Testimony
Of
T.S. Wiley
before the
Special Committee on Aging
United States Senate
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Mr. Chairman, Members of the Committee, I am T.S. Wiley and I would like to thank you for inviting me here today to share my expertise and experience with menopause and, of course bio-identical hormone replacement therapy and compounding pharmacy. I am a medical theorist in the field of Darwinian Medicine and writer/researcher on the use of hormones, particularly in postmenopausal women.

I have devised and developed a new method of hormone replacement therapy (HRT) called the Wiley Protocol for women to use as a more accurate form of replacement for lost endocrine function. The remedies available to women suffering from hormone deficiency are woefully inadequate. The commercial pharmaceutical offerings are either bio-identical and too low in dosage to have efficacy, or synthetic drugs, far too dangerous to take. Here in the United States, there are over 40 million women between the ages of 40 and 60.

Worldwide, about 25 million women enter menopause annually. It is estimated that by the year 2030, that number will increase to 47 million women per year. Since 1900, in the developed countries, the life expectancy of women has increase from age 47 to well over age 80, however, the average onset of menopause has remained at 50 as recorded for the last 150 years. That means, overall, women are living at least thirty years longer than they did at the turn of the century.

Our society has never felt the impact of the majority of women living 30 or more years in a hormone deficient state. It won't be pretty. Right now, modern medicine keeps us propped up with antibiotics and surgery, thanks to blood transfusion and anesthesia. But just being alive does not assure "quality of life." Without it, extended lifespan is far less than a gift. It's estimated that eighty percent of women experience a variety of

transiently debilitating symptoms in menopause and 30% of those are classified as severe.

About ten years before women ever have a hot flash or a migraine, we have odd, too-short menstrual periods, we're up half of every night and we start to *look* old. And almost as soon as we start to look old, we start to *feel* old. Exhaustion coupled with plummeting sex hormones creates a life in tatters and a mind like Swiss cheese. Sex would be a memory, if we could remember anything. Our joints twinge and, worst of all, we can't fall asleep or stay asleep. It is anecdotal common knowledge that older people wander around all night limping and bumping into things when they should be out like a light.

Given the evidence that these symptoms of menopause, which can begin for women as early as their late thirties, are the same as the daily challenges the elderly face -- that we become, in fact, "old" when our hormones start to plummet -- we can probably assume we're going to be sick, too, if we aren't already.

Because it is, again, anecdotal common knowledge that old really equals sick in the preponderance of cases -- and sick and old in our culture means usually means cancer, diabetes, heart disease, glaucoma, depression, even Alzheimer's, and since we've established that menopausal symptoms are the same symptoms "old" people experience, then, ***menopause must really equal sick***, and since all those outcomes above of "sick" can be life-threatening, menopause, itself, must really be *life-threatening.*

If menopause might really equal cancer, diabetes, heart disease, glaucoma, depression, and Alzheimer's, why is it, then, that in those ads for "menopause products", and in the health advice from the North American Menopause Society (NAMS), the Women's Health Intiative (WHI), the Food and Drug Administration (FDA), the American College of Obstetricians and Gynecologists (ACOG), no one ever mentions any of the life-threatening disabilities associated with hormonal decline and urges women to accurately replace those hormones that have gone missing?

Confusion and Media Hype

Instead, women are told that the FDA sanctioned hormones from Big Pharma are really way too dangerous to take (WHI) and biodentical compounded hormones have never been studied (AMA). The most twisted take on the current predicament women face when trying to decide on a mode of relief is the one taken by Barbara Kantrowitiz and Pat Wingert, columnists for *Newsweek* magazine, who have written their own book called, "*Is it Hot in Here or Is It Me? , The Complete Guide to Menopause."* Wingert and Kantrowitz, ostensibly women themselves, oddly have written an article blaming women for not being resilient enough to tough it out without HRT. They portray menopause as a transitional state that anybody with enough planning can live though. After all, they report that you should not consider yourself "a lost cause," you're just passing through "menopause milestones". As if, on the other side of this *change,* your life and health will suddenly just fall back into place. It doesn't. It's never the same again.

Generations of women (and men) before us knew forty was almost "old" and fifty was as close to sixty as it was to forty. Most of our parents had children in their twenties when they were our age. We knew *they* were old. How do we continue to deny how old we really are?

Baby Boomer women have certainly had help sustaining this mass hallucination. The feminists of our youth, like Betty Friedan and Germaine Greer, have written books exalting this new "undiscovered country" and all of Gyneculture has a whole cable channel called *Lifetime Network* to celebrate it. The trend was to embrace our reproductive denouement -- sort of. "Medicated" conventional menopause was becoming more and more acceptable until the WHI report. Doctors handed out PremPro like Pez and no one questioned it.

Every gynecologist with word processing software has told us the sum total of their knowledge on the subject and has been interviewed by every morning show on every network. So, we all really understood "menopause" and we were OK with it. Those were the good old days. Women knew it was something they couldn't avoid, unless they lived fast, died young and left a beautiful corpse. We all know that unless you go out young, the only certainties in life are *death, taxes* and ***menopause.***

In that list only taxes aren't natural, right?

The Inevitable is Acceptable Because it's Natural

Not even. Menopause is certainly not "natural." *There is no menopause in nature*. They never mention that on Lifetime. You'll get more accurate scientific reporting on Animal Planet. The animals always die when they're no longer reproductive.

Otherwise, we would hang around and compete for the food supply with the offspring of the reproductive (young) animals. That scenario benefits no one. That's why there's a fail-safe in nature. When a female runs out of eggs and her hormone levels bottom out, its *game over*. Her judgment flags, her spirits plummet, her immune system freaks out, homeostasis goes out the window and she goes not so gentle into that goodnight, unless someone does the right thing and pushes her out to sea on an ice floe for the good of the "group".

The elderly experience auto-immune conditions like arthritis or Lupus or Parkinson's disease and the more obvious degenerative states like Alzheimer's or cataracts and macular degeneration. But, what if real hormone replacement could really mimic youthful hormone levels, not just mask a few obvious symptoms, and therefore; was a cure for those diseases? It does make logical sense. After all, *young* women don't have those diseases and the difference between young women and old women is reproductive capacity and the attendant hormones. Therefore, it's logical that the majority of women *with normal hormones* don't have those diseases.

Menopause, and andropause in men, are states of hormone depletion akin to the failure of Type I diabetics to produce insulin from their own pancreas. ***Type I diabetics take a bio-identical molecule of insulin, using a short needle, through their skin, dosing it as their bodies would have produced it—after a meal, depending on what the meal consisted of,*** and they live long, pretty comfortable, healthy, productive lives. One of the shining moments in medicine in the last century was the synthesis of insulin for replacement in Type I's, and yet medicine refuses to acknowledge the obvious -- that the replacement of sex hormones in the same manner might put a serious dent in the diseases of old age.

Instead, the *Today Show* offers health advice like "herbs, acupuncture, aromatherapy and massage" for menopausal "discomfort." *Aromatherapy*?? We'd like to

see a doctor tell a diabetic near coma to go get a massage instead of taking insulin. That would be tantamount to murder, but that's what women in 2003 got from the WHI historic report on synthetic drugs with hormone-like effects, PremPro and Premarin.

These substances were donated by the pharmaceutical company that had sold them since 1942 because the assumption was the drugs would be found safe and effective. Nothing could have been further from the truth. After nearly 800 million taxpayer dollars and 14 years later, the overly emphasized negative results of the Women's Health Initiative were released in May 2002. This study was poorly designed, strangely monitored and incompetently analyzed.

