# SUMMARY OF NATURAL PROGESTERONE RESEARCH

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## NATURE IDENTICAL HORMONE THERAPY

### Introduction

There is increasing interest in the area of steroid medicine for both men and women. The greatest interest is coming from perimenopausal and postmenopausal women who have a perception that the faithful supplementation of their natural physiological hormone levels with bioidentical progesterone, or natural progesterone, provides an attractive option for hormone replacement.

The intense interest in the use of natural hormones was initially generated from the work conducted by Dr Katherina Dalton in Great Britain. Dr Dalton published widely in the medical literature between 1953 and 1983 and has 41 original papers to her credit. It was her own use of natural progesterone in treating migraine that led her to publish an article in 1973. (1) Doctors who have worked in the United Kingdom are likely to have seen the clinical use of natural progesterone for the treatment of PMS. The Philson Library at the University of Auckland has copies of two of Dr Dalton's books, Premenstrual Syndrome and Progesterone Therapy (1977), and The Premenstrual Syndrome (1985).

The New Zealand public is more aware of the work of John Lee MD who collaborated with Ray Peat PhD in investigating the scientific research and publishing articles on the use of natural progesterone. Dr Lee prescribed natural progesterone for his patients over some twenty years. He has strongly influenced American public opinion and since retiring from practice, has maintained his involvement in this field.

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In Sydney, Dr Sandra Cabot MBBS, DRCOG, has been advocating the use of natural hormones for some years. She makes regular tours of New Zealand giving public lectures on women's health. Topics she promotes to women include the use of natural hormones and liver detoxification strategies for the improvement of health. It should be noted that many women are compromised through poor phase I and 2 liver detoxification pathways which reduces their ability to efficiently metabolise estrogens into the non toxic/stimulatory form 2OH and away from 16OH estrone .

Widespread public interest in the United States is now spilling over to New Zealand. There is increasing interest in the use of phytoestrogens such as lignans and isoflavones, derived typically from flax, soy or red clover. When consumed in appropriate quantities these phytochemicals promote weak estrogen like effects that can ameliorate some of the symptoms experienced during the menopause.

## Women's Health Initiative Trial

**The failure of the WHI Trial has raised considerable interest in natural hormone replacement although some medical practitioners are confusing physiological replacement of nature identical hormones with the use of equine derived estrogens and medroxyprogesterone. This represents a failure to understand the steroid differences between the synthetic and natural molecules and the proven protective effects of bio identical progesterone and oestriol in particular**

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## Mexican Wild Yam (Dioscorea Villosa)

There is widespread confusion regarding the properties of Mexican wild yam. The active ingredient is diosgenin, which has phyto-medicinal properties that can help control some of the symptoms of menopause. Contrary to advice emanating from the health food sector the human system cannot convert wild yam into progesterone. Diosgenin does not have important properties attributed to progesterone such as breast tissue and endometrial protection, osteoblast receptor activity, control of fluid reserves, maintenance of sex drive etc. However, diosgenin sourced from Mexican wild yam is used as a precursor molecule for the industrial production of natural progesterone. Soya is also used for this purpose.

While medroxyprogesterone (Provera) and other synthetic progestins also originate from natural sources, they are chemically modified patentable hormones that are not biosynthesised in the human system and do not act in the same way in the human body.

There is a great deal of concern medically, that post menopausal women should receive optimum benefits from hormone replacement therapy and many major trials have been undertaken to examine efficacy and safety. In following the history of standard HRT therapy it is evident that barriers to effective therapy are obvious. These include poor compliance, increased rate of breast cancer from both unopposed estrogens and premarin plus medroxyprogesterone, an increased incidence of Lupus and blood vessel disease and the question of endometrial protection. Work published in 1995 has also shown an increase in vasospasm (heart attacks) in primates who were given medroxy progesterone acetate. In this comparative study progesterone was protective in this respect.

