fetus.

The thymus is a soft, triangular-shaped organ found in the chest posterior to the sternum and superior to the heart. The thymus produces hormones called thymosins that help to train and develop T-lymphocytes during fetal development and childhood. The thymus changes its size and function during our life cycle. It is largest and most active in newborns, infants and in the years prior to adolescence. By the early teens, the thymus begins to shrink and thymus tissue is replaced by fatty tissue. Nevertheless, a small amount of T -lymphocyte production and education continues throughout adult life.

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## *Early Endocrinology, Menopause, and the rise of Estrogen*

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Modern hormone therapy can be traced to research and work begun in the 1900's. The nature and work of chemical messengers in the body had attracted the interest of scientists curious to find some answers. Experimental work by pioneers such as Arnold Adolphe Berthold in Germany and Claude Bernard in France, in the middle of the nineteenth century, established the concept that some sort of chemical communication takes place between different organs in an animal. Later in the same century, several physicians described the successful treatment of patients with certain disorders by administering extracts of animal endocrine tissues, such

as the thyroid, adrenal glands and pancreas; they subsequently showed that these disorders were due to hormonal deficiencies. In 1902, English physiologists Ernest Starling and William Bayliss discovered the first-ever hormone. It was called Secretin and it helped maintain water homeostasis throughout the body. This discovery proved to be a significant milestone. In 1925, modern scientists unveiled human hormonal make-up and began to differentiate between hormones. Researchers concentrated their efforts on identifying the source of these internal messengers, with the result that many hormones were named after the gland or organ from which they are secreted, such as thyroid or adrenal. This system of nomenclature is not always perfect, because distinct hormones can be secreted by the same gland, as, for example, with the pituitary and the pancreas. None-the-less, scientists succeeded in deciphering the chemical nature of hormones. Less than 20 years after Starling had coined the word 'hormone', Edward Calvin Kendall at the Mayo Clinic in Rochester, NY, USA, purified and determined the structures of Cortisone (a steroid) and Thyroxine (an iodoamino acid).

In 1926, Sir Charles R. Harington in London performed the first chemical synthesis of a hormone, Thyroxine. His breakthrough work was soon followed by the characterization of the nature and activity of the pancreatic hormone Insulin—a protein—by Sir Frederick Grant Banting and Charles Herberg Best. In the 1920s and 1930s, Adolf Butenandt, Tadeus Reichstein and Edward Adelbert Doisy discovered and characterized various steroid hormones, including Estrogen, Testosterone and Progesterone. This increasing knowledge of physiological actions led to many hormones being named according to their actions, such as growth hormone and