The Study that Still Needs to be Studied

The WHI is now the "gold standard" regarding hormone therapy. Interestingly, the WHI never looked at *hormones*, only drugs with "hormone-like" effects that were dosed in a regimen far from that of human replacement. This study has led us to believe that conjugated equine estrogens (from pregnant mare urine) and a synthetic progestin (Prempro) dosed on a daily basis in static doses is clearly very harmful to women after only a few years, and yet, in contradictory reports from the same agency, PremPro seemed to have had positive effects as well. The other drug studied, daily Premarin, seemed to show substantially less harmful effects. Even though the death rate for all arms of this study was equal, the study was dramatically halted early in a very public effort to "save lives."

This confusing and frightening media spin caused millions of women to immediately stop taking their Premarin or Prempro, or any other product deemed a hormone. Physicians also threatened by the negative media reports stopped prescribing them, thus leaving millions of symptomatic women without any reasonable clinical guidance, except the ludicrous exception to the bad news, that lower doses of Prempro, the killer drug, taken for less years is safer.

This advice has not left women feeling safe.

As was alluded to in the beginning of this testimony, the mortality and morbidity of menopause is substantial, as substantial as it is being elderly. Young people *very*, *very*

rarely experience heart disease, diabetes and cancer. Old people *very, very often* do. And the difference between "young" and "old" is what happens in the middle or mid-life -- hormonal *fall-off*. The incidence of heart disease for women equilibrates (catches up) with men ten years after menopause. The big clue there could be the sudden absence of estrogen for the first time in their lives.

There is enormous data from two researchers named Grady and Rubin, who looked at 85% of the world's data on estrogen and cardiovascular effects and found that the positive cardiovascular effect of estrogen in decreasing blood pressure and lipid profiles was unparalleled by pharmacological agents. Could the just *lack* of hormones explain why the rate of heart attack among women in this country is ten times less than it is in men *until menopause* or, gasp, the epidemic of breast cancer from forty on in women? Makes us wonder. Everybody "knows" estrogen causes cancer. But do we *know* that, or, have we just been *told* that?

Reasoning vs. Rationalizations about Estrogen

Common sense belies the logic that natural (not synthetic drugs with hormone-like effects) hormone replacement, in and of itself, could ever *cause* cancer. If estrogen and progesterone, or even testosterone, caused cancer, all young women would be dead. They're full of it. So if logic tells us that estrogen doesn't actually cause cancer in and of itself, then there must be more to the story—like what kind and how much estrogen and when to take it.

There are too many pieces of evidence that real estrogen replacement, not PremPro, also negates the need for *bisphosphonates*, the commercial pharmaceutical treatment for osteoporosis. Those drugs in newer data are implicated in actually weakening bone. Because this class of drugs blocks old bone resorption and there's no progesterone to normally build new bone—it turns into a substance akin to petrified wood. Bisphosphonates are now known to cause micro-fractures in bone that must have a normal estrogen/progesterone metabolism to be healthy.

Estrogen also alleviates mild to moderate depression, the most common diagnosis in women ages 40 to 50. However, Dr. Joanne Manson of Harvard, who, too, has written her own book, called "*Hot Flashes, Hormones and Your Health,*" insists hot flashes "are

the only compelling reason to take hormone therapy," (what an understatement) and that "hormones are best used for only two to three years." What are the depressed women aged 40 to 50 to do three years later – live on Prozac, when a natural substance would have put them right instead?

Follow the Money

The importance of understanding the biology of menopause and its morbidity must be a primary medical economic concern to America. Relief of menopausal symptoms such as improved sleep will likely translate into a more productive woman whether in the workforce or as a mother or a spouse. Healthcare dollars can be spent more wisely than in Medicare reimbursements for constant doctor visits and endless prescriptions and procedures. Quality of life will improve for most symptomatic women and hormone replacement is an important choice for women since estrogens are known to be the only effective treatment for estrogen-depleted states.

Although no formal medico-economic analysis is yet available, Dr. Julie Taguchi, oncologist at Sansum Clinic in Santa Barbara, California predicts that there would be a substantial medical savings. In prescription drug costs alone, scientifically proven safe and effective HRT could reduce the use of anti-depressants, blood pressure medications, lipid lowering agents, sleeping aids, gastrointestinal drugs, etc. to such an extend that the estimated annual savings in the 10 to 20 billion dollar range would not be unreasonable. Additional cost savings in office visits, hospital stays, productivity are hard to estimate.

The failure of the WHI trial is partially due to the lack of understanding of the biology of the reproductive and menopausal state as well as, the indiscriminant choice of study subjects without well defined entry criteria, such as on the average enrolling subjects 12 to 15 years into menopause, creates unfathomable noise for the outcome.

A larger issue is the administration of drug molecules that are not natural to women's bodies as compounded versions of plant-derived hormones could be. The choice of the molecule, the dosage, and timing of the onset of therapy are the most important variables in the search for safe and effective HRT and the WHI spent almost a billion dollars and never approached any of the most important questions..

Women, now suspicious of drug companies and their compliant physicians, yet desperate for relief of menopausal symptoms, are turning to other treatments or plant based bio-identical hormones in droves. These plant-based hormones of different sorts seem to be the most widely used and promising alternatives at this point in time in the infancy of the endocrinology of menopause. It is clear that the conjugated horse urine estrogens (Premarin) with progestins (Provera) were the number one drug(s) most likely NOT to be refilled. Studies confirm that women can feel a difference between the kinds of hormones taken, so much so, that women prefer black cohosh and lachesis (homeopathic literal snake oil) to Premarin and PremPro.

Alternative medicine is really making a killing (literally and figuratively) on this one. Women are so distraught and physically miserable that they are looking for any answer that doesn't involve a hysterectomy or chemotherapy. Their disillusionment with Western medicine has driven them to herbal and homeopathic "cures," that may or may not do even more damage. They've placed the same blind faith in alternative medicine that has usually been reserved for their Western doctors.

But Western medicine and science have issued edicts that say women can *only* have a medicated menopause courtesy of the drugs they, themselves, have already deemed dangerous or we can grit our teeth (what we have left of them) and try to survive it without any relief. Estrogen is responsible for: *memory, eyesight, bones, heart, teeth, sleep, ability to withstand stress,* and *progesterone* since ovulation is impossible without estrogen (even using natural progesterone, at this point the receptors aren't "reading" its action because *progesterone receptors* are created by estrogen) And without progesterone women risk: *cancer, sudden vaso-spasm* (female heart attack), *migraines, psychotic behavior, auto-immune diseases like lupus, arthritis, rashes, rosacea, neuralgia, no bones, no libido, high cholesterol and carbohydrate craving, possibly obesity, Type II diabetes.*

Hormone Replacement from Plants is Not a New Idea

Whether or not women replace their missing hormones is not up for debate. Living without them is far too miserable and dangerous. So then, the question becomes "how"? Replacing missing estrogen, progesterone or testosterone with molecules of the

identical hormones synthesized from plants make the most sense. The original hormone substances, before they were changed in the lab to be patentable, in pharmaceutical HRT came from animals and plants, too.

Human beings, like all animals, have receptors in brain and body cells to receive everything that the planet has to offer, from nicotinic receptors to cannabis receptors. "Natural" hormones are made from molecules called phyto- estrogens that, despite their name, are synthesized into natural progesterone first and then tweaked into testosterone and eventually estrogen. The source of these plant-derived hormones is most likely soy beans or Mexican yams, but unlike *progestins* (the artificial molecules served up by pharmaceutical companies as the real thing), the unpatentable natural version fit perfectly into human receptors.

