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The Examiner of Alternative Medicine

## Another Perspective on Estrogen

I wish to comment on a recent brief article: "High Levels of Estrogen Associated with Breast Cancer Recurrence" (*Townsend Letter*, Aug/Sept 08). This is the kind of imprint I expect to see in an AMA journal not in *Townsend Letter*. This report is so imprecise and so narrow and therefore perpetuates the myth that "women are allergic to their own biology." As a primary researcher in the biochemistry of different estrogens, I wish to state the following: a) most women who initially develop breast cancer have low, not high levels of 17-beta estradiol; b) it is the electron withdrawing effect on metabolites of estrone that has the greatest impact on proliferation potential.

Specifically, when a woman ages, the E1-estrone levels rise, and the E2-estradiol levels diminish. This is when women feel their worst in terms of mood factors and fatigue – when they do not have sufficient E2. If in the down-regulation of the metabolites of estrone, these form in proximity to the double bonded oxygen on the aliphatic end of the structure. This creates immense functional stability in the molecule, and the toxic metabolites stay in the female body for days instead of hours.

Just reporting on breast cancer recurrence without another perspective on estrogen further embellishes the fear around hormones, which has hurt women, particularly those vulnerable to depression, so very much. "In Defense of Estrogen," which first appeared in *The Journal of Orthomolecular Medicine* would contribute much to the discussion here, and I hope you will consider printing it in *Townsend Letter*.

Phyllis Bronson

## In Defense of Estrogen

by Phyllis J. Bronson, PhD

The etiology of the aging female has taken on a life of its own in the Western world today. Yet, the most basic academic aspects of how to contain the aging process are shunned, often in the quest of the "addiction to perfection." So women seek BOTOX® to numb their wrinkles and their faces, plastic surgery for every flaw.

The most important hormone of the female biology, 17-beta estradiol (E2), has recently been misinterpreted and vilified as if women are supposed to believe that they are allergic to their own biology. As a result, many women have begun to seek answers from pharmaceuticals instead of working to replenish their own bio-identical chemistry. Estrogen is the critical molecule for the aging female and acts as a defense against depression and loss of cognitive function. A wealth of data suggest that if E2 is started at the proper age, it has profound, beneficial effects on all aspects of a woman's healthy biology, including moods and emotion, heart disease, memory, bone density, and cancer risk. Even Alzheimer's disease may be slowed or halted due to regulatory mechanisms on beta amyloid protein.<sup>1</sup>

Progesterone is a secondary female hormone, but also of great importance to a woman's health and moods. The introduction of synthetic "progestins" as analogues of true progesterone has led to a great deal of confusion among both women and their physicians. This is why birth control pills, for the purpose of sustaining hormones in mid-life women are the wrong choice: they contain synthetic progestins, and many women feel very bad when using them, particularly emotionally.

On the other hand, since the original work with progesterone by Katarina Dalton, MD, in England many years ago, physicians trying to establish the importance of progesterone have deemed it the molecule of most significance for women. This is simply untrue and misleading. Estrogen must be present in sufficient quantity to be properly "mediated" by progesterone. If this is not the case, and women simply use progesterone to excess, those vulnerable to depression will become more so. Progesterone is anxiolytic. Estradiol is a mood elevator, due to its impact on the catecholamine and indolamine families.

Estrogen in the female human is a composite of three molecules produced by our bodies: estrone (E1), estradiol (E2), and estriol (E3). For the purpose of this article, estradiol is of primary interest and is identified as 17-beta estradiol, or E2. Estradiol is the most potent form of estrogen and makes up about ten percent of the estrogen produced by the ovaries.

Estrone is 12 times weaker in terms of biological impact and also makes up about ten percent of a woman's normal estrogen levels, however, it is a much more toxic estrogen. In fact, it may be the principal culprit in estrogen toxicity as will be explained further. Until recently, it was assumed that there was a simple equilibrium reaction between estradiol and estrone, that estrone was produced via synthesis from estradiol in the liver primarily. The current interpretation is that as women age, they produce a great deal of estrone in their fat cells (and many women gain weight and have bigger fat cells as they age), thus there is more estrone production.