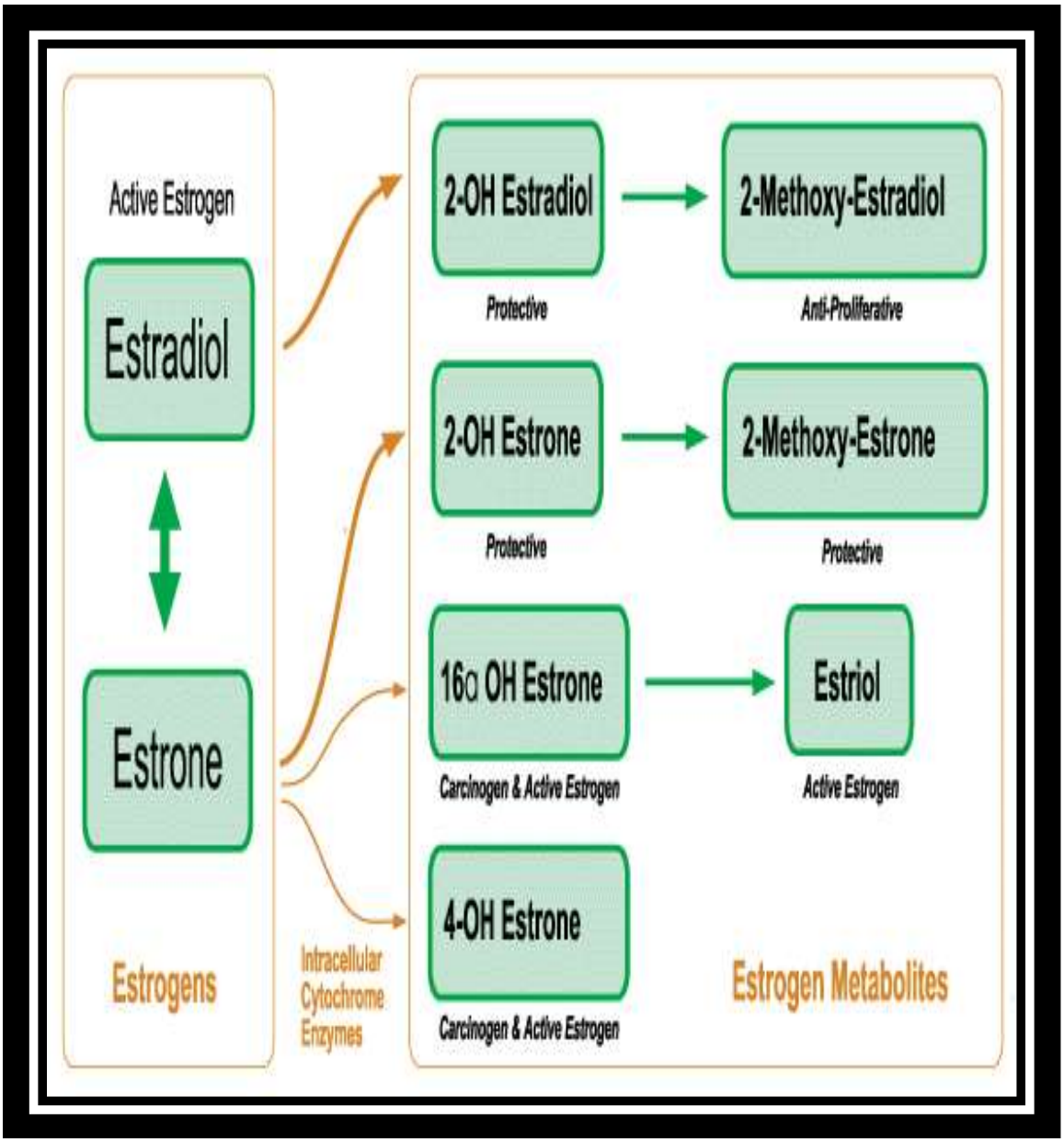
prolactin. However, this nomenclature can be unsatisfactory as various hormones exert different actions in different target tissues or organisms at varying developmental stages. (This difficulty in definition with endocrine systems and treatments holds to this day with modern discussions of hormones and their effects!). Over the next few decades there would be interesting and exciting discoveries about hormones. Researchers discovered the exact mechanism of hormone signaling and interaction in the body, including the fundamental understanding of hormone action being a communication between the central nervous and endocrine systems. They found interesting tidbits of cross-species actions of hormones – ones that revealed how extracts of horse thyroid tissue can induce precociously the complete metamorphosis of frog tadpoles into adults! They also discovered the interesting fact that some neurotransmitters, such as serotonin, are signaling molecules in plants. While many animal hormones are found in primitive organisms, they have obviously been put to different uses throughout evolution. (This discovery of hormones in plants provides proof of plant/herb use in balancing the human endocrine system!). This time period also saw important understandings of how hormones like Insulin work in the body and gave detailed understandings of hormone receptor mechanisms. The “lock and key” layman’s explanation for how hormones work was developed. Hormone action was easily explained as what happens following the secretion of a hormone from a particular endocrine gland. The secretion travels through the bloodstream looking for specific protein receptor sites with shapes like tiny wombs that exist on the cell wall. The receptor sites were labeled “locks”

waiting to be opened by a specific hormonal "key". When the hormone enters the binding site and snuggles into the pouch, it is said to be bound to the receptor. This binding then facilitates the programmed action of the cell. This easy explanation is still used today.

The hormone researchers first focused on that paved the way for HRT and BHRT is Estrogen. Estrogen is one of the hormones most responsible for programming the way all our bodies grow and develop; it actually organizes our development in utero. There is NO SUCH THING as ONE singular hormonal substance called Estrogen. Estrogen is actually an umbrella term for a class of chemically similar hormones and hormone metabolites. This class can be divided into three groups, each responsible for various actions of growth in the body. The 3 sisters of Estrogen are **Estrone**, **Estradiol**, and **Estriol.**

- **Estrone** is the estrogen associated with the menopausal woman. It is made in the adrenal glands, ovaries, and also derived from BODY FAT. Women who store more fat (to a certain point) seem to complain less of menopausal symptoms because of the presence of greater amounts of this circulating hormone in their bodies. (Part 2 of this research discussion will showcase this biological adaptation as a protective mechanism and how to use this occurrence for a client's benefit).
- **Estradiol** is produced mainly by the ovaries each month and is the estrogen most constant in the body through life. Unopposed estradiol is most implicated in an increased risk for breast cancer.

- **<u>Estriol</u>** is produced in the ovaries and the placenta during pregnancy and is the weakest of the three estrogens. It is a breakdown product of the other two and helps keep the body in equilibrium.