Hormone replacement therapy from plants was never dangerous. Real, natural hormones synthesized from plants have been known throughout history to be safe and effective birth control and death defiers. Only when drug companies got into the act did our lives get shorter and more painful. Hormone replacement from nature's bounty directly to our receptors was as natural as child spacing through lactation. Women always knew how to take care of themselves and each other. Women have always self-medicated with plants for contraception, beauty products and hormone replacement.

It's All Downhill from Here

While estrogen and testosterone levels slide steadily downward from twenty-six years of age on, when human growth hormone slows, the biggest difference between a woman in her twenties and a woman in her late thirties is in the levels of *progesterone* she can produce.

In a normal twenty-year old, the act of ovulating -- which produces progesterone, once a month for fourteen days -- is dependent on a system of feedback loops between the ovaries and the brain which are regulated by levels of estrogen.

Estrogen production is directly dependent upon the number of eggs a woman has left every month after ovulation, deducted from the finite number we are born with. Ovulation uses up about 150 every month in an effort to produce one "good" one. From conception until puberty, eggs are destroyed by a genetic clock. As fetuses, in utero, we

had about one million eggs, but by the time we were born -- we were down to half a million. At puberty we're down again by half, to a quarter of a million. Every seven years after puberty the number of eggs diminishes by one half of the declining base number, until we reach about thirty-three, when the decline picks-up speed, and the number of eggs are halved every three years.

In the ten to fifteen years before we actually hit the wall sometime in our fifties, and run out of eggs, the declining estrogen falls in step-fashion with the declining egg base. Therefore, ovulating the remaining eggs gets "iffier" as time goes by (since the system is run by estrogen) and fertility is truly at risk by the time we are in our mid-thirties; because we don't have enough estrogen to tell the brain to send the signal to ovulate, at least not on a regular basis.

So, as we're running out of eggs, the estrogen signal from our ovaries to our brain is weak. The weak estrogen signal is ultimately responsible for the loss of progesterone since progesterone seeps from the blister that housed the egg. -- No pop, no progesterone.

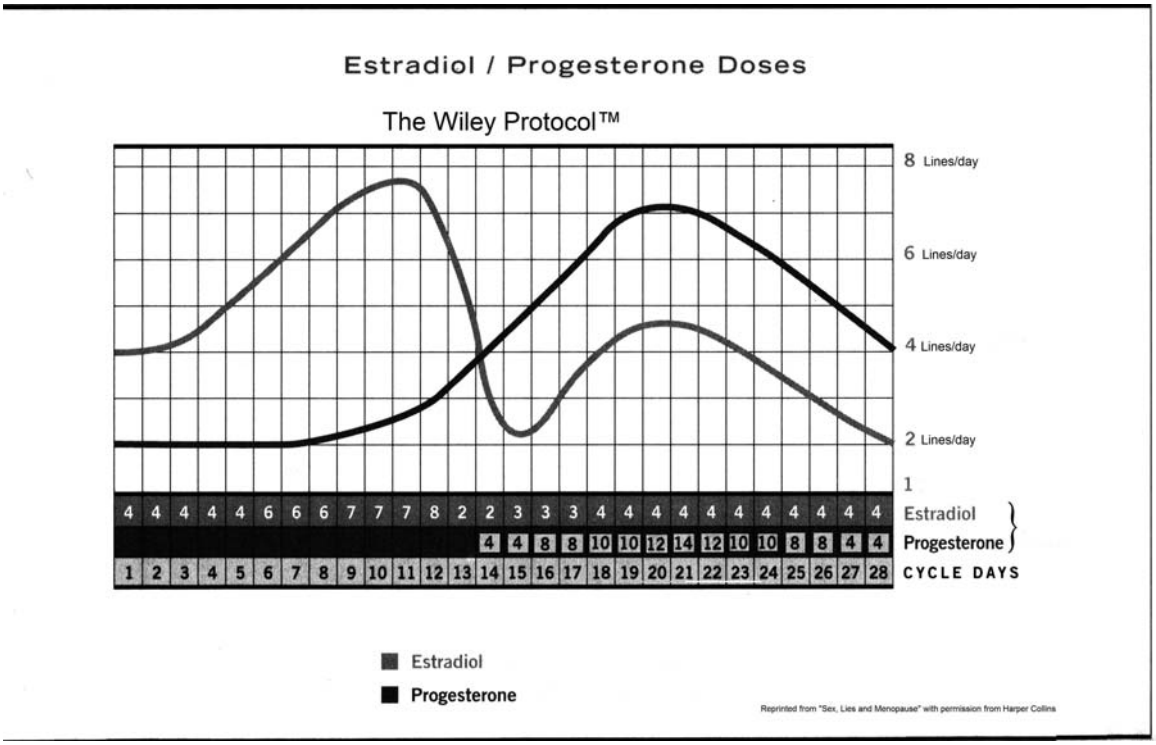
The first hint of estrogen depletion is shorter or longer menstrual periods as I mentioned on page one. The other earliest symptoms are sleeplessness, inability to concentrate or "mind noise," loss of libido and weight gain. And let us not forget the wrinkles. In peri-menopause (age thirty-three to fifty), internal estrogen levels certainly aren't high enough anymore to reliably ovulate, but they are *just high enough* ***for too long*** to be "normal." Normal levels of progesterone would bring it down. But we don't have normal levels anymore. It's like a game of dominoes.

It's Only Rock and Roll

The problem is one of "priming." The estrogen must create the internal environmental potential for the progesterone to wipe out the growth and start over again. One just doesn't work properly without the other. They are for lack of a better term, "in tandem" rhythmically as long as a woman is young, healthy and fertile. It is impossible to be one out of that list of three without the other two. That's why the menstrual cycle has two peaks that cease to be when one goes missing.

Everything alive has a rhythm.

The world as we know it, from bacteria to blue whales, the whole universe, in fact, is all about timing, within each of us and in relation to everything outside us. The individual rhythms overlap into larger patterns that then weave in and out of each other. Human beings swim in and out of this sea of rhythms. The moon provides more light with its full face and sure enough as the new moon ends, every twenty-eight days females bleed. The circadian clock in every cell of our body measures one spin of the planet, and the moon tracks the repeating 28 of those days 13 times in one revolution around the sun.



To see a graph representation of a menstrual cycle is to see what appear to be two mountains. There's a peak of estrogen and then a peak of progesterone. If one imagines that picture strung together over a year, one month connected to the next, there's a rhythm of unending ups and downs. It's a balancing act. Estrogen's solo in the first half of our cycle sets the stage for pregnancy all over our body. Estrogen *grows*, hence its reputation in cancer research. But estrogen, by way of creating *progesterone receptors*, has sealed its own fate. Progesterone generated by the popping of the egg, steps on stage to end that song of creation.

Cancer

The progesterone that we make naturally, in the second half of our cycle when we're young, protects us from cancer on the molecular level. Natural progesterone is a *genomic effecter for apoptosis.* (In English: natural progesterone latches on to switches on the genes called *promoter regions* for "cell suicide."). Cell suicide is the mechanism that causes the death of the one for the good of the many. *Natural* progesterone in a normal menstrual cycle controls the *destruction phase* which kicks in about half way through your cycle when no conception has occurred.

It's only when the fat lady *never* sings and the opera never ends**,** when we stop popping eggs and producing progesterone regularly as we head toward menopause -- that estrogen can continue to grow cells unchecked.

And this doesn't just happen in the uterus, either.