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## Faithful Replacement of Nature Identical Hormones

According to Hargrove, using the sex steroids which occur naturally in humans represents faithful replacement of the steroids lost at ovarian failure. By using timed measurements of the replaced steroids to ensure attainment of premenopausal levels of the deficient hormones, women can be assured of the adequacy of therapy - not too little and not too much. This method of hormone replacement has been evolving for more than 20 years. An estimated 50 million doses have been given to a large number of women during this period of time. This is an inexpensive therapy that gives good relief of symptoms and is well tolerated. The endometrium is protected, and uterine bleeding is infrequent. Patient compliance is good, and the positive effects of this hormone treatment encourage most patients to seek long-term therapy.(2)

Part of the interest in the use of natural hormones rather than cross species or altered molecular entities is being generated by the substantial amount of information appearing on the Internet. Many women are exposed to this information and there are numerous reports from doctors confirming these phenomena.

Although there are many significant studies showing the efficacy of natural progesterone there is not the depth of published literature that is a feature of HRT. The major reason is that natural hormones are not available for patent protection. This negates the commercial advantage a patent provides and therefore there is less incentive for commercial interests to undertake trials. That said, the published studies on progesterone do not contain the bias seen in studies financed by commercial interests as the great majority have been conducted through university institution funding.

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## 1998 FDA-Approved American Society for Reproductive Medicine Trial (Vasomotor Hot Flushes)

The women in the study were one to five years from their last period, the average age was early fifties, none were on estrogen, the majority were experiencing vasomotor hot flushes. A broad spectrum of blood tests as well as serum and salivary levels of progesterone were taken. Associate Professor Helene Leonetti MD, the physician who conducted the study, reported that after one year there was a resounding difference in hot flushes.

Of the women on progesterone 83% had total cessation compared to only 19% in the placebo group. In addition the women on progesterone reported a considerable improvement in feelings of well being and there was a significant reduction in lumps and hardened tissue in breast tissue. Some noticed that libido improved and others had thyroid function improve and were able to discontinue thyroid medication. Bone mineral densities were repeated at the end of the first year and although many women showed an increase in bone density, the difference between the two groups at the end of twelve months was not statistically significant. The researcher noted that changes in bone density were not likely to show up before 3 years.(3)

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## The PEPI Trial

Results of the PEPI trial were published in JAMA in early 1995. 875 postmenopausal women were randomly assigned to receive either 1. placebo, 2. premarin, 3. premarin + provera or 4. premarin + oral natural progesterone (micronised). Levels of HDL in the placebo group decreased by 0.03% compared with the baseline. In the premarin group HDL levels increased substantially over baseline. In the premarin plus provera group HDL increase was marginal, however in the premarin plus natural progesterone group nearly all the HDL protection available from premarin was maintained. Both provera and natural progesterone reduced total cholesterol and LDL compared to placebo. The strength of the result from natural progesterone surprised the investigators. A prominent cardiology researcher Elizabeth Barrett-Connor MD who headed the PEPI trial stated that if a woman was worried about heart disease or if she had dyslipidemia and low HDL she would consider prescribing natural progesterone.(4)

## Progesterone and Coronary Vasospasm

It is worth noting that researchers at the Oregon Regional Primate Research Centre have demonstrated that natural progesterone may help prevent heart attacks. The London National Heart and Lung Institute have shown that progesterone has a direct impact on reducing platelet aggregation through its ability to enhance endoethelium-derived relaxing factor (nitric oxide) and is superior in terms of both its safety and effectiveness in protecting post menopausal women against heart disease and osteoporosis.(5-9 )

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## Breast Protection

Progesterone appears to have a protective role against breast cancer. A 30 year retrospective study at John Hopkins University found that women who were progesterone deficient had 5.4 times the incidence of breast cancer and there were a greater number of deaths from cancers of all kinds.10 A double blind randomised study has shown that progesterone actually slows the rate of cell division induced by estradiol in breast duct cells.(11)

Progesterone at a concentration similar to that seen during the third trimester of pregnancy exhibited a strong anti proliferative effect on at least two breast cancer cell lines.(12) At a world conference on menopause in the mid 1990's, European specialists advocated the use of progestins which are as biochemically close to the natural progesterone molecule as is possible.(13)