**Estrogen and It's Metabolites. Estrogen metabolism occurs primarily via four pathways, starting either with estradiol or estriol. The ratio of the various metabolites to each other can be associated with various forms of cancer risk in women.**

Estrogen has proved to be a stunning and interesting molecule to study. The arena of Estrogen receptor sites has proved to be enlightening in terms of how they work and what they do. Receptors are protein structures designed to snag passing hormones. Receptors for hormones that poke through the cell membrane are called membrane receptors. Other receptors are inside the cell (intracellular receptors) in the cytosol, and more receptors are in the cell nucleus. The number of receptors is not stagnant, and varies according to nutrients and the environment. Estrogen travels through the blood stream looking for receptor sites present in breasts, and uterus as well as the brain, heart, liver, and bones. Initial research thought there was only one type of receptor but the last decade of Estrogen research discovered the existence of a 2nd type of Estrogen receptor site. Existing sites have appropriately been named ER-***Alpha*** and ER-***Beta***. Alpha is highly expressed in the uterus, prostate stroma, ovarian theca cells, Leydig cells in testes, epididymis, breast, and liver. Beta is highly expressed in prostate epithelium, testes, ovarian granulosa cells, bone marrow, lungs, and blood vessels. Both are abundant in the ovaries and brain. How does knowing about the presence of differing Estrogen receptors matter for health? Come to find out, lots when looking at a disease like cancer! Estradiol binds to both alpha and beta receptors with equal strength. Estrone binds to alpha receptors five times more tightly than to beta receptors, and Estriol binds to ER-beta 3.2 times more tightly than it will bind to ER-alpha. The amount of Bcl-2 (a protein produced by hormone stimulation in the cell nucleus of cancer cells) being produced is dependent upon which estrogen is binding, how strongly it is binding, and the

concentration of each type of receptor. This breaks down to Estrone being considered potentially more pro-cancer, with Estriol being considered potentially more anti-cancer. Overall, Estrogen Receptor Beta (ER-Beta) stimulation has a positive result, which is that the production of the Bcl-2 protein is down-regulated, thus depriving cancer cells of their immortality. Moreover, it also has an anti-inflammatory effect. Overall, Estrogen Receptor Alpha (ER-Alpha) increases inflammation and the production of the Bcl-2 protein. These differences in Estrogen potential and receptor site are important for understanding Bio-identical hormone products vs synthetic products. A dominance of ER-Beta receptors is generally a good thing.

It's worth noting that Progesterone also has two receptor types! Receptor B diminishes the production of Bcl-2 when activated, thereby also depriving cancer cells of their immortality. Fortunately, Receptor B's tend to predominate, making the presence of progesterone typically more anti-cancer than pro-cancer. Progesterone Receptor A increases Bcl-2 and stimulation of this type of receptor is associated with BRCA1 and BRCA2 mutations. According to Dr. Edward Friedman, a theoretical biologist, the few women with these mutations also have increased numbers of Progesterone Receptor A. This leads to increased Bcl-2 production that protects cancer cells! Dr. Friedman is noted for his work showcasing how membrane androgen receptors for hormones like Testosterone and DHEA behave differently in men than in women. In women, stimulation of these receptors causes a decrease in Bcl-2; in men, it causes an increase in Bcl-2. In both men and women, stimulation of the intracellular

androgen receptors decrease Bcl-2 and cause the production of other anti-cancer proteins. Friedman's research is finding that if there is a shortage of Testosterone to stimulate the intracellular receptors, the shortage favors more cancer cell growth. There's tremendous amount of importance and understanding when it comes to hormone receptor sites and every decade provides more insight on these marvelous structures. From a naturopathic perspective, the importance and relevance of doing simple therapies such as cleansing cell receptor sites with essential oils takes on additional meaning and importance.

Once researchers had a strong understanding of Estrogen, they began working on how to use Estrogen to deal with a variety of physical and emotional symptoms associated with menopause. These findings were the roots of the Hormone Replacement Therapy treatments used today. There is an important question to answer with the beginnings of HRT and it's a simple one of why Estrogen became the star player in HRT? Researchers of the time knew about many hormones and their biological actions were being discovered daily. Estrogen, however, took center stage. Unfortunately, much of the reason this happened had nothing to do with human well-being or the desire to alleviate illness. Societal attitudes, profit, and marketing were involved with the development of hormone treatments, specifically for women in menopause. The accepted roles of women during the beginnings of hormone therapy, mixed with a few key players and industry set the stage for the overload and lack of understanding prevalent in the world of endocrinology. According to Dr. John Lee, M.D., if one were to pick a year during which Estrogen therapy entered public consciousness, it might be