These rapidly multiplying estrogen-driven cells exist in our breasts and brain, too, and they have progesterone *receptors* on them. The receptors are waiting for progesterone to signal the final act. The chemical *listening* for that signal from progesterone will go on indefinitely as long as estrogen continues to pour, unless we artificially drop the curtain on the show by replacing from the outside the natural hormones we lack.

Does estrogen cause cancer? No or all young women would be dead.

Can estrogen cause cancer? Yes, but only in the absence of progesterone.

Cells, fed by estrogen and insulin that continue to grow in the absence of progesterone past a programmed growth phase, have all sorts of potential for genetic and immunological mistakes to be made.

We call those mistakes *cancer.*

In reality, the mutational changes that are the hallmark of metastatic cancer are not caused by mistakes during repeated cellular divisions or assaults by toxic pollutants, *rather those changes are caused by the fall-off of regulatory hormones that control the switches on your very DNA for the growth and death of your cells.*
(see abstracts Formby/Wiley)

Knowing that progesterone deprivation is the key to cancer at midlife for women makes the research showing that women who have given birth multiple times, and

thereby experienced long periods of placental progesterone, have much less cancer --it makes those findings make sense in a whole new way. When we examine the statistic that the incidence of breast cancer in our grandmother's day was 1 in 21, and in our mother's generation it was up to 1 in 18, it becomes painfully obvious that our standing at 1 in 8 (in one generation) is self-inflicted.

Our lack of childbearing has prevented the long periods of progesterone exposure necessary to buy time. Repeated pregnancies and bouts of lactation added up to a savings of at least 150 eggs a month or 1350 per birth, and if Grandma nursed for a year or so, another 2100. That means a savings of about 3500 eggs per child. Do the math. Grandma, in her day, would have given birth four to eight times; maybe Mom had three or four. That's 10,000 to 15,000 eggs for Mom and twice that for Grandma. That means Mom and Grandma extended their reproductive lives at least two extra years for every child made viable. Eight children would have extended Grandma's hormonal protection sixteen extra years. Not a bad deal, all in all.

That formula pretty much explains not only the above statistics, but why we experience *peri*-menopause for fifteen years and why they, on the other hand, went from child bearing to menopause at a later age and with fewer physiological repercussions. So the smug assumption that if our mothers and our grandmothers were just fine *without* hormone replacement then we will be too, may be far from a reasonable one. For all time, the only way to beat the reaper was to rack up points by winning at the game of life. For a woman--or any animal, for that matter--that meant to be fruitful and multiply.

Apparently, biology is destiny.

Evidence and logic amply support the theory that random and irregular ovulation due to declining egg stores creates a scenario that features an *over-abundance of estrogen hanging in the balance against a hit-or-miss supply of progesterone* for a good ten to fifteen years. .

What about the Women Who Survive Without HRT?

Grandma's shift to an expanding middle, a little thinner hair on top, and a few chin whiskers was part of her salvation. When estrogen declines and progesterone production stops, all that's left is the testosterone that once upon a time fed our libido. In

the grand scheme of things, old women – aren't women at all past a certain point. If this phase-shift happens quickly -- say after decades of childbearing and breastfeeding --some of us make it through it without getting cancer. But, if it takes too long, we're targeted for transformation, because cancer is an *evolutionary* function in nature. All of the genes active in cancer are active at only one other time in life. They are all switched on in the high estrogen/low progesterone state of the first nine weeks of life in utero when we are neither man nor woman. Since nature abhors a vacuum and is about duality, we must be one or the other -- man or woman.

We can't remain in limbo for more than nine weeks or nature will take over, trying out combinational strategies in an effort to make us become "something". Cancer is no plague on mankind, it is life, it's just the new you. It's a group of cells turned on to rapid unchecked growth by genes that are exactly the same in fetal tissue. That's why they call them *fetal* oncogenes in research.

That's also why cancer isn't something you can kill like a germ with an antibiotic. You can't burn it, poison it or take it away because it is *us* -- or at least what's become of us in the absence of performing a role in nature. Cancer is actually the genetic creativity shown in nature when an organism ceases to fit into The Plan.

Of course, a lot of us die from this evolutionary function, but many of us live with it, too. 93% of elderly men show some degree of prostate cancer on autopsy, but it's not listed as the cause of death. Most of us will likely die *with*, not *of*, some form of cancer.

Cancer is only transformation, unless it kills you first.

I believe there is an alternative. We can turn back the clock with the products nature has to offer. The catch is, how do we prove it? You see only the bio-identical molecules do this. The product from Wyeth does not. The hormone receptors can tell the difference. The bio-identicals need to be compounded from bulk materials and left in their unpatentable form. All that means is that the drug companies won't make as much money as they would by turning it into a drug. That also means there's no money for research because drug companies foot the bills for scientists and those drug companies will never be able to patent a "natural substance" and their already patented drugs don't work the same way on almost any system in a woman's body. Oh, and then there's the impending Kennedy, Burr, Roberts Bill that could literally put an end to it all.

Bio-identical progesterone replacement is a shoe-in as a cancer treatment because cancer was never about cellular *overgrowth*. It has always been about ***not*** enough death--*in the presence of overgrowth*. But cutting edge medicine has never equated menopause with cancer, even though cancer strikes at the time in a woman's life when her hormones are disappearing. The Standard of Care treatment plan is to further remove her estrogen. Taking estrogen away from women, or selectively blocking it without ever considering the synergy between the estrogen and progesterone, *the most selective potent apoptotic factor known in the human body*, is not the way to eradicate cancer.

It's the way to cause heart disease and Alzheimer's.

Are They Bioidentical Hormones Bio-identical or Not?

Even natural bio-identical hormones are not bio-*identical* unless your body can recognize them as hormones. Since natural hormone replacement is possible, the other half of the question is how to take bio-identical hormones? The scientific studies looking at the differences in Oral (by mouth) and Transdermal (using a neutral cream base as a carrier of the hormone) show significantly less side effects when hormones enter the bloodstream through the skin and fat base barrier just like Type Is take insulin. So through the skin is "how". What remains is "when". Replacement is not replacement unless you truly replace what has been lost.

The idea that hormone "replacement" could be affected by a one time a day, same dose every day regimen is illogical. The hallmark of an endocrine system is pulsitilty and amplitude, meaning that hormones pulse every few seconds and their amounts go higher and higher, depending on the time of the month in the case of estrogen and progesterone. So it seemed to me that the way to achieve HRT with least side-effects was to use a bio-identical molecule for both hormones, transdermally, in doses that could increase and decrease over time.

Natural hormones are not bio-identical unless they replace precisely the "natural" rhythmic levels of your own estrogen and progesterone when you were a young woman. Currently, the standard hormone replacement therapy you would receive from a doctor would be PremPro, or Premarin, if you've had a hysterectomy. And doctors who want to

prescribe natural hormones but who aren't familiar with the fact that hormones should mimic your natural hormone rhythms will merely prescribe natural hormones in the same way they prescribe synthetics. The Women's Health Initiative has already found the Standard of Care to be dangerous, what if it's not just the synthetic molecules that are dangerous?

Or, conversely, what if it's really the missing rhythm that matters?

The Wiley Protocol

I decided it was all three, the molecule, the delivery system and the timing. I devised a dosing schedule accomplished in 3cc capped syringes with 30 lines on the each. An average 1 month prescription has nine syringes of estrogen and nine syringes of progesterone. The hormones are dosed in “lines” on the syringes. The dose escalates every three days to address the issue of 72 hour “receptor roll-over”. In other words, we wait for the receptors for the hormones to catch-up to the dose before raising it each time. The Basic Wiley Protocol® dosing schedule is the same starting point for all women using this method of BHRT, but it can be individualized by raising or lowering the dose of either hormone by 2 lines in a 28 day period or making more amplitude by raising the dose of the appropriate hormone two more lines on the peak days of Day 12 and Day 21.