A 12 year cohort study in France, followed over eighty thousand women, 70% of whom had been taking various forms of HRT therapy. This study showed that using estrogen alone (mainly estradiol formulations) increased the risk of breast cancer by 22%, but opposing the estrogen with natural progesterone reduced the risk back to the same as non use of HRT, indicating a strong protective effect on breast cancer risk by the use of natural progesterone.(37)

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## Ovarian Protection

Progesterone has been shown to reduce the risk of developing ovarian cancer in postmenopausal women. It has an ability to markedly up-regulate the anticancer p53 gene expression. (14)

## Endometrial Protection

There are a number of studies that demonstrate progesterone's ability to protect secretory endometrial tissue. Although these are not large double blind randomised trials they do confirm the protective role of progesterone.15-19 Helene Leonetti MD the gynaecologist in charge of the 1998 FDA sponsored trial on progesterone has 7000 patients in her practise.

She reported by personal communication that she is very generous in conducting endometrial biopsies and notes that no patients have presented with cancer or endometrial hyperplasia with atypia. Subsequent to the above report, in January of 2003 Dr Leonetti published a pilot trial in the Journal Fertility and Sterility. Topical progesterone was used in a randomized, double blinded, placebo controlled fashion. The study recruited healthy, non smoking post menopausal women between the ages of 45 and 75 years, all of whom had taken oral HRT for 12 months. All discontinued HRT before entering the study. The study revealed that progesterone cream had an anti-proliferative effect on estrogen-stimulated postmenopausal endometrium.(36 )

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## Progesterone Absorption

A study whose results and conclusions have subsequently shown to be erroneous was undertaken by the Menopause Clinics, Kings College Hospital and published in the Lancet in April of 1998. A transdermal application of progesterone was applied in the form of Progest (manufactured in the United States).

It was the opinion of the researchers that systemic absorption of progesterone as measured by plasma levels, was not sufficient enough to provide endometrial protection if estrogens were used and the uterus was intact. This evidence is contrary to what clinicians have found over 20 years of continuous prescribing of progesterone and goes against all other available evidence. WHO accept that salivary measurement (not plasma levels) is a reliable assessment of available active progesterone and levels measured over a substantial population indicate that topically applied cream achieves receptor levels that produce an optimal therapeutic effect.

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## The FDA Recognises Salivary Measurement

According to Lee and others it is not possible to accurately measure available progesterone from serum and plasma. However salivary assessment provides an accurate assessment, which is substantiated in the literature.(20-22) Thus there is a reliable and measurable relationship between active and available progesterone, which can only be determined by salivary measurements. Increasing numbers of United States diagnostic laboratories use salivary measurements to assess available progesterone and New Zealand now have Canterbury Health Laboratories in Christchurch providing the service at a very moderate cost. (Contact Steroid and Immunobiochemical Labs (03)364-0888.)

It should be noted that the transdermal delivery of natural progesterone can produce relatively high salivary levels and women should addjust their daily dose based on response as well an occasional salivary measurement. Opinion based on progesterone's positive effects on many women would indicate that transdermally applied progesterone reaches target tissues. Dr John Lee and other medical specialists, experienced in prescribing and following patients, takes issue with the Kings College Hospital Lancet study.

## Progesterone as a Bone Trophic Hormone

There is evidence that progesterone has an ability to promote osteoblast activity. Unfortunately there are no large controlled studies, which would remove clinical doubt. Helene Leonetti in her Vasomotor Hot Flush Trial saw a positive change in bone density over twelve months.

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Dr John Lee used serial bone desity measurements on his practice patients and reported a 10% mean increase in bone density in the first 6 to 12 months with annual increases of 3% to 5%. These patients used dietary and exercise interventions as well as progesterone 23 JC Prior, publishing in Endocrine Reviews has identified progesterone as a bone trophic hormone. (24)

A small study at Center for Fertility and Reproductive Endocrinology, Connecticut involved 52 women to evaluate the relative efficacy of 12 months sublingual administration of micronized estradiol and natural progesterone on bone mineral density and biochemical markers of bone metabolism. This combination favorably decreased serum and urine markers of bone metabolism, prevented bone loss, and results in a

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It is encouraging to see that a recent grant has been appropriated by the National Institute of Health to study the effect that progesterone has on bone mineral density. A study to assess the influence of progesterone on cardiovascular disease, bone mineral density and endometrial protection is to be undertaken at the Chelsea/Westminster Hospital in London. There are numerous anecdotal reports of post menopausal women increasing bone mineral density.

## Neurosteroid Effects

Some interesting work has been done with metabolites of progesterone. It is reported that progesterone can positively improve mood and this seems to be borne out by these studies.(25) A common message from the American health food industry to women is that progesterone is the "Feel Good Hormone". In studies, the anxiolytic effect of progesterone has been compared to benzodiazepines (valium and ativan). This gives an indication of progesterone's useful anti-anxiety effect for many women. (26) Doses of I00mg to 200mg transdermally and up to I000mg orally per day have been used at the higher dose end to initiate control of PMS and endometrial disease. At higher doses patients may experience a hypnotic like effect.(27) For long term therapy much lower doses are prescribed.

**Alleviation of Premenstrual Symptoms** Metabolites of progesterone play a physiologic role as anxiolytic agents and modify mood and reduce anxiety. In a sub-category of nervous symptoms, a significant improvement is seen in symptoms related to tension, mood swings, irritability, anxiety, and lack of control. The use of 200mg of progesterone vaginal suppositories twice daily was an effective treatment for the alleviation of symptoms related to premenstrual syndrome. Topical application appears to provide similar results to pessaries.(28)

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## Post-Partum Depression

There are marked alterations of the binding sensitivity of brain GABA receptors in pregnancy and during the postpartum period. This is linked directly to psychological changes accompanying these states. The metabolically stable anxiolytic steroids of progesterone appear to be very specific and effective in alleviating both mild and severe cases of both postpartum depression and premenstrual syndrome depression.(29)

## Progesterone and endometrio sis,fibrocystic breastdisease

There are many clinical reports from experienced prescribers indicating that progesterone will oppose and reduce the stimulatory effects of estrogen on susceptible tissues thereby down-regulating symptoms3. When the biochemistry of hormones is understood the reason for this hormone “balancing” activity becomes obvious.

## Progesterone and Fertility

Selenium supplementation in ruminants up-regulates progesterone production in the estrus cycle. This is an interesting finding as in New Zealand it is recognised that we have significantly low soil selenium levels which has consequences in both animal and human health. Low production of progesterone from the corpus luteum is significant in infertility and the maintenance of a pregnancy.(30)

## Tubal Ligation

Progesterone production declines slowly after sterilisation resulting in a lowest value 12 months after the procedure. Menstrual cycle length, follicular phase and luteal phase lengths do not change.31

## Male Infertility

Progesterone may help male infertility as it has been shown to cause an immediate increase in free cytosolic Ca2+ in capacitated and non-capacitated human sperm. Calcium influx is triggered within a few seconds of treatment with progesterone.32

## Blood Lipids

Natural Progesterone when given to 366 individuals together with equine estrogens (0.625mg daily) reduced lipoprotein levels by 17% to 23%.33

## Brain Cell Protection following Traumatic Injury

This in turn leads to the sparing of neurons.(34) The brains of progesterone-treated animals contained one third of the oxidant marker 8 - isoPGF2A found in the brains of non-treated animals.(35)

## Side Effects: Potential Allergy

A very simple non ionic cream base should be used to deliver progesterone transdermally. There are a small group of women who may experience an allergic reaction to a cream and in these cases progesterone is compounded by the pharmacist into an inert and stable oil base. It is preferable that any preservative used does not carry a phenolic ring. Capsules are widely used in Europe and the United States. As progesterone is degraded at the first pass by the liver, higher doses, in practise – in the region of 10x are required for oral treatment compared to when a transdermal cream is used (20mg transdermally equates to 200mg orally).

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