1964. The January 13, 1964 issue of Newsweek carried a one-page story entitled “No More Menopause?”. It reported on the work of a Dr. Robert Wilson who was reported to have been studying menopause since the 1920’s. He had reached the conclusion that “change of life” stemmed from a lack of female hormones Estrogen and Progesterone. He described the menopausal woman as the equivalent of a eunuch: unbearable, suicidal, incapacitated, and incapable of rationally perceiving her situation. Wilson was joined by another doctor who provided equally degrading work and thought, Dr. David Reuben, M.D. He was the author of the popular “Everything you always wanted to know about sex” and he maintained that the essence of femininity is tied to a woman’s ovaries. Once the Estrogen was shut off, a woman comes as close as she can to being a man! Such a woman is not really a man, he explained, but she is no longer a functional woman. These menopausal women live in the world of “Intersex”. As absurd as this is, dangerous aspects of this mentality remain entrenched in popular culture! During this same time a writer in London named Ann Walsh happened to read the article and was struck by the similarity of what happens when one’s ovaries stop functioning and her own set of symptoms. She came to the United States and did a whirlwind tour of interviews with everyone she could find involved in hormone research at the time. By 1965 she produced books titled “Now! The Pills to keep women young!” and “ERT The first complete account of the miracle hormone treatment that may revolutionize the lives of millions of women”. The good-looking and popular gynecologist Dr. Robert Wilson then produced his own book entitled “Feminine Forever” (which was financed by Wyeth-Ayerst) that was widely disseminated to

doctor's offices all over the country. Even though his research found that both Estrogen and Progesterone were missing in menopausal women, his book ONLY promoted Estrogen for hormone replacement therapy. In the years of 1964 and 1965, the lay press suddenly blossomed with Estrogen replacement therapy articles. They had titles like "No more menopause", "The springs of youth", "Oh what a lovely pill", and "How to live young at any age – straight talk from a famous doctor". All the talk generated attention and excitement from the financially minded, as the Wall Street Journal even carried a few articles on the subject. All of this occurred during a time when Marilyn Monroe was the cultural ideal of beauty and women were thought to be at their best pleasing their husbands sexually and raising happy children. American women raised to be happy homemakers were suddenly approaching middle age and menopause. Their children were leaving, their hair turning grey and their breasts sagging! Symbolically their usefulness had come to an end. If they were no longer raising children and no longer sexually attractive, of what use were they? Psychological problems such as depression became common among women of this age. Millions of women became hooked on valium and other tranquilizers. Menopause was officially being declared a disease and the perfect storm of events followed.

## *HRT and it's beginnings*

Premarin, one of the more well-known hormone pharmaceutical products, entered the market in 1942 as a hormone pill and in 1949 as the first hormonal preparation. Premarin is an

oral compound known as CEE or Conjugated Equine Estrogen. Equine means "horse" and the drug's name tells the clear story of how it is derived. *Pre-mar-in* is made from pregnant mare's urine. A mare is confined in a concrete stall for more than 11 months of her pregnancy. She is unable to turn around and barely gets to move while the urine is collected from a cup fastened to her body. After giving birth the mare has a few months of freedom before being forcibly impregnated and returned to confinement. Premarin has been able to tout the label of "natural" since it comes from a living animal but chemically it is unlike the hormones produced by women. The ratio of various types of estrogen in a human female is:

**Estriol – 60 to 90%, Estrone – 10 to 20%, Estradiol – 10-20%.**

The ratio of estrogens in Premarin is:

**Estrone – 75-80%, Equilin – 5-6%, Estradiol and other horse estrogens – 5-19%.**

Note the difference in both kinds of Estrogen and amounts of hormones. The estrogen found in the greatest amount in the human female body, Estriol, is left completely out of the mix, and the proportion of Estrone ranks far higher in Premarin than occurs in women naturally. Equilin and other horse estrogens are not molecules we find anywhere in the human chemical makeup. They are specific to horses. It is currently not known how Equilin affects a woman's body as the drug companies have spent no money pursuing this question. It is the opinion of many doctors and clinicians that the reason some women suffer terrible side effects from Premarin is because it is foreign to a woman's body. Premarin is not metabolized in the body

the same way human hormones are. A woman's body contains all the essential enzymes and cofactors it needs to process its native hormones when they are present in their natural proportions. The more potent hormones, such as Estradiol naturally break down into weaker daughter compounds. Premarin, however, doesn't contain any ingredients to metabolize Equilin, and as a result, the horse estrogen stays in the body longer, producing a more potent and long-lasting effect on estrogen receptors. These foreign molecules are appropriately recognized by the liver as toxins and processed as such by the liver's detoxification system. The net result of a drug like Premarin is extra burden on the liver and a possible decrease in it's longevity over time – all in the name of hormone balance! Let's remember that Estrogen therapy was conceived in an era with the tagline of "better living through chemistry". These postwar years were filled with the desire to control the natural environment through chemicals and the chemical companies were happy to provide product. The pharmaceutical companies saw a similar philosophy for their product and determined that there was a drug to cure every human ailment. Plastics, pesticides, and antibiotics were going to save the human race.