The formulation and manner of dosing bio-identical HRT started out as a "thought experiment" in my book, Sex, Lies and Menopause. In the book, I asked the question - "if hormone replacement was made of real bio-identical hormones and dosed to mimic the ups and downs of the hormone blood levels in a normal menstrual cycle in a 20 year-old woman, would all of the symptoms and disease states of aging decline or even, disappear?"

Well, so far we have watched over a thousand women here in Santa Barbara and it looks like the logic holds - because it was the rhythm that was always missing in other regimens. I asked the doctors to prescribe no more than 3 months at a time and require blood tests of estrogen and progesterone at month 3 on the peak days of the cycle to see if we had attained the levels in serum blood work for a woman twenty years-old, or if we

had reached optimum theoretical therapeutic levels. Women intact, or without hysterectomy, have normal menstrual periods, no matter what their symptoms of irregular or absent cycles were previously. We have made every effort among the many doctors and women involved to report adverse events to Dr. Julie Taguchi, in Santa Barbara. The Wiley Protocol is the only HRT or BHRT Protocol developed under the scrutiny of an Oncologist. No other HRT or BHRT can make that claim. Dr. Taguchi has recently reported on 58 cancer patients in her practice, post diagnosis, without active cancers receiving the Wiley Protocol for a median of 2.5 years, 28 of whom had breast cancer. The expected recurrence rate is 1 in 10. We saw only 2.5 recurrences in 58 people and remarkable attenuation of osteoporosis, fibroids and, of course, the garden-variety disabilities of menopause in general. (see slides J. Taguchi, MD)

Any doctor or healthcare practitioner who offers "hormone" replacement that does not result in a 4 to 5 day period of bleeding at the end of 26-30 day cycle in a woman with a uterus has not offered ***hormone*** replacement. Replacing only *some* of our endocrine function does nothing but create *different* disease or, in the case of estrogen without progesterone, sometimes even cancer.

Doctors

Right now, in the wake of the National Institutes of Health (NIH) Women's Health Initiative (WHI), getting hormones, at all, is difficult. Doctors are leery of even the "Standard of Care" approved synthetics in this time and place. Getting legitimate insurance-covered physicians to prescribe even bio-identical hormone molecules of any sort, let alone the Wiley Protocol has, for the last twenty-years or so, been, at best, a roll of the dice.

The majority of Western medicine has been on a wild goose chase for the elusive proof that being completely hormone-less will save our lives, in the face of massive evidence that even with all of our estrogen blocked at every turn, we still keep dying of cancer. In the burst of the Baby Boomers becoming menopausal, doctors from all specialties—ER docs, Internists, Family Practice and GPs along with the usual Ob/Gyns, Naturopaths, Chiropractors, Nurse Practitioners and the occasional Neurologist have clamored to the forefront to be of service. (guesstimates of the incredible revenue stream

are mind-boggling) The problem is, they have no idea how to prescribe hormones for women. Most of them didn't even do a rotation in endocrinology in med school.

They flock to large seminars held on bioidentical prescribing by the larger compounding pharmacies and associations like the American College for the Advancement of Medicine (ACAM) or American Academy of Anti-Aging Medicine (A4M), who can afford the more expensive "talent" (other self-proclaimed physician experts) to draw a crowd. Right now physicians are in serious need of re-education that bears some resemblance to endocrinology. The way women are treated skirts dangerously close to fad. The flavor de jour in BHRT really does change every day.

Doctors who prescribe the Wiley Protocol are in the vanguard of an elite group of forward-thinking physicians and researchers trying to put the scientific method back into medicine. All HRT and bio-identical hormones, particularly, still reside in a no-man's land of uncertainty when it comes to prescribing because of the lack of long-term study and testing. By asking the physicians to use one of the many pharmacies that I've trained with other licensed pharmacists (Dana Nelson, Paul Lofholm R.Ph D.) Registered to dispense the Wiley Protocol® prescriptions, we have eliminated all the guess-work and potential errors in prescribing natural hormones.

Big Pharma is willing to educate the physician, minimally, about synthetic hormones and, of course, all drugs, but, here and now, the only commercial enterprise handing out natural hormone information to any professional group is PCCA (Professional Compounding Centers of America). PCCA aims to educate Compounders on the "hows" and "whys" of preparing bio-identical hormone preparations and, unfortunately, a lot more information that is of questionable value to women. We have a better plan, a plan that keeps the pharmacist from encroaching on the physician's territory.

With the opportunity for our Registered, trained in methods and material, pharmacies to have a Wiley Protocol® Clinical Practice Guidelines Manual, as well as their Wiley Protocol® Methods and Materials Guide, the Doctor and the Pharmacist can be sure that the patients treatment guidelines are consistent, reducing the possible variables for further diagnosis which will make safety and efficacy possible. The doctor

and the patient can be can reassured that the hormones that prescribed are the same compound made with the same raw materials every time.

Compounded Bioidentical Hormones.

As many as two million women in the U.S. use customized hormones for menopause symptoms. Compounding pharmacy can provide a service that industry cannot and will not meet. This service is customizing individualized medications. Put simply, the medications provided by the drug industry do not always come in the dosage forms, strengths, or drugs needed by specific patients. Compounding pharmacies are the only resource that has been able to make and dispense these medications.

The first college of pharmacy in the U.S. was established in 1821 and they had laboratories that taught compounding. The processes of compounding continued to be taught in schools of pharmacy well up until the 1980's. This means each pharmacist was taught standardized methods for compounding. These pharmacy schools were regulated by accrediting bodies. In the 1980's, pharmacy training turned away from its historical roots in compounding and concentrated instead on clinical pharmacy. What this means is that a trained pharmacist became a medicine "cop", whose purpose was to ensure that there were no drug interactions or misuse of medications. Today, there is a much different landscape.

Why did this happen?

Drug companies started to designate dosage forms and drug doses. While they may have been based on scientifically justified conclusions, they certainly left no room for individual variation. The thinking by drug companies was that they would be able to come up with every drug needed by each person at an effective dosage level. With few exceptions, physicians and pharmacists went right along with the drug industry's mandate. However, if we look at reality, compounding never really went away. It continued to exist and be in demand.

Dermatologists realized early on that in order to treat their patients effectively, they would need to combine medications in dosage forms not available from drug companies. Even more prominent, hospital pharmacies continued to compound IV additives and parenteral feedings and specialized medications because there was nothing

available from drug companies that could respond to the individualized need of hospital patients. As pharmacy schools backed off from educating pharmacists in compounding, the art and science of compounding was nearly lost.