Estriol is the weakest form of estrogen, and though it is 80 times weaker than estradiol, it makes up about 80% of a woman's estrogen. Estriol is produced by conversion from estrone. This occurs through the down-regulation of estrone to the toxic 16-alpha hydroxy estrone and then to the relatively inactive estriol in the liver. Estriol appears to counterbalance estrone's toxicity. Asian women who eat a diet high in traditional, fermented soy products and have higher levels of estriol appear to have less gender-related cancer, and the inference is that estriol somehow plays a "protective role," possibly by creating less toxic metabolites. Epidemiological studies have linked soy to a decreased risk for breast cancer. Soy isoflavones, sometimes referred to as natural selective estrogen receptor modulators (SERMs), show interference with the binding of certain estrogens to SHBG.<sup>2</sup>

### Estrogen 2/16 Metabolism

The important role played by estrogen oxidative metabolism in hormone-sensitive diseases has been elucidated by studies of estrogen-dependent neoplasms of reproductive organs. With respect to breast cell malignancies, estradiol is believed to act primarily as a promotional factor, causing increased growth rates in breast cells already transformed to a cancerous state. However, estradiol is not the only active estrogen in the human body. Other metabolites formed from estradiol have the capacity to act as estrogens and, in some cases, as anti-estrogens.<sup>3</sup>

Considerable work has shown that the major metabolites of estradiol and estrone are those hydroxylated at either the C-2 or the C-16 $\alpha$  positions, although forms hydroxylated at the C-4 and C-15 $\alpha$  are present in relatively lesser amounts. There exists a complete divergence in the biological properties of the 2- and 16 $\alpha$ -hydroxylated metabolites of estradiol (2OHE1 and 16OHE1, respectively).

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The 2-hydroxy estrone metabolites inhibit cellular proliferation, and the 16-alpha hydroxy estrone enhances proliferation.<sup>4</sup>

16OHE1 has several unique and potentially harmful properties: it is capable of binding covalently to the estrogen receptor,<sup>5</sup> the nuclear histone proteins,<sup>6,7</sup> and DNA. Because of this covalent linkage to the receptor, 16OHE1 shows persistent biological responses,<sup>8</sup> and the formation of 16OHE1 is elevated in women at high risk for breast cancer.<sup>9,11</sup>

Estrogen plays a major role in the neurobiology of aging because all women experience a significant drop in this hormone at menopause. At the turn of the past century (1900), women achieved menopause at about the same time as their life expectancy ran out. In this last century, a woman's life expectancy has almost doubled, and she can expect to spend about half her life in menopause. There is no precedence for transition into the mid-life years or indeed into older age. Concurrent with this increase in life expectancy, over the past 50 years, menopause became a medical condition and has been treated as such by the pharmaceutical industry and the medical establishment. In response, the medical profession told most women approaching menopause to take estrogens. About 25 years ago, as a result of observed endometrial problems, doctors were told that women needed "progestins" to protect them from endometrial problems. This began the introduction of the synthetic progestins to the pharmaceutical scene. This has been a catastrophe for women.

Progestins are synthetic analogs of progesterone but are not actual progesterone. In fact, their mechanism of action is quite distinct, and these drugs have harmed many women. For example, true progesterone is an incredibly strong diuretic, while the synthetic progestins actually promote fluid retention due to the water-holding effect driven by the acetate in the synthetic molecule. This shows perfectly in the hydration peaks at 3400 on the Fourier Transform Infrared Spectra.<sup>12</sup>

For years, the standard practice in gynecology has been to put women on Hormone Replacement Therapy (HRT). Then in July 2002, the Women's Health Initiative Study was abruptly halted. This was due to the inference that women on these drugs had various degrees of developing pathology. What was not noted at the time was that the demographic of the study was so flawed that a statistically relevant number of the women in the study had hypertension, diabetes, or were obese. Further complicating matters was the fact that the

majority of the women had started on HRT well past the onset of menopause, averaging ten to 15 years. It is now suspected that major aspects of aging happen at the time of menopause and are much more difficult to rectify later, in fact may become worse with treatment, although this is certainly being challenged. The study had two components: Prempro for women with intact ovaries and uteruses (terminated in July 2002) and Premarin only for women who had had hysterectomies (terminated in March 2004).