Estrogen therapy alone was the first big player in the hormone market but from the beginning it had problems and was very poorly researched. Estrogen's approval as a prescription drug was based on a dubious study with a relatively small number of women in Puerto Rico who took birth control pills. The pill used at first was only a progestin, which was later found to be contaminated with estrogen-like substances. When estrogen was taken out

of the birth control pills they didn't work as well, so a synthetic estrogen was intentionally added. Twenty percent of the women in the study complained of side effects but were dismissed as neurotic. The three women who DIED while taking these pills were never autopsied to find out cause of death. (There has been ample evidence since this first crude study that these pills caused blood clots and strokes, but the evidence was dismissed and suppressed for the supposed good of controlling the population explosion). After this first study fiasco the pharmaceutical companies scrambled to find a combination of synthetic hormones that had fewer side effects. From 1965 to the mid-1970s the Estrogen replacement bandwagon sailed along with more and more women taking them with the promise of "being young forever". By 1975 the bottom dropped out of the Estrogen replacement bandwagon. Women on Estrogen therapy were developing uterine (endometrial cancer) at a rate four to eight times greater than in untreated women. Multiple researchers confirmed the link between Estrogen supplementation and uterine cancer. When the news hit the papers, sales dropped precipitously. This only stalled the movement for a while. A spate of papers were produced arguing the question of whether Estrogen "caused" endometrial cancer or merely "promoted" it. Medical authorities regrouped and changed the name of their therapy to "HORMONE REPLACEMENT THERAPY" or HRT. The difference was the addition of the Progestins or synthetic versions of Progesterone. Fairly solid research existed or was soon accomplished to show that only "unopposed" Estrogen was the culprit; estrogen combined with Progestins actually prevented endometrial cancer. The same fear of Estrogen causing

breast cancer was addressed in the same way. Studies of women were reported to show less breast cancer in women on HRT than not. The question was never truly resolved but the results set HRT back on track.

The next step up for HRT was the promoters determining that Estrogen and Progestins could cure other ills. They soon declared that HRT would lower a woman's risk of heart disease and prevent Osteoporosis. These assertions were followed by massive marketing campaigns to popularize Osteoporosis and educate women about it. These myths were never proven true yet still persist to current times. Somewhere in the development of the HRT industry, Progesterone was not only forgotten it was mislabeled and mistaken as it's distant cousin, synthetic Progestin. Even well-researched books on menopause tend to make this error and it has proven to be a costly one as the crucial role of true Progesterone in women's health is fully understood. HRT had a good run until about the mid-1990s, when there was ample scientific evidence that HRT was not living up to its promise and even that it was probably doing more harm than good. There were many excellent studies done at the time showcasing this but they were ignored in favor of continuing hype from the drug companies about the cure-all nature of HRT. The majority of physicians were solid in their belief that every menopausal women should be on HRT, even though only 25 percent of patients continued on it because of the side effects. Many women, rather than being taken off the HRT when they complained of weight gain, bloating, breast tenderness, anxiety, depression and insomnia, were instead given sleeping pills and antidepressants, which made them feel worse.

In the summer of 2002, two major studies were published in the Journal of the American Medical Association (JAMA) which dropped a stick of dynamite into the whole realm. The first blow to HRT came from the huge Women's Health Initiative (WHI) study, one part of which looked at the effects of the most common form of HRT, PremPro. This arm of the study was abruptly cut short after five years (three years early) because of a clearly greater risk of invasive breast cancer, heart disease, and strokes among women using PremPro. PremPro was a combination of Premarin the "horse estrogen" plus Provera, a synthetic Progestin. The study was the gold standard in terms of study parameters and scientific evidence. It analyzed the health of 16,000 healthy, diverse, and postmenopausal women aged 50 to 79 years. It was designed to definitively answer nagging concerns about HRT. The women were divided into various groups, some took Estrogen plus Progestin, others took a placebo. As in all double-blind studies, the two groups were compared and evaluated; neither the women being studied nor the researchers knew whether they were in the group receiving the real drug or placebo. The long awaited study was ended abruptly when a routine monitoring board examined the results and sounded the alarm! They proclaimed to the world that **after five years, those using PremPro had a 29 percent higher risk of breast cancer, a 26 percent higher risk of heart disease, and a 41 percent higher risk of stroke.** To make the numbers really relevant, it's important to project them out into the general population: If 6 million or more women are reportedly using PremPro, this would translate to approximately 4,200 women who would get breast cancer, 4,800 women who would get heart disease, and 10,800