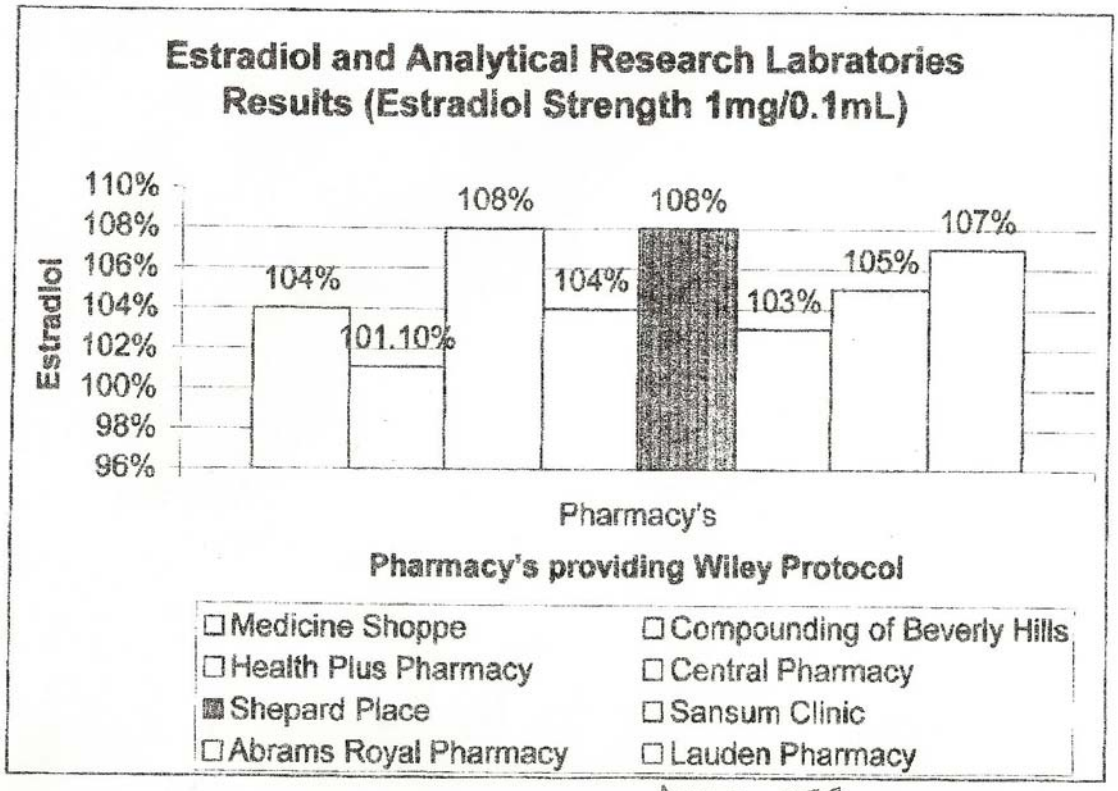
But not surprisingly, the need for specialized drugs with individualized dosing did not go away. Now there is a resurgence of demand for compounding pharmacy, driven by the needs of patients not met by the medications available from the drug industry, patients who cannot be treated with standard dosage forms.

Examples of this include Hospice patients who cannot swallow their medications and need compounded medications in the form of Transdermal creams; patients that are allergic to preservatives and need preservative free medications; patients that are lactose-intolerant and need lactose free medications; neonates and pediatric patients that require drug dosages not available without compounding; and patients that need medications the drug industry has deemed no longer profitable and discontinued.

Standards and Over Site on the Wiley Protocol

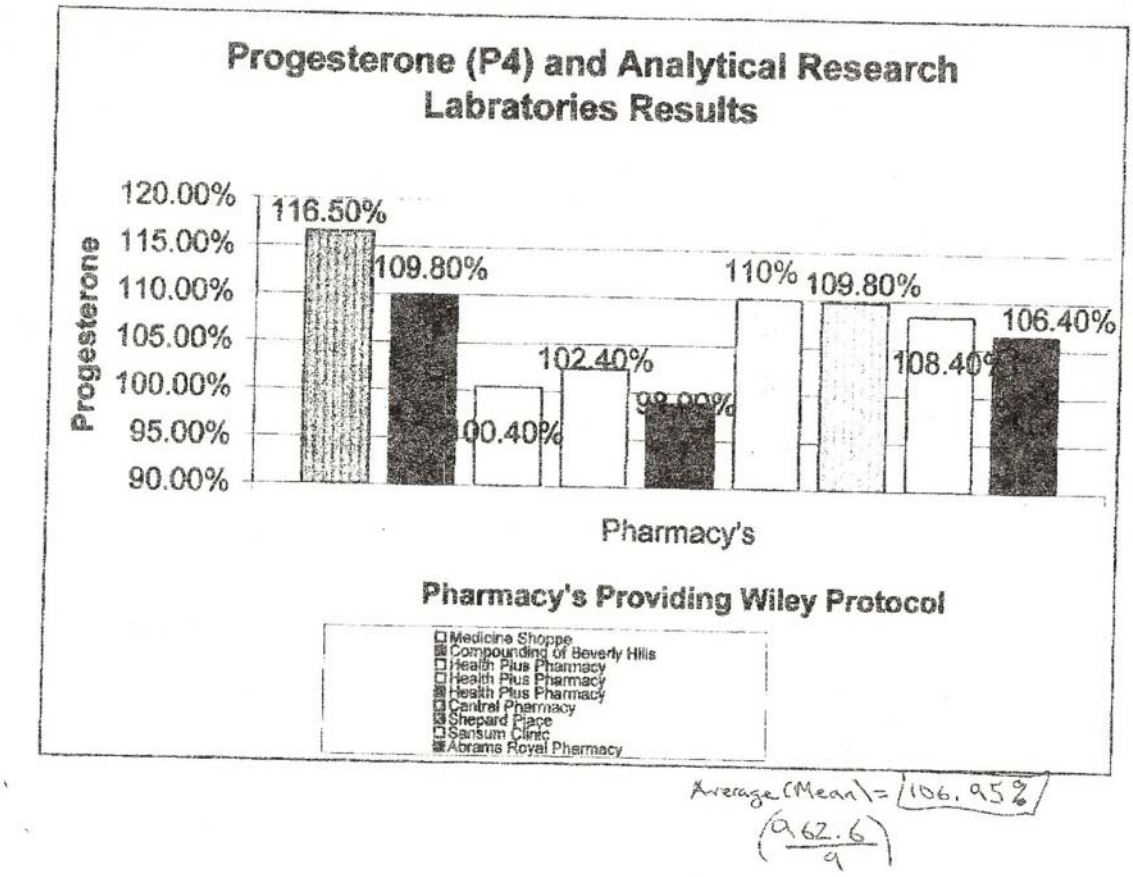
For the Wiley Protocol the patient doses in a fashion which replicates the reproductive hormonal cycle in serum blood levels. The preparations are not commercially available and are applied to the skin, so, must be compounded by a compounding pharmacist. We have had very significant success in women who can not take other bio-identical or synthetic pharmaceutical medications by mouth, Transdermal route or injection. We will soon publish our accomplished standardization of a Compounded bio-identical hormone results. Contact plofholm@aol.com

Below is just an example of the potency analysis we require of the Registered Pharmacies:



Average (Mean) 105%

Median 104.5%



Who's Watching Women Using the Wiley Protocol?

We are also waiting for our "study number" from the University of Texas at Tyler's Nursing School's IRB Committee. Contact janithwilliams1@msn.com The proposed study is a longitudinal, observational study measuring many of the parameters of the WHI in women currently using the Wiley Protocol.

Though many physicians have been prescribing them for decades, there is a paucity of data in our literature due to the fact that there has not been any pharmaceutical support for plant-based products (considered food and therefore not patentable). They can be compounded by a pharmacist. Another point here is that the same compounded hormone prescription can vary widely from pharmacy to pharmacy, making them virtually "un-studiable."

Thus no standardization exists in this area of hormones for research heretofore.

A controlled systematic pilot clinical study of the most promising few plant based hormone therapy alternatives would quickly yield to a well-organized national multi-centered clinical trial of a large heterogeneous cohort. A short duration observational study with biologically correct endpoints associated with menopause and with periodic measurements of clinically significant biochemical markers should be the next step to jumpstart the WHI-2.