The Prempro study showed an increase in breast cancer in around 2.5% of women; this is not statistically relevant. The study rightly was stopped but not for the right reasons. The scientific community has known since 1997 that Provera has negative implications on the female cardiovascular system because it decreases vascular function.<sup>13</sup> The Premarin-only study data showed no increased risk of breast cancer or heart attacks but did show an increased risk of stroke for women over 60.<sup>14</sup>

### Impact of 17-Beta Estradiol on Mood and Emotion

Women are faced with a myriad of choices regarding menopause, and confusion reigns. The assertion in this paper is that the science is often being overlooked and other variables given precedence. Data from numerous laboratories indicate that hormone replacement can have multiple benefits on cognition and general brain function.

Over the past 20 years, there has been a developing body of clinical work looking at neurological changes as correlated with declines in estrogen, particularly whether loss of primary estrogen, i.e., 17-beta estradiol, is predictive to onset of clinical depression in the demographic of vulnerable women. In a study of women with treatment-resistant depression conducted at Massachusetts Institute of Technology (MIT),<sup>15</sup> Edward Klaiber found a correlation between high monoamine oxidase levels and low levels of estradiol and testosterone. Monoamine oxidase is a potent catecholamine inactivator. It scavenges serotonin, norepinephrine, and dopamine. Dr. Yutaka Kobayashi, a biochemist at the Worcester Foundation, and Don Boverman at MIT found a strong statistical relationship between low levels of MAO and high levels of serotonin and testosterone. Dr. Klaiber started giving the women higher than average amounts of testosterone and estrogen, and the depressions lifted in a significant number of cases.

Far from being the "cause of problems" in the aging female human, the lack of hormones – most significantly, 17-beta estradiol – the data strongly suggest, precipitates lack of well-being in mid-life women, and this pattern is

acknowledged to exist as a precursor to many degenerative conditions, notably mood and sleep disorders. According to S.L. Berga, key systems mediated by estrogen are the basal forebrain, which regulates attention, and the forebrain cholinergic system, which regulates memory.<sup>16</sup>

The Women's Health Initiative Memory Study (WHIMS) showed that women using conjugated equine estrogens plus medroxy progesterone acetate (MPA) had an increase in dementia over a five-year period. Data from the physical chemistry lab of the University Of Denver suggest that the difference in progestin vs. progesterone molecules is extremely significant and is overshadowed by other aspects in these large randomized studies.<sup>17</sup>

In May 2007, the Food and Drug Administration (FDA) asked makers of the selective serotonin reuptake inhibitor (SSRI) drugs to expand its warning labels to include adults age 18-24. The labels already include similar warnings for children and adolescents. Eli Lilly and Co., the maker of Prozac, Zolof manufacturer Pfizer Inc., and other pharmaceutical companies said they would comply with the FDA's request.

The endless prescriptions for antidepressants go on and on. Physicians, primarily but not exclusively male, have been observed to lecture that "women don't need hormones, they need Prozac" (Pers. Obs.) despite the fact that the significant factor in mood regulation for women is allegedly hormonal. Women themselves are consistent in reporting that their major mood changes have occurred throughout their lifetimes in synergy with hormonal fluctuation. Bronson, Bruice, and Whitcomb tracked women over 12 years, looking at transitions in serum estradiol levels correlating with flat affect depression.<sup>18</sup>

The data clearly shows correlation with E2 trends and mood. Two-thirds of women reporting long histories of flat affect, resignation, and depression stated that "the only time they were mentally up" was in the week after menses, days 7-14. This correlates with the time of rising estradiol. As women age, the E1 levels rise naturally, due to increased density of fat cells, and the corresponding increase in E1 production from these cells. To overcome this, women need more E2 to drive the reaction the other way. As E2 levels rise with exogenous, transdermal application, and E1 levels diminish, the depression often lifts. Women report feeling this effect in as little as two hours after use.<sup>19,20</sup>