women who would have a stroke in a five year period because they were taking this form of HRT. If the numbers are extended over a decade, nearly 40,000 women would be harmed and many of them killed by taking these drugs. That qualifies as an epidemic and that doesn't count all the other side effects like fatigue, depression, headaches, low thyroid, low libido, and blood clots that are the result of taking these types of medication. The full report also showed additional risks of invasive breast cancer, more coronary heart disease events, more strokes, and pulmonary embolisms. It needs to be noted that this study only used two particular hormone products – there are and were MANY OTHERS. The study also focused on just one single-dosing oral regimen. There's no way to know if the results can be extrapolated to lower doses or to other formulations. Executives as Wyeth-Ayerst, the drug company that supplied pills for the study and provided them to many midlife women, certainly must have gone numb as they watched the firm's stock plummet 24% IN ONE DAY! The FDA finally stepped in during the fiasco and insisted that all prescriptions be accompanied by warnings about the risk of cancer, blood clots, gallbladder disease, and other complications. Without a moment to lose, the American Pharmaceutical Manufacturer's Association and the public relations firm for Ayerst Pharmaceutical produced sales strategies and an intense promotional campaign. This included articles sent out to magazines (Reader's Digest, McCall's, Ladies Home journal) and 4,500 suburban newspapers in order to "preserve the integrity of Estrogen replacement therapy as effective, safe treatment for symptoms of menopause". The monied interests were so opposed to the FDA's plan for packaging the warning inserts that they took legal action.

They stated that “patient information would reduce sales of Estrogen drugs and, therefore, reduce profits”. Other organizations that joined in opposition were the American College of Obstetrics and Gynecology, the American College of Internal Medicine, and the American Cancer Society. They claimed that “giving patients information violated the physician’s right to control how much information to disclose to patients and threatened medicine’s professional autonomy”. Eventually the U.S. National Women’s Health Network introduced a brief to the court in favor of the FDA and the FDA won out. To this day, every HRT product is required to have a warning label on possible side effects!

Shortly after the WHI study was halted, another study was released, this one from the Breast Cancer Detection Demonstration Project, part of a nationwide breast cancer screening program. It showed that Estrogen-only hormone replacement increases the overall risk of ovarian cancer by more than threefold. Given what was already known by then about unopposed Estrogen’s cancer-promoting properties on a woman’s reproductive system, the concept of giving only Estrogen to women without a uterus should never have taken hold but it did. This second study provided more damning evidence in relation to breast cancer risk but the results were not as conclusive. The authors wrote: *“Our results suggest that the combined Estrogen-Progestin regimen is associated with greater increases in breast cancer risk than Estrogen alone. Assessing the comparative risk of Estrogen alone vs. Estrogen-Progestin was complicated by the fact that use of Estrogen alone was associated with increased risk in lean but not heavy women.*" The authors found differences between the two regimens (Estrogen-

only and Estrogen-Progestin HRTs) among lean women, but they were unable to draw definitive conclusions among heavier women.

Why were these two studies so damaging yet pivotal? The answer is both financial and psychological. The numbers of women taking hormone products BEFORE the disaster of 2002 were astounding. 38% of U.S. women between the ages of fifty and seventy four used HRT. In 2000, 46 MILLION PRESCRIPTIONS OF PREMARIN made it the second most popular medication in the United States; it raked in more than a billion dollars in sales for Wyeth alone. PremPro, which is Premarin with a synthetic progesterone added, was in the neighborhood of 20 MILLION PRESCRIPTIONS and showed no sign of stopping. As soon as the 2002 WHI results hit the scene a mass panic happened among woman on HRT at the time. The millions of women on HRT suddenly had no faith in any of their doctor's recommendations and worry/stress levels of this population went through the roof. Millions of women discontinued their treatments immediately, only to find their symptoms returning. Some chose to continue taking their pills, hoping they would miss becoming one of the unlucky ones to find a lump. Still others turned to herbs, soy, and whatever else they could find that would provide relief. This reality set the stage for the somewhat triumphant "return" of Bio-identical hormones.

## *The Beginning of Bio-identical hormone replacement therapy (BHRT)*

The modern term of Bio-identical hormone replacement therapy (BHRT) started out as Natural hormone replacement therapy (NHRT). The early research that provided

understanding of hormones and the endocrine system set the stage for NHRT, the same as for conventional HRT. The year 1900 showcased the role of ovaries being understood. 1926 was the discovery of Estrogen and 1929 gave the discovery of the corpus luteum. This crucial component for a successful pregnancy gave rise to the hormone Progesterone, i.e. "pro-gestation". Progesterone would prove to be the heavy hitter in the NHRT world, primarily because Progesterone's role as the primarily balancer of all estrogenic sources was and is sorely needed. This imbalance is primarily due to excess intake of processed foods and excess toxin exposure – exposure that often starts in the womb. Early research of Progesterone happened slowly and then decade by decade gained steam. In 1930 samples of Progesterone were obtained from sows' ovaries and minute quantities of it limited research. By the late 1930's the placenta was found to synthesize Progesterone in relatively large amounts and this led to the harvesting of placentas after childbirth and quick-freezing them for extraction of Progesterone in quantities sufficient for experimental work and clinical application. In 1939 the chemist Russell E. Marker devised a method to convert a Sapogenin found in the sarsaparilla plant into a Progesterone-like compound. Soon after he was able to convert disogenin from the Wild Yam (Dioscorea villosa) into Progesterone with an excellent yield of 40 percent. With this method of production, the price of Progesterone fell from $80 per gram to $.50 per gram. By the mid 1940's it was discovered that Progesterone was a fat-soluble compound. Given orally it was relatively ineffective but dissolved in vegetable oil and given by injection, was RAPIDLY absorbed and thoroughly effective. They soon found that injection,