All Wiley “Registered” Pharmacies use ingredients that are all purchased from the same supplier. At the Registered Pharmacies, The Wiley Protocol® is made in small batches (lot# identified) in uniform standardized steps outlined in the Wiley Protocol® Methods and Materials Training Manual and packaged in our unique color-coded identifying system of purple and green for progesterone and estrogen, respectively.

I have recruited these Registered Pharmacies, not only to insure quality control on a very variable treatment - BHRT, but to make sure that in the future a real and legitimate study could be affected on the Wiley Protocol® by requesting 10 pro bono prescriptions per pharmacy for a national study. Also, BHRT has never been studied in any Standard of Care controlled environment because the “study substance” in any legitimate trial has been mandated by the NIH to be donated to the participants. Of course, no small compounder can bear the economic burden of donating 4000 compounded prescriptions, however; the eventual 400 or so Wiley Registered Pharmacies can and will, together. The donations will have been standardized to Good Compounding Practices, so the results of such a study can be taken seriously at any level of scrutiny.

Who’s Watching Wiley?

In the spirit of financial disclosure and complete transparency, I trade the Pharmacies the use of my name and list them on the website thewileyprotocol.com in exchange for their commitment to make the bioidentical hormones used in the Wiley Protocol in the standardized method I require and agree to donate a percentage of their volume to a future national study of the Wiley Protocol. They must buy the packaging (purple and green stamped with a 28WP logo) from my company Wiley Systems. The proceeds from the sales of packaging have built the website and paid for the development of the University of Texas study, so far. I take no personal income from Wiley Systems.

It is self-maintaining financially and it's profits are only used to promote the Wiley Protocol to doctors and academic institutions and to develop educational materials like the website.

Our Process for Standardization

In an effort to standardize the compounded preparations of Estrogen and Progesterone we have asked the pharmacists to do several things in order to minimize the potential for variation:

- Drug specifications: we use the bulk drugs estradiol and USP progesterone which are recognized and standardized by the United States Pharmacopoeia. We compare the USP Standards with the Certificate of Analysis which accompanies each bulk drug shipment. We want to assure ourselves of that the Purity and Identification Standards are met.

- Formulation Specifications: We use a detailed formulation so that the prescription conforms from batch to batch. The formulation is spelled out like a recipe (formulary) and the quantities are recorded with the lot numbers, expiration dates, if any, and manufacturer's or supplier's name.

- Method of preparation is detailed and for our preparations we use specific equipment for weighing, measuring, and mixing. i.e. an ointment mill

- In order to assist the patients in measuring the correct dose, we use a special syringe. The objective in using this measuring device is to apply to the skin a specific amount of cream containing a particular content of hormone. The calibrations on the syringe allow for the physician's prescription of the Wiley Protocol to be "individualized" in the spirit of a compounded product to the variation in endocrine physiology from woman to woman. So with the Wiley Protocol we have provided "standardization in customization", something no one has ever done before, except in the case of commercial pharmaceutical products like the Vivelle® and Climera® patches which are offered in a range

of set doses. The Wiley Protocol's delivery system allows for far more individualized, unique, "finger-printing" of a woman's own original menstrual cycle.

- We supply typically a one month supply of medications with a beyond-use date based on literature review, scientific studies, or USP monograph specifications.

- We sample our medications and send them out for independent analysis to validate our work. (see attached evidence)

- We also test our Compounders for the presence or absence of the "drugs" they are compounding for us in their blood stream to assess potential exposure to the hormones that they are working with.

- On the clinical side, we encourage Wiley Protocol prescribing physicians to order blood work for their patients on Days 12 and 21 of the 28 day cycle to assess hormone absorption, compliance and ultimately correlate the findings to the clinical picture so that the patient is best served when adjustments are necessary.

- We support PCCA's invented "physician-pharmacist-patient triad" only in the sense that we stipulate the necessity for Collaborative Agreements between Prescribing Physicians and Wiley Registered Pharmacies allowing the Pharmacist to advise WP patients from the WP Clinical Practice Guidelines Manual only when authorized by a WP prescribing physician, assuring that all patients get the same answers and information to any and all unique questions, creating, again, a standardized mode of follow-up that keeps the physician in the loop and on the same page.

- We support the pharmacy's exemption from the rules which govern manufacturers, while we expect the FDA to enforce standards and principles relating to labeling, purity, content, etc. We believe that the regulation of the healing professions is the purview of the States and should remain there as long as rigid guidelines for methods and materials are maintained by regular State Inspection.

- We support extended education and training for all pharmacists who compound and provide specific training in the above requirement methods for compounding the Wiley Protocol.

The Future of Compounding

While we have a rigorous protocol for the preparations that comprise the Wiley Protocol that our pharmacists compound and we are confident that our preparations contain what they say they contain due to rigorous and frequent testing (evidence attached), should the detractors accuse the profession of custom Compounding to fall short of quality benchmarks in general or in specific cases, more over site of the profession by the States, is long overdue and not an unbearable burden, fiscally. The conundrum is how to regulate compounding pharmacists and pharmacies.

The logical answer is to look back at history. Pharmacy schools need to once again assume the responsibility of training compounding pharmacists. Academic accrediting bodies need to be in charge of credentialing compounding pharmacists. State Boards of Pharmacy need to be in charge of inspecting and monitoring compounding pharmacies. In most states, the State Board of Pharmacy is responsible for licensing sterile compounding; there is no reason why they should not assume to responsibility of licensing non-sterile compounding as well.

If the Federal Government stopped the practice of compounding, all it would achieve is leaving millions of patients without resources to alleviate various conditions. We certainly need the federal government to support Schools of Pharmacy, State Boards of Pharmacy and accrediting agencies, to ensure that compounding pharmacies are meeting the required highest of standards.

I'd advocate for either Accreditation by the Pharmacy Compounding Accreditation Board [PCAB] or equivalent or provide more moneys to the States so that they can hire and train many, many more Compounding Inspectors. A hefty increase in the Licensure Fees for Compounding as was affected for Sterile Compounding would also create a healthy revenue stream to State coffers for recruitment and training of a legion of stringent regular inspectors. As far as models of National, not Federal, regulatory bodies are available for template: the National Association of Insurance Commissioners (NAIC) acts as a forum for the creation of laws and regulations for the insurance industry, with each state's Insurance Commissioners reporting to them.

This model also assumes the registering body would be responsible for the ethics of the profession, but in the UK there has been a move to separate the two roles. Other nations use representation and regulation at the national level such as, the Royal Pharmaceutical Society of Great Britain (RPSGB), the Pharmacy Guild of Australia and we do have our own American Pharmacists Association (APhA) which is a weakly structured organization. A pilot project among interested States could be a good way to start restructuring and remodeling the regulation of compounding pharmacy to Good Compounding Practices (GCP) at a national level.

On the other hand, we have an Accreditation Body who could provide the basis for inspecting to Good Compounding Practices (GCP) as I have mentioned above. For those women relying on the Wiley Protocol for hormone replacement therapy, a compounding pharmacist is essential. I would ask for your support in the potential re-regulation of compounding pharmacy at the States level to achieve Good Compounding Practice (GCP).

While the amount of prescriptions which are compounded is relatively small, compared to the economic Goliath of the big pharmaceutical companies, for those people who need the service, there is no manufacturer who *can or would do it*. The pharmacist plays a vital role in meeting those specific patient needs, if the patient is to be offered a pharmacologic solution.