### Progesterone and the Relationship to Neuroinhibition and the GABA-A Receptor

The data also show how the up-regulation of GABA at the GABA-A receptor is strongly

connected to the down-regulation of progesterone to allopregnanolone, and these processes can be modulated via exogenous administration of transdermal, compounded progesterone.<sup>28</sup>

GABA and glycine are known to be the main inhibitory transmitters in the central nervous system acting through ionotropic receptors. This is documented in the work of Bohlen and Halbach on neuromodulators, and we link the modulation of the chloride ionic channel to the alpha-4 subunit on the GABA-A receptor and the impact of progesterone down-regulation.<sup>22</sup>

According to Sheryl S. Smith at SUNY Medical Center, the critical interchange between the neurosteroid metabolite from progesterone, allopregnanolone, and the down-regulation of the alpha-4 subunit of the GABA-A receptor is the critical link to achieving and maintaining neuroinhibition.<sup>29</sup> The binding of two GABA molecules between the alpha and beta subunits allows the chloride ionic channel to open, which increases inhibition. Therefore, when the relationship does not occur, either due to a deficiency of GABA or a lack of progesterone at crucial times, anxiety is manifested.

The assertion from our work at The University of Denver correlates with the above. We have found that when there is enough GABA and transdermal progesterone is applied, anxiety reactions are halted. This has been replicated many times. The author further suggests that if there are not enough GABA molecules present it is very easy to become addicted to benzodiazepine (BDZ) medication. While these drugs can be helpful in the short term, they can create extreme dependency. Women (and men) who learn how to modulate their own biochemistry in response to a predilection to anxiety report that much less BDZ is needed and often BDZ doses are stopped or used only at "extreme times."

### Estradiol Impact on Memory and Cognition

Numerous laboratories have shown that estrogen has a major impact in hippocampal neurons in rats and that rats perform significantly better after receiving estradiol than a placebo.<sup>30</sup> Woolley has shown that in young ovariectomized rats, two days of estradiol use resulted in a significant increase in the number of dendritic spines.<sup>29</sup> Estrogen increases NMDA (N-methyl-D-aspartate) responses.<sup>28</sup>

The neuroprotective action of E2 is well-documented. Hippocampal neurons pre-treated with estrogen and then exposed to excitotoxic glutamate respond with an attenuated rise in Ca<sup>++</sup> and increased survival capacity.<sup>29</sup> Protecting neurons from glutamate excitotoxicity enables them to perhaps resist neurological degeneration in diseases such as Alzheimer's.<sup>28</sup>

### Implications on Cancer

The molecular structure has a great deal to do with the possible impact on cellular proliferation. Apparently, it is the unique orientation of 16alpha-OH group with the keto group of estrone that leads to the potent effects of this estrogen metabolite.<sup>29</sup> We further suggest that the increased molecular stability induced by this format allows toxic metabolites to stay in the body for days instead of hours, thus increasing the probability of proliferative action.<sup>29</sup>

There are references to the impact of di-indole methane (DIM) on limiting the HPV virus that is closely linked to cervical cancer. DIM is found in cruciferous vegetables.<sup>31</sup> Here, the suggestion is that the actual type of estrogen used can have an even greater impact on limiting the aggressive estrogens and promoting the desired mood elevation.

### Conclusion

The past four years have been a lonely battle for researchers in primary hormones. It is difficult, but absolutely necessary, to take a stand against the medical establishment for the future of science and man/womankind. Knowing the molecular aspects of hormone biology as we do, it would be wrong not to speak up. The unfortunate result of the interface of the pharmaceutical and medical worlds, as is dominant in today's medical culture, is that research is not unbiased and that science often gets pushed aside if the results are contradictory to the goals of the pharmaceutical industry. Pure, basic research remains a critical area and must confront the medical status quo. This is happening now with the hormone issues. For example, many doctors know, empirically, that many women thrive on estrogen yet are dictated to by their peers to halt HRT until better drugs come out. Our assertion, from the field of Orthomolecular Medicine, is that there are often no better "drugs" than the human hormones and other chemicals that already exist in the body, which simply need to be restored or enhanced with bio-identical chemicals. This is the ideal way to approach imbalances in hormone and other biochemical systems.

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