though effective, proved to be locally irritating and somewhat limited with use. Even with that limitation, physicians attuned to intricacies of hormone balance found Progesterone remarkably effective in treating patients with PMS, ovarian cysts, and in preventing miscarriage. They found that it was well absorbed when given as a suppository in the rectum or vagina. By the 1950's active hormone-like substances were found in thousands of plant varieties. This led to the creation of Bio-identical forms of Estrogen, Testosterone, and Progesterone being created as well as synthetic forms of them all.

Dr. Katharina Dalton spent most of her career focusing on Bio-identical Progesterone. Her work is legendary and especially important because the concept of a women's health movement may very well have started with her work! She made a huge contribution to modern understanding of hormone disturbances, and she is also the one who coined the term Pre-menstrual Syndrome or PMS. At age 32, Dr. Dalton was a pregnant medical student. She wondered why she was suddenly free of the severe headaches she had experienced monthly. She took her observations to Dr. Raymond Greene, an endocrinologist, and speculated that Progesterone, which is abundant during pregnancy and should be abundant during the luteal phase (the second half of the menstrual cycle), might be the key. She and Dr. Greene first published their clinical experiences and theory in British medical journals in 1958, and proposed the term Premenstrual syndrome. By then, Dr. Dalton had successfully treated premenstrual asthma, epilepsy, and migraine headaches with Progesterone. Dr. Dalton ONLY used Bio-identical Progesterone and was adamant that other synthetic derivatives of

Progesterone could not be used. This ran contrary to what her medical colleagues of the time believed. One of Dr. Dalton's observations was that some of the symptoms of PMS (including edema, hypertension, and albumin in the urine) seemed to also occur as early signs of toxemia in pregnancy. She began trials of intervention with Progesterone, in collaboration with a maternity hospital. The hospital records showed an average incidence of toxemia to be 9%. After the first patients who were treated delivered babies in 1955, the incidence dropped to a low of 1.0%. Each patient was given a test dose of Progesterone when early symptoms occurred, and then treated continually if symptoms resolved, while moderating the doses according to symptom relief. One of Dr. Dalton's big contributions to the understanding of Progesterone was recognizing that men, women, and children all have Progesterone receptors in operation throughout their lifetime. She hyper-focused her attention on Progesterone receptors for a good reason - only Bio-identical Progesterone snugly fits the receptors. She felt strongly that this was the only appropriate hormone to use. In her work with Progesterone, she found TWO systemic factors that affected the proper uptake of this important hormone. The first was Adrenalin, and if too much adrenalin was being produced, Progesterone would not be able to be picked up by the receptors. Secondly, if women were experiencing swings of low blood sugar from improper diet, Progesterone would not activate the receptor. These findings are KEY to understanding the proper use of Progesterone. (These revelations are expanded and fleshed out in Part 2 of this work.) By 1968, Dr. Dalton had firmly placed herself as an unapologetic CHAMPION of Bio-identical Progesterone.

By 1978 the Journal of the American Medical Association or JAMA was publishing extraordinary revelations regarding natural hormone replacement. 1980 showcased a study that displayed the value of both Estrogen and Progesterone receptors in treating breast cancer (Cancer. 1980 Dec 15;46(12 Suppl):2884-8. ***The value of estrogen and progesterone receptors in the treatment of breast cancer.)*** 1980 also showcased a study that synthetic Progesterone altered the intestinal flora - which in turn influenced the plasma levels of it's metabolites and compounds for the worse. The study showed that Bio-identical progesterone and it's metabolites are extensively metabolized in the intestine to compounds with less progestational activity – hence doing exactly what the body would normally do with the Progesterone had it produced it itself (J Steroid Biochem. 1980 Feb;13(2):231-44. ***Biliary excretion and intestinal metabolism of progesterone and estrogens in man***). In 1985 a placebo controlled, double blind crossover study showcasing Progesterone's ability as an anti-hypertensive was done with a small sampling of men and women. The subjects had mild to moderate hypertension and were not receiving any other antihypertensive drugs. When compared with values recorded before treatment and during administration of placebo Progesterone, a significant reduction in blood pressure occurred. By 1989 the research of Dr. Joel Hargrove, M.D. on micronizing Progesterone for better absorption appeared in the Journal of Obstetrics and Gynecology. 1991 saw a landmark review by Dr. Jerilynn Prior, M.D. on Progesterone and the prevention of Osteoporosis that was published in the Canadian Journal of OB/GYN and Women's Health Care. (The complete list of studies on Progesterone is