Furthermore, as I said, compounding is essential in the hospital environment where intravenous prescriptions are compounded daily. In the Los Angeles Times, April 9, 2007, Times Staff Writer, Melissa Healy eloquently investigated three new promising

treatments for stroke, neurogenerative disease and brain trauma. She looked at natural progesterone, creatine and magnesium. In her piece entitled, *"Search for the Brain's First Defense*", she said "When under attack — from ischemic stroke, head trauma or many degenerative diseases — a small cluster of affected brain cells basically commit suicide and, in so doing, release toxins that kill off their neighbors in droves. Neurons tumble like dominoes to their death in a process that can take hours (in a stroke or a head trauma) or years (in Alzheimer's or Parkinson's disease)".

But what if there were a simple way to fortify human neurons against the brain's many disparate enemies? What if some safe, readily available compound, taken before or just after a stroke or injury or even long before a neurodegenerative disease takes hold — could protect the brain against many kinds of insults and injuries in both men and women?

Progestrone's Not Just for Women Anymore

This summer, the National Institute of Neurological Diseases and Stroke is expected to approve and fund a national clinical trial designed to see if high doses of compounded progesterone, a hormone that is present in all human brains — can help disrupt the rapid death of brain cells that frequently follows a trauma to the head. The quest for neuroprotection is driven not only by a deepening understanding of how injury and disease damage the human brain but, by a growing sense of urgency.

In the wars in Afghanistan and Iraq, traumatic brain injury has become widespread, a problem for which the military's medical establishment is poorly prepared. Almost 1,900 U.S. soldiers have been treated for traumatic brain injury, and some Pentagon estimates have suggested that as many as 28% of the 1.4 million troops that have served in Iraq and Afghanistan may have sustained at least mild brain injury from the concussive effects of bomb blast.

As the United States enters its fifth year of war and the U.S. military ponders a world in which its troops will remain vulnerable to improvised explosive devices, the Pentagon has become deeply interested in the science of neuroprotection. In July 2006, the armed services' medical leaders huddled at a military installation outside Washington,

D.C., and established a goal to "develop better neuroprotectants for acute head injuries ranging from severe penetrating injuries to mild traumatic brain injury." Last month, the Pentagon announced it is spending $14 million to conduct more research on blast injuries and to help medics in the field better diagnose mild brain injury. This will include a look into compounded natural USP progesterone. Of course, the big pharmaceutical company trying to steal back its lost market to bio-identicals would have you believe the money they are losing in the interstate commerce of compounded products is the big issue here, but it’s not.

Seventy-eight million baby boomers (that’s voters, to you) are reaching the peak years for stroke and degenerative brain diseases. Already, in the United States each year, 700,000 Americans suffer a stroke, and as many as 500,000 are diagnosed with a neurodegenerative disease (1.4 million suffer a traumatic brain injury). Such numbers have helped propel the search for an agent that could limit or hold off disability across a range of illnesses.

All of the substances under investigation, like progesterone, have, in some form, long been in safe use in the medical arsenal. And all have shown promise in protecting the brain against other types of injury and disease. Progesterone, for instance, seems to fortify the brain cells against degeneration caused by multiple sclerosis and has shown early promise as a protectant in stroke. "The graveyard of neuroprotectants is absolutely full. It's depressing," says Dr. David Wright, a professor of medicine at Emory University Medical School in Atlanta who has been a leader in testing progesterone for head injury.

But his hopes have been buoyed by early studies suggesting that quickly elevating levels of progesterone, a steroid present in the brains of both men and women, may help save many with traumatic head injury and improve their outcomes. In a three-year trial involving 100 such patients brought to Emory's Grady Memorial Hospital, 80 received a high dose of progesterone over 72 hours and 20 did not, receiving standard care only.

The study suggested that those receiving a rapid infusion of progesterone were 50% less likely to die. And among those who got the progesterone, there was less disability at the one-month mark than would normally be expected, considering the

severity of their head injury. "We think it's just shifting the whole curve," making all but the most severely injured patients better off, Wright says. "It way outdid what we were expecting."

This Could Be Your Son, Brother, Father or Grandson

Marcus Baskett of Commerce, Ga., was one of those patients. A passenger in a head-on automobile collision just three weeks shy of his high school graduation, Baskett was evacuated by helicopter to Emory and received the progesterone infusion upon his arrival. In addition to broken bones, early tests of his brain function suggested massive and disabling head injury, and he spent almost three weeks in a coma.

But seven weeks after his April 2004 injury, Baskett was released from the hospital with lingering physical injuries but little evidence of the severe trauma to his brain. Three years later, a 21-year-old Baskett keeps up a rapid-fire conversation and lives close to his parents' home but independently, keeping track of appointments and birthdays on a cell phone scheduler.

"I wouldn't have believed that a woman's compounded hormone would help my body and brain in a situation like that," Baskett says. "I'm back almost 100%, and I don't think I'd be here if it weren't for progesterone."

Senators Kennedy (D-MA) Burr (R-NC) and Roberts (R-KS), among others are as I write this, considering legislation (Safe Compounding Drug Act of 2007) that would severely restrict and possibly deny access to critical medications. This draft bill is supported not only by Wyeth in an attempt to retrieve their lost revenue stream from Compounders dispensing Bio-identical hormones which out perform Wyeth’s PremPro, but by Astra Zeneca, through their funding of Mothers of Asthmatics. Astra Zeneca, by working through this ostensibly public and non-commercial Mothers of Asthmatics has falsely portrayed the *Safe* Compounding Act as a patient-driven. There has been no harm to asthmatics, only to Astra Zeneca’s bottom line, because Astra Zeneca believes that Compounders have “knocked-off” one of their inhalant products.

If this legislation passes, federal regulators, not the doctor, will decide what medicines can be taken. I believe that it is fundamentally the right of the consumer to choose and the practitioner to practice.

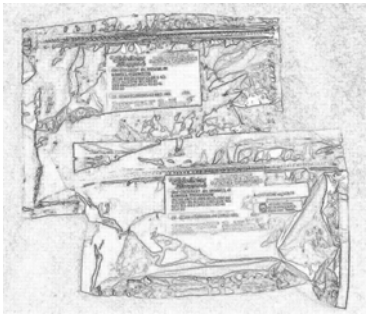
Among other things, the so-called Safe Drug Compounding Act would give the Food and Drug Administration the power to:

- *Broadly eliminate the availability of many critical, commonly compounded medications that many patients rely on* **(most especially bio-identical hormones for women).**
- *Determine when compounded medicines are needed - a decision that has always been and should always be made by doctors.*
- *Restrict the compounded medications the doctor can prescribe even if he or she determines the need for them.*

Among those left with little or no choice will be menopausal women and andropausal men; the Autistic community; individuals living with HIV/AIDS; infants and young children with conditions like gastroesophageal reflux disease (GERD); hospice and nursing home patients; and people who are extremely allergic or sensitive to fillers, dyes, and additives in medicines. And now we can add researchers with imagination like Dr. Wright in Georgia and head trauma victims like the young man, whose life and mind was saved by a Compounded bio-identical hormone. Please don't let this happen.

This is a sample of the patient inserts in every package of the HRT devised by T.S. Wiley:

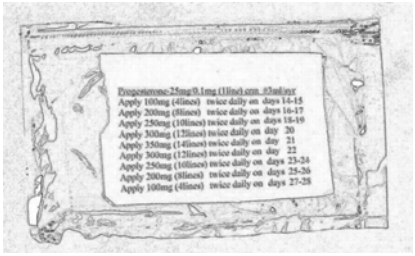
Use Directions for the Wiley Protocol ™



You have received two silver packages.

One has 10 syringes of Estradiol which have Evergreen colored caps and foil labeling. The Estradiol is in a cream base at the concentration of 1mg of Estradiol for each