

Mood Biochemistry of Women at Mid-life

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Abstract

This study examines the effect of hormone and amino acid levels on mood changes in women at mid-life. The research involved both a clinical trial of the application of hormones and amino acids to effect mood changes in women at mid-life, and a laboratory analysis of synthetic and natural progesterones. The clinical trial involved a detailed biochemical study of two women and a less intensive study of two other groups of women identified as Estrogen Dominant or Estrogen Deficient. Depending on whether the women were Estrogen Dominant or Estrogen Deficient, they responded well to natural progesterone or estrogen, respectively. Even when natural estrogen was given, it was never without natural progesterone.

The clinical study found that a deficiency of progesterone is clearly implicated as a primary factor in mid-life anxiety patterns. Changes in serum levels correlated with the qualitative input given on questionnaires and interviews. Mid-life anxiety was more extreme during the latter two weeks of the menstrual cycle. The data showed that there is often too much estrogen to be mediated by the body's available progesterone. When neuro-inhibitory amino acids were used in conjunction with pharmaceutical grade, natural progesterone, women thrived and reported greatly increased calmness, even during the normally difficult pre-menstrual phase.

Laboratory analysis of synthetic and plant derived progesterone revealed significant differences in their structures and revealed discrepancies between the published and actual structure of the synthetic progesterone, Provera.[®] The primary distinction between natural progesterone and its synthetic counterpart turned out not to be in methylation, but rather in hydroxylation

and the presence of acetate in the synthetic molecule. The laboratory analysis provides insight into why the two progesterones have different effects on women.

This pilot study has already had an important impact in the area of helping women solve the riddle of mid-life mood changes.

Clinical Research on Women at Mid-Life

This study focused on the moods and biochemistry of women at mid-life. Specifically it addressed the following issues:

1. Does a deficiency of progesterone affect anxiety patterns in mid-life or peri-menopausal females?
2. Is mid-life anxiety in women connected to low progesterone levels or estrogen dominance?
3. Are amino acids and/or plant-based hormones effective in the treatment of anxiety?

Definition of Terms

Estrogen Dominance: Estrogen levels, measured as dominant estradiol E2, that are too high relative to progesterone levels.

Estrogen Deficiency: A low level of estrogen, measured as serum estradiol, at either follicular, mid- cycle or luteal periods.

Laboratory Analysis of Natural and Synthetic Progesterone

This section of the research delved deeper into the molecular structures of natural, plant-derived progesterone and synthetic progesterone. The question here was: Are there structural differences between plant-derived and synthetic progesterones that can account for differences in their effects on women?

Methods

Clinical Trials

The subjects of this study fall into three groups.

1. Two women (the author being one of

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them) who were intensively studied and for whom relatively large numbers of blood samples were taken.

2. Six women showing tendencies toward "Estrogen Dominance"

3. Six women showing tendencies toward "Estrogen Deficiency"

The second and third groups were comprised of women followed over time, but for whom the blood samples were not taken as frequently as in the intensive group. All women reported here were informed of the nature of study and agreed to participate. Each of them was guaranteed the confidentiality of the data and signed a consent form for participation.

Formulation of Natural and Synthetic Hormones

Pharmaceutical grade, trans-dermal hormone creams were formulated by the Women's International Pharmacy. Both the estrogen and progesterone were extracted from a soy base. Users of this cream were subjected to regularly scheduled blood tests to determine how the use of this product affected their progesterone levels. Their reports of feeling depressed or anxious were correlated with what their blood tests actually showed.

Questions on Mood and Mid-Life Biochemistry

Mood changes were observed and chronicled using questionnaire below. The results are reported together with observable data from laboratory serum analysis and menses. Women were asked all ten questions during each session. Some of the questions are historical in nature (especially #10) and were not repeated each session.

1. Are you anxious? (irritable, short tempered)
2. Are you depressed? (lethargic, low energy)
3. Where are you in your menstrual cycle?
4. Are you having trouble sleeping?
5. Are headaches an issue?
6. Do you have a general sense that life is working?

7. Are you sexually interested?

8. Do you have obsessive thoughts?

9. Do you exhibit compulsive behavior?

10. Do you have a history of difficult periods, PMS, cramps?

Sample Size and Research Methodology

The sample sizes for this study were necessarily small, due to the high cost of obtaining the laboratory serum analyses, lack of funding for the study and most importantly, the individualized care given to the subjects. The research methodology adopted was that of "single case" study. After an extensive review of quantitative and qualitative research methods, it was decided that this was the correct approach for this research with its emphasis on biochemical individuality.

Laboratory Analysis of Plant-Derived and Synthetic Progesterones

Progesterone from two sources was analyzed by infrared spectroscopy at the research laboratory of Dr. Dwight M. Smith, University of Denver, Department of Chemistry and Biochemistry.

Plant-derived Progesterone: Pharmaceutical grade progesterone was obtained from the Women's International Pharmacy, Sun City, AZ, where it was extracted from a soy base.

Synthetic Progesterone, or Medroxy-progesterone Acetate: This progesterone was pharmaceutical grade "Provera", generic name Medroxyprogesterone acetate. Provera is a progestin prescribed by doctors to treat menstrual disorders. It was obtained by prescription in the form of 2.5-mg tablets produced by the Upjohn Company, Kalamazoo, MI.

Clinical Trial Results

Group 1: Focus Group: 2 women (the author being one of them) were studied intensively for 26 (Subject 2) to 29 months (Subject 1). Subject 1

Data were collected on subject 1 forty-four times from September 1996 through February 1999 and are presented in Figure 1, below, Figure 2, p. 4 and Figure 3, p.4. The data correlated with the symptoms as follows. The initial test, drawn from serum in September of 1996 at mid-cycle or ovulation, indicated very high levels of estrogen to 641.8 picograms/milliliter (pg/ml), high for non-pregnant women in their early to mid forties should be 443 pg/ml, and that is considered high. The progesterone was at 5.1 nanograms/milliliter (ng/ml), while the objective high should have been in the 15-25 ng/ml range. To mediate the carcinogenic, and other, effects of heavy estrogen the level of progesterone would have needed to be upwards of 20 ng/ml.

This was a startling revelation; that it really is about the interaction of the levels not just the objective levels themselves. The data were examined by several physicians, notably Dr. Wilson (OBGYN) and Dr. Whitcomb. One question concerned the

difficult pregnancy for subject 1. Heavy estrogen dominance is a major factor in extreme nausea during pregnancy. In fact, the subject was hospitalized with hyperemesis, extreme nausea and unable to eat. These levels are now suspected to respond favorably to high doses of natural progesterone to mediate the estrogenic impact. This is now known to be a major factor in post-partum depression and is often countered with natural progesterone.¹

After seeing this, the conjecture was developed to look at the emotional impact on peri-menopausal women of low progesterone levels. It is suspected that high estrogen levels produce an imbalance in the system that aggravates or causes symptoms of tension and anxiety. Subject 1 felt unusually irritable at mid-cycle when low progesterone was first established. This emotional pattern was observed subsequently every time the imbalance manifested itself in serum levels.

A protocol was established after first

Figure 1. Progesterone Levels: Subject 1.

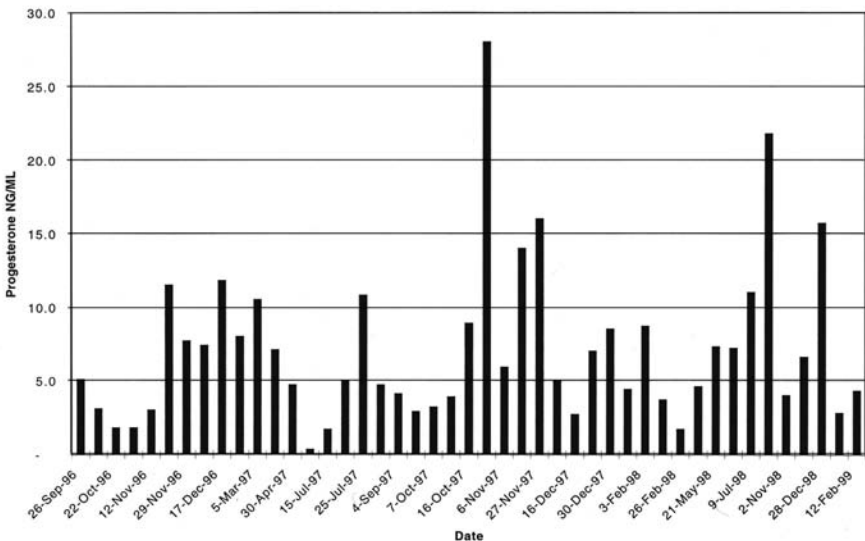


Figure 2. Estradiol Levels: Subject 1.

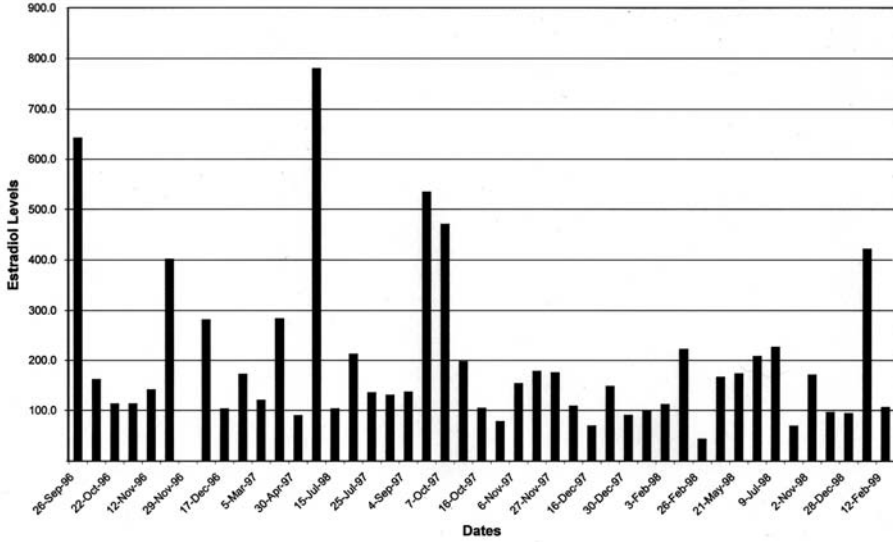
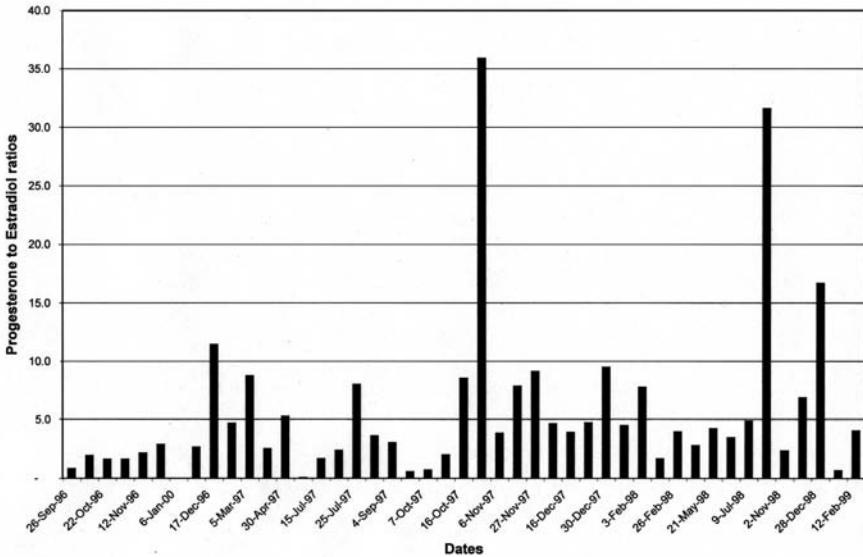


Figure 3. Progesterone to Estradiol Ratio: Subject 1.



levels were observed: 100 mg. of pure (natural) progesterone cream applied transdermally, (through the skin) bid. This amount was increased if the feeling of intense irritability persisted. From the beginning the serum levels responded to the progesterone increase by general elevation in progesterone, and a dramatic, over time decrease in elevated estrogen. Specifically, one month later the estradiol, which is the most commonly used form of estrogen for measuring overall serum values, was down to 400.3 pg/ml and the progesterone had climbed to 11.5 ng/ml. This trend continued for a year. Subject one continued to experience increased feelings of well-being. The objective measurements correlated strongly with the interpretive aspects: there were continued and generally improved feelings of calmness and factors related to the neuroinhibitory receptors in the brain, the part of the mid- brain which regulates anxiety. This is where progesterone does its neuro-chemical work. Estrogen works primarily on the serotonin pathways that affect depression, not anxiety as much as the benzodiazapine receptors do.

Subject 2:

Data were collected on subject 2 twenty-five times from June 1996 through August 1998 and are presented in Figure 4,

below, Figure 5, p. 6 and Figure 6, p.6.

Subject 2 was extremely interesting: Her feelings of increased well being correlated with the use of natural progesterone over time, however there is an important distinction between her symptoms and those of subject 1. When her estrogen was high, and her progesterone levels were low, she would exhibit extreme rage, followed by conciliatory, self-defeating demeanor the next day. As time went by and her progesterone levels came up, she no longer became as depressive following periods of anger and rage, which is how she manifested anxiety.

Interestingly for subject 2, all her adult life she had thought she was prone to significant depression. She had been treated with psychotropic medications, specifically Paxil and Prozac with little relief. After treatment with natural progesterone for fifteen months, from October of 1996 until December of 1997, she finally felt really well premenstrually for the first times in years. This has continued but with some variations.

Subject 2, it is now believed, had so much rage that after she calmed down she could focus on the depression that has lurked for years under the surface. Interestingly, subject 2 decided to try medication for short term for depression and now the drug (Paxil) is helping her. When she is

Figure 4. Progesterone Levels: Subject 2.

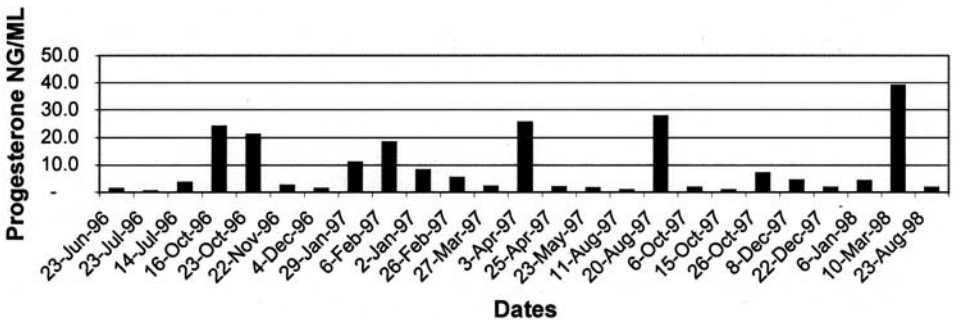


Figure 2. Estradiol Levels: Subject 1.

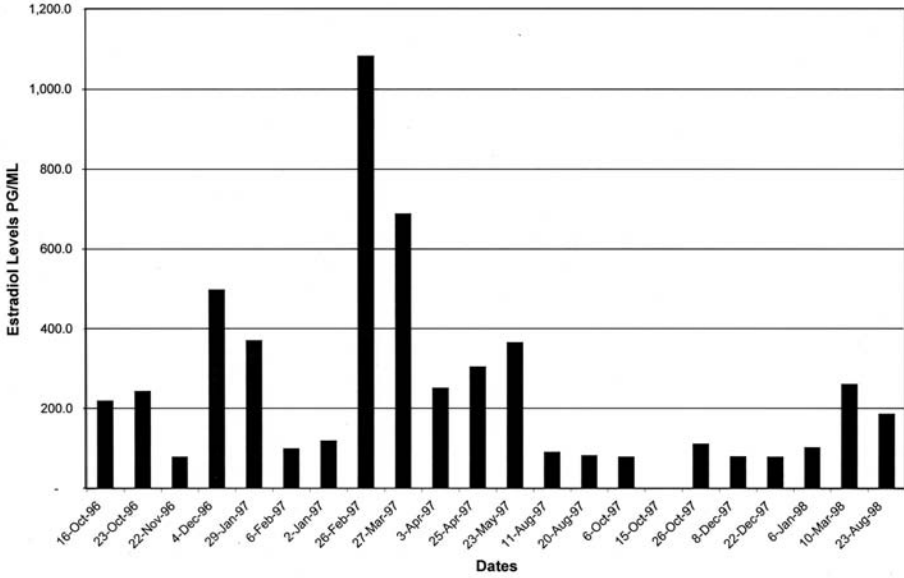
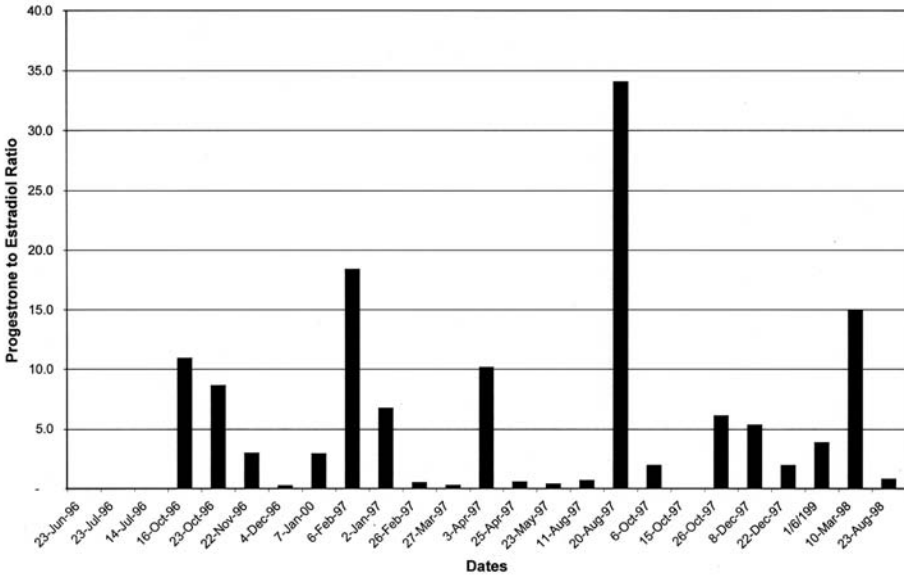


Figure 2. Estradiol Levels: Subject 1.



ready, I would like to see her work with more biochemical options with depression as well as for the anxiety.

Her progress has been slower than that of subject 1 but significant. She reported feeling best at times when progesterone levels came up at least to 4 ng/ml, and estrogen levels decreased below 100 pg/ml.

On December 8, 1997 she began a period of well being which was the best she had felt in many years. At that time the estrogen showed 79 pg/ml and the progesterone was at 4.2 ng/ml.

In the time following the pilot study, the author has found that when anxiety-prone women get the progesterone serum level above 15/mg /mL, true calmness sets in.

A major contrast with these two subjects is that subject 2 tends to cry easily when she is tense and angry. She also likes alcohol, very much, which subject 1 can "take or leave."

The general improvement in mood over two years for each woman has been remarkable. The amino acid treatments provide overall biochemical improvement in equilibrium; however pre-menstrual tension continued to run high in both these women, albeit with somewhat distinct manifestation of symptoms. After the introduction of micronized progesterone, in the form of transdermal progesterone cream, pre-menstrual tension has essentially been obliterated.

It is important to note that the six women in this phase of the study were initially given over the counter 1.6% progesterone cream. This is "micronized progesterone" in the physiologic doses recommended by John Lee, MD. Physiologic dosing refers to doses comparable to those that occur naturally in the female body. Four of the women reported improvement in pre-menstrual and menstrual cramping. Three women reported less brain fog and cognitive dysfunction. Only one of the women in the initial dosing group reported any improvement in neuro-chemical or emo-

tional symptoms of mood biochemistry. This was a two-month introductory phase before the clinical trial began. The mood changes occurred when there was a discernible shift in the progesterone/estrogen ratios as discussed from figure three, these data carried the same implications in the broader study as well. In case after case, as serum levels of progesterone rose with continued treatment, the mood improved in these women. The broad implications are being observed because we are seeing this trend show up in many more subjects not in the original study but being seen at our clinic.

Each woman in the two-year study reported that in the week prior to menstruation the cream would disappear (transdermal absorption) within fifteen seconds, as contrasted with earlier in the post-ovulatory phase often taking two to three minutes. This was observed by each subject independently. The vehicle for transdermal uptake is penetration of micronized progesterone through the skin. This is consistent with the observations of K. Dalton as reported in *The British Medical Journal*.² This would indicate very active receptor site availability.

Group 2: Estrogen Dominance

Six Women Showing Tendencies Toward "Estrogen Dominance:" With the second group of women, the focus was on correlating aspects of mood dysfunction with hormonal imbalance and other criteria as well. These women were being treated for general mood symptoms of mid-life with amino acid therapy. We then expanded their protocol as we began this study to include natural hormones. The first group of six women was prone to anxiety and tension, more than depression. Most had made considerable progress on amino acid therapy alone and improved considerably when natural progesterone was added to these protocols.

These women were informed about being part of this study and signed release

forms. They were delighted to have this tracking of mood symptoms because generally they felt that their various mood symptoms were dismissed as being peripheral instead of perhaps generative of other problems with their health.

The women discussed below are representative of the broader study in that their symptoms typify estrogen dominant patterns.

The following women were anxiety type patients who turned out to be estrogen dominant. Serum levels were measured at, or post, ovulation two to three times over a nine month to one year period.

The first woman, D, came in because of severe PMS. This refers to Pre-Menstrual Syndrome that can involve headaches, bloating, significant mood changes, tension and sometimes rage. Her gynecologist had treated her with various drugs, including one to suppress testosterone; strangely, progesterone was not on the list. Her initial serum progesterone at mid-cycle showed negligible progesterone at 1.4 ng/ml, not nearly enough to mediate the high levels of estrogen. Her marriage was failing because she was so irritable and she could not control it. She was one of those miracle cases; we have several of these now. She said the first two week trial of using progesterone was dramatic—she felt like herself for the first time in years. Initially we gave her 1.6% over the counter progesterone. As her menstruation date approached some symptoms intensified, notably irritability, and so we then ordered 6% progesterone from Women's International Pharmacy, compounded to our specifications. She has continued to thrive. I am continuing to follow her progress.

M is another anxious and irritable woman. Her husband said he felt she was obsessing about his mid-life depression and was using that to avoid looking at her own extreme hyper-irritability. In fact, she was increasingly angry with her husband for being depressed. According to her, he had

no right to be depressed since her family had done so much for him financially. In fact, this was part of his problem. Her problem was that she was so tense she could think of no one but herself, her mind raced and she talked incessantly. Interestingly, her mother, while much older, had similar personality traits and had been on Premarin with Provera, synthetic progesterone for years. Her mother had negligible progesterone serum levels even after years of being on synthetic methyl progesterone.

M reported irregular periods, which started after the birth of her fourth child. She also had post-partum depression that increased after she weaned her last baby. This is an often over-looked time of post-partum problems.

She reported incredible mood swings; her husband said she was simply angry, not seeing his perspective. She felt overwhelmed and the slightest trigger could send her into a rage. Also, three of her four children had symptoms of hyperactive behavior or attention deficiency, one of them is severe.

The subject was given "Anxiety Control"³ to use as a base nutrient. This is a 24 hour neuro-transmitter support formula for anxiety, based on utilizing glutamine and glycine to "walk" GABA across the blood-brain barrier. This helped calm her rage. Adding 10% natural micronized progesterone two weeks before her next menstrual cycle began has helped her distressed mood during that time even more. Although she has been a difficult woman to work with, she is showing improvement. She had initial mid-cycle progesterone levels of 0.4 ng/ml with an increase to 5.2 ng/ml over four months.

The third woman, B, in this phase of the study demonstrated the classic symptoms of the estrogen dominant female more than any other I have seen. She had negligible (not measurable) luteal progesterone of less than 0.4 ng/ml, which is essentially off the scale. She came to our of-

face hysterical saying she could not calm down and was having recurrent panic attacks daily. She reported obsessive thought processes that were traumatic for her. She was extremely high strung and felt she has "no containment" for these virulent emotional swings that upset her a great deal. She felt out of control with panic, rage, and anger, mostly directed toward her husband.

Subject four, Q, was the extreme of a group of three women, with cases five and six showing similar symptoms, but not as severe. So, in telling about Q, I see these other two cases mirrored but their behavior was not as extreme. Q would show no impulse control when angry and has wounded people irrevocably, or so it would seem. Q was given high doses of the neuro-inhibitors GABA and Taurine at 750 mg. and 1000 mg. for three months. This helped her enormously in reducing her feelings of panic. Cases five and six were given similar nutrients but in smaller doses. During the luteal phase, particularly the week prior to menstruation, the rage use to intensify. She has experienced steady improvement since she started using 100 mg. of natural progesterone six times a day. This is the dose that keeps her sane. Over time, if she is able, this might be reduced. In the meantime there is absolutely no harm in this protocol and it may help save her marriage. The other two subjects in this subgroup responded to 300 mg. and 400 mg. during this time period. Again, they were quite similar but less severe cases.

Group 3: Estrogen Deficiency

The women showing low levels of estrogen are fewer in our perimenopausal group by about 5 to 3. Most of the women in this age range tend toward estrogen dominance. This group is important here primarily as a statistical control: there are conjectures made by people working in the field that all women should throw out estrogen and only use progesterone. This

is not solid science. Theoretically, in the cascade of hormones, progesterone will convert to estrogen eventually. However, in some women this happens very slowly and sparingly.

Women in peri-menopause in this group show a great deal of consistency in their symptoms. There was little to no anxiety and no panic attacks were reported. The general complaint was depression and fatigue. Autoimmune illnesses seemed to be pervasive in this group. Three of these women had autoimmune indication in their blood. One had significant lupus, one had chronic fatigue and one had fibromyalgia. Lack of motivation was another factor. Four women reported that "it is an effort to do anything." They were generally not in touch with their anger because they were too tired. Researchers have suggested that women who can not express anger introject emotions, or turn them inward. My associate, Dr. Whitcomb, speculates that these women are prone to degenerative disease, often autoimmune illnesses.

The women in this control group were followed by the gynecologist we work with and used Bi-Est, a natural estrogen, made from soybeans comprised of 80% estriol, the overlooked yet safest, non-catechol, non-conjugated estrogen, and 20% estradiol to closely mimic the woman's estrogen. This was always accompanied by natural progesterone to counter the potentially carcinogenic effects of even the safest estrogens.

Laboratory Analysis Of Plant-Derived And Synthetic Progesterones

Pure samples of Medroxyprogesterone acetate (MPA) (Figure 8, p.11) and plant-derived progesterone (Figure 7, p.11) were analyzed by infrared spectroscopy at the research laboratory of Dr. Dwight M. Smith, University of Denver, Department of Chemistry and Biochemistry. Infrared spectroscopy was utilized instead of our originally intended vapor phase chromatography/mass

spectroscopy because the molecular weight of the progesterone molecules was too high for vapor phase chromatography. Both of these processes are used to establish the structure of molecules.

The data transformed certain previously held beliefs about the chemical structures of these molecules. Figure 8 shows the structure popularly known as medroxy-progesterone acetate and referenced as MPA in the cardio-vasospasm study.⁴ The spectral analysis revealed that it has a distinctly different configuration than has been assumed, even by pioneers in medicine using natural progesterone, such as in the writing of Dr. John Lee, Dr. Jesse Hanley and others. Natural progesterone is conventionally distinguished from synthetic by the emphasis on additional methylation; both synthetic and natural progesterone contain methyl groups. Figure 8, the synthetic molecule of Provera, in this case, shows great distinction from Figure 7 not in methylation but in hydroxylation and the presence of acetate.

Figure 7 shows the structure commonly referenced in the popular literature on alternatives to synthetic hormones and differs because of the lack of hydroxylation, not just the lack of a methyl group as commonly stated.

The synthesis of androgens (male hormones) starts with the hydroxylation of progesterone at C-17. The side chain consisting of C-20 and C-21 is cleaved to produce androstenedione, an androgen. Testosterone, another androgen, is formed by the reduction of the 17- keto group of androstenedione. Androgens contain 19 carbon atoms. Estrogens are synthesized from androgens by the loss of the C-19 angular methyl group and the formation of an aromatic A-ring.⁵

Summary and Conclusion

This research addressed two areas: first, a clinical research project focused on

the moods and biochemistry of women at mid-life, and second; a laboratory analysis of synthetic and plant derived progesterone.

Clinical Study

The clinical study addressed three specific questions (see page 1 above), which are reiterated with the results below:

1. Does a deficiency of progesterone affect anxiety patterns in mid-life or perimenopausal females? The clinical study found that a deficiency of progesterone is clearly implicated as a primary factor in mid-life anxiety patterns. As women increased the uptake of natural progesterone at 100 mg/dose, serum progesterone levels increased and seemed to mediate excess estrogen. These changes in serum levels clearly correlated with the qualitative input given by these women on questionnaires and in personal interviews.

2. Is mid-life anxiety in women connected to low progesterone levels or estrogen dominance? Mid-life anxiety in women correlated with anxiety being more extreme during the luteal phase, or latter two weeks of the menstrual cycle. Even though objectively this is when there is a gradual natural increase in progesterone production. The data showed that there is often too much estrogen to be mediated by the body's available progesterone.

3. Are amino acids and/or plant-based hormones effective in the treatment of anxiety? In the follicular phase, or first two weeks of the menstrual cycle, women predisposed to anxiety patterns reported significant improvement in their well being while taking neuro-inhibitory amino acids alone (GABA, Taurine, Glutamine). However, as the ovulatory peak of estrogen dominance started, and moved into the luteal phase, these effects diminished, even in women using physiologic, low doses of progesterone. When neuro-inhibitory amino acids were used in conjunction with pharmaceutical grade, natural progesterone, women thrived and reported

Figure 7. Infrared spectroscopy analysis of Pure samples of plant-derived progesterone.

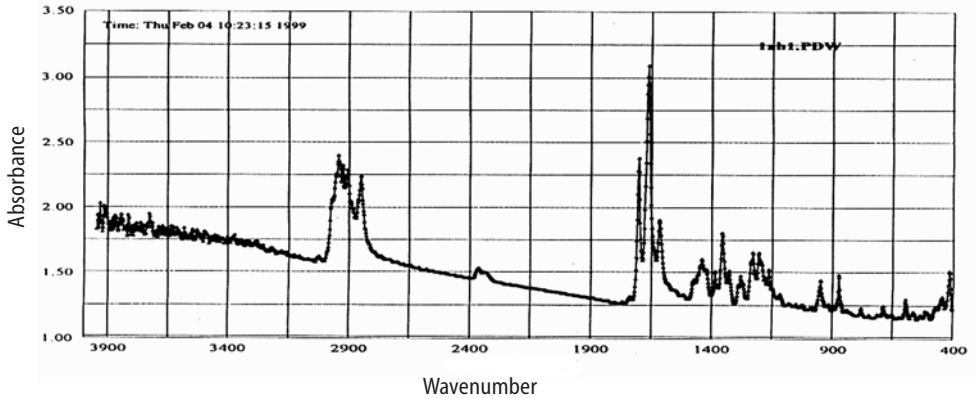
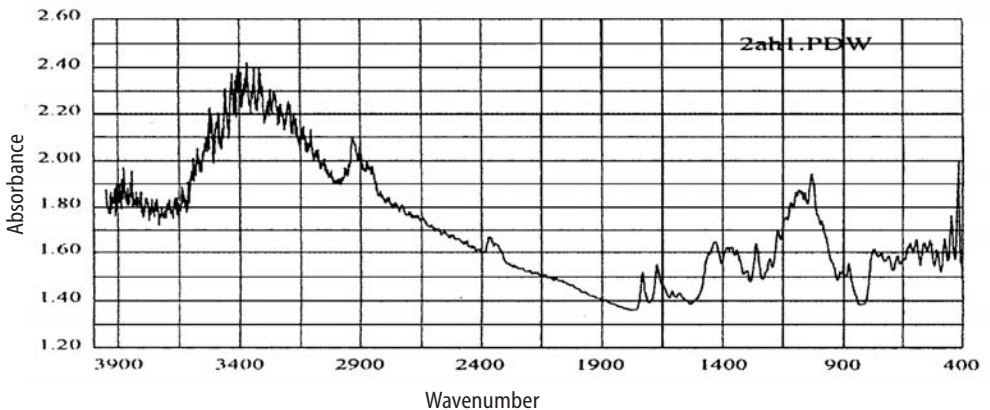


Figure 8. Infrared spectroscopy analysis of Pure samples of Medroxyprogesterone acetate (MPA).



greatly increased calmness, even during the normally difficult pre-menstrual phase
 Laboratory Analysis of Synthetic and Natural Progesterone

The laboratory analysis of synthetic and plant derived progesterone revealed significant differences in their structures and revealed discrepancies between the published and ac-

tual structure of the synthetic progesterone, Provera. The primary distinction between natural progesterone and its synthetic counterpart turned out not to be in methylation, but rather in hydroxylation and the presence of acetate in the synthetic molecule.

Discussion

Clinical Results of this Study: Perimenopausal women balanced over time and then developed some other symptoms that were analogous with drops in estrogen precipitated by the leveling effects of progesterone and by the fact of perimenopause itself. This became intriguing in the context of the premise that good science is frequently counter-intuitive.^{6,7}

These data infer that the women in the study were in treatment for various symptoms that are usually considered constitutive of anxiety (many of these symptoms had been assessed as clinical anxiety by a physician or psychologist).

We used the National Mental Health Association clinical depression checklist to gather more information.

The women with anxiety were treated with neuro-inhibitory nutrients, specifically amino acids such as GABA or Taurine. While there was initial improvement on amino acid therapy alone, the improvement diminished in the premenstrual two-week period of time. We therefore conjecture that the calming effect of progesterone might be because it augments the effect of GABA, and acts like a benzodiazepine itself.

Over the initial six months the results were consistent and extraordinary. The data suggest that the incidence of anxiety decreased markedly when women were using trans-dermal natural progesterone cream that largely bypasses liver function. Affirmative answers to question 1: "Are you anxious?" decreased over time congruent with the use of natural progesterone.

These women being assessed quantitatively were also questioned qualitatively during the time of blood studies. This component was extremely useful, as there are many gradations in the perceptual experience of anxiety, from mild discomfort or feeling nervous to panic episodes.

Specifically, in the two women followed over four years, there were parallel responses in terms of "changes in mood." Similar results were seen in the expanded shorter

study with the larger group of estrogen dominant women. The basis of this study could be expanded into an outstanding larger study if the funding becomes available.

The evidence points toward the premise that in anxiety prone women, when progesterone levels are low relative to estrogen, these subjects feel tense and irritable, and exhibit other criteria of general anxiety. Relief of these symptoms is generally seen when progesterone is measured at 8-15 ng/ml. The mood changes were qualified as follows. As the progesterone levels rose gradually, most symptoms of acute anxiety disappeared. Chronic symptoms took longer to dissipate, although they too diminished over time. The subjects also reported that if they were not diligent about using progesterone, symptoms recurred. As each woman was viewed individually, required progesterone levels varied, based upon their biochemical individuality. These fluctuations are reflected in the data.

Most of this inquiry developed over the realization of the disturbing errors in perception I see being applied in traditional medicine, specifically the danger of molecules such as medroxy-progesterone acetate. Those issues are obvious to the reader by now, and are addressed thoroughly in this paper and my related work.

A less obvious finding, which emerged later in this work for me, was the lack of pure scientific information by those supposedly invested in this alternative discourse. I refer here to the recent work of John Lee. He is the pioneer in the use of natural progesterone. Lately, while I have always maintained that he is myopic I have found him misguided. In his zealotry to promote the use of his "physiologic" dose of progesterone I see women getting led astray. He insists that women need only small amounts of progesterone to get relief for their peri-menopausal symptoms.

This study strongly contradicts Dr. Lee's approach. The women seen repeatedly

reported that the changes in mood happened congruent with elevated serum hormone levels of progesterone, usually accompanied by a drop in high estrogen levels! Early in our research these changes did not occur at physiologic doses (as promoted by Dr. Lee) or when low dose progesterone was used at 1.6%.

I conjecture that the petrochemical estrogens in the environment, as well as E1 and E2 found in animal foods, elevate our own estrogenic response significantly. These catechol estrogens are a definitive link to many cancers in men as well as women. Therefore due to higher than normal exposure to estrogenic substances today, the increased proportions of progesterone are necessary to mediate the toxicity by blocking receptor activity. The head of Women's International Pharmacy has come to similar conclusions to mine from years of research and is excited about the importance of this study.

This is a powerful study of mood changes at mid-life and beyond. This research has profound implications on the connection of hormonal changes and amino acid biochemistry. Further, in women of peri-menopausal age there are substantial data linking women who are estrogen dominant, i.e. top heavy in estrogen relative to progesterone, and irritability patterns and/or rage. Women tend to get more irritable and men tend more toward intense anger. There now appears to be a biological basis to this, as well as a neuro-chemical one. There are data to support the premise that estrogen itself is neuro-excitatory. High levels of estrogen may predispose certain women to high levels of anxiety, including panic attacks.

Dr. Ray Peat⁸ has been looking at this neuro-excitatory pattern for years. Dr. John Lee has also discussed this,⁹ and we have great regard for his work. However, we are finding that for neuro-chemical purposes, higher doses are required to alter the neurotransmitters in the brain and nervous sys-

tem than are available from Dr. Lee's physiologic amounts. These data are corroborated by researchers at Women's International Pharmacy and other compounding pharmacies. These pharmacies make hormones from substances that occur naturally, and mimic the way our own bodies manufacture hormones. The primary source for these hormones is soybeans. This is in sharp contrast to traditional hormone replacement therapy, which is dependent on conjugated, unnatural estrogens and progestins or synthetic progesterone.

Natural progesterone has neuro-inhibitory or calming effects similar to GABA, taurine and other neuro-inhibiting or calming amino acid precursors to brain chemicals. The neurotransmitters are the chemical languages that one part of the brain speaks to another domain. People who have trouble focusing, concentrating, or remembering how to do something are deficient in these biochemical messengers.

We now believe that there is too much estrogenic effect on women and men of the wrong type of estrogen, E1 and E2, due to environmental and dietary factors. These estrogens contribute to many cancers which are estrogen fed, and have a significant impact on the brain.

That is why many biochemists are horrified at the return to an emphasis on animal based or Paleolithic types of diets advocated in certain pop nutrition books today. We believe there is a connection between the anxiety epidemic and the high estrogen in animal foods.

We do concur with one aspect of *Enter the Zone* by Dr. Barry Sears,¹⁰ that people eating too many carbohydrates may become insulin resistant. We advocate a plant-based diet high in proteins. The return to animal based eating does not make sense for mid-life women because animal food, especially chicken and beef contain the wrong estrogens. This is the basic premise of Dr. Neal Barnard, head of the Physicians Committee on Responsible

Medicine, and the author of several fine books. In addition, we urge readers to read or reread *Diet for A New America*.¹¹

Implications For Future Study: This is a pilot study; already the impact has been enormous in helping some women solve the riddle of mid-life anxiety. This is the first study to look at correlations between fluctuations in estrogen/progesterone ratios and amino acid and neuro-transmitter levels that are genetically and biologically driven.

My vision is to expand this into a context for working on other mood disorders in as significant a manner. I want to use the data to continue the research into a foundational study on "Alternatives to Ritalin" for children. In terms of social impact, this is imperative. How can we tell children not to take drugs when we try drugs¹² in one form or another to solve every problem?

Human beings must come to peace with the dance of being human. We each bring a rich and varied history to life. This history becomes the fabric of who we are. Similarly, we each bring a biochemical blueprint and a biologically driven make-up to life. To quote Heidegger: "We are thrown to be a certain way."¹³ We must learn to integrate our psychology into who we are, not attempt to eradicate symptoms which can, and often should, become powerful teachers. I do not mean to imply that people should suffer needlessly. There is a series of fine lines here. Nevertheless, we must start to evolve into a species that takes responsibility for our individual lives, including our health, with proper guidance.

To close, I shall quote Caroline Myss from "Anatomy of the Spirit" where she states: "One cannot be a victim and be consciously creating one's own reality at the same time."¹⁴

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