beyond the scope of this paper but they do exist and are available quite easily for anyone interested in their findings). Following this landmark work, champions of Bio-identical Progesterone emerged like Dr. John Lee, Dr. Raymond Peat, Dr. Alan Gaby, Dr. Jonathan Wright, Dr. Betty Kamen, Dr. Norman Shealy, and Jane Heimlich. Even with the solid research, clinical and real-world application, and basic biological understandings of how Bio-identical hormones work in the body, Bio-identical hormone replacement suffered a failure to launch and gain broad mainstream support. Conventional HRT had the backing of the pharmaceutical industry and the conventional medical establishment. Because Bio-identical hormones were considered "organic" by molecular structure, that made them a naturally occurring product. As such, no patent could be placed on them. This of course meant the profit potential for Bio-identical hormones was LOW. This stark reality hindered their popular acceptance and use. The health professionals who chose to champion their use from the 1980's on were subject to much maligning talk and ridicule – that group being Naturopaths of all sorts, chiropractors, and holistic physicians. Initially, obtaining Bio-identical hormones was a fairly easy process for the professionals choosing to use them. It simply meant locating a quality source of hormones either over-the-counter or directly through a compounding pharmacy. The tide slowly turned, however, as the pharmaceutical industry worked to create Bio-identical products that could be patented by name and/or due to their DELIVERY SYSTEM into the body. This proved to be a game changer. Using compounded products only obtainable through a visit to an M.D. or D.O., creating novel delivery systems like patches, pellets, and reformulations that are sometimes

patented, and then providing the flow-through mechanism of a trip to a compounding pharmacy increased the possibility of pharmaceutical profit. The value of Bio-identical products went up, thereby providing pharmaceutical companies a means of offering a "safe" and "natural" product to consumers. This is one of the current realities of BHRT. Another reality though, is what is available to Traditional Naturopathic practitioners and the lay public. The heavy hitter of BHRT, Progesterone, can be obtained in quality formats both over-the-counter and directly from excellent companies that make the product. This exciting realm of what's available will be discussed in Part 2 of this work.

## *Summary*

To recap, here are the simple questions this research work looks to answer about Bio-identical hormones:

- *Are Bio-identical hormones the same as hormones our bodies produce?* The answer is unequivocably YES.
- *Will the body respond to Bio-identical hormones in the same manner as if they'd been produced by the body?* YES.
- *Are Bio-identical hormones safe to use and suggest provided there's understanding and knowledge about them?* YES.

Here are the most important points to take-away about Bio-identical hormones:

1. All Bio-identical hormones used are chemically identical to human hormones.
2. Some Bio-identical hormones are commercially available and some are available in compounded dosage forms. Compounded products are made at specialty pharmacies in doses that are customized for each client. The dosage can be individualized to a patient's specific hormonal needs and can only be obtained by prescription from an M.D., D.O., Naturopathic medical doctor or Chiropractor in certain states.

3. Bio-identical Estrogens include Estrone, Estradiol, Estriol, 17 β-Estradiol, and Estradiol hemihydrate.

4. Bio-identical Progesterone is available, as are Testosterone, Androstenedione, Dihydrotestosterone, and DHEA.

5. Over-the-counter or (OTC) Commercial preparations are available of Progesterone, DHEA, Melatonin, Pregnenolone, Estriol, and Estradiol.

6. Commercially-available Bio-identical products come in specific strengths that cannot be customized.

7. A good majority of hormone balancing can occur with the workhorse and overall balancer of the endocrine system, Progesterone.

8. Careful attention and scrutiny to all hormonal products is needed due to the co-opting of the word "natural" in relation to the product's formation and use.

9. Semantics matters when describing and detailing ALL hormonal products. Current medical professionals, the lay public, and even researchers use the names of hormones interchangeably. This is both inaccurate and misleading. A very common error is seeing PROGESTERONE, PROGESTOGEN, and PROGESTIN used interchangeably. They are NOT the same thing.

## *Conclusion*

The field of BHRT is an ever-changing one that has it's roots firmly in the mechanics of the human body and endocrine system. Traditional Naturopathic practitioners have at their fingertips the ability to use these supplements as part of a program to improve and enhance the health of all the clients they encounter. Despite a difficult history and beginning of this therapy, it's roots in the true functioning of the human body will allow it to move forward into the future. As people are increasingly witnessing the limits of conventional drug therapies, this arena provides an optimistic and highly-vetted alternative. It's an exciting time to be a part of the BHRT revolution! The position of Traditional Naturopathic practitioners has never been stronger in regards to the use and understanding of BHRT. The Traditional Naturopathic approach of incorporating all aspects of Mind, Body, and Spirit PLUS the incorporation of therapies like BHRT provides a unique positioning point. Part 2 of this research work goes into detail about the production of Bio-identical hormones, how to suggest them based on current products available, how to assess inputs of diet, herbal alternatives, and discusses how to obtain laboratory tests for hormones using blood, urine, and saliva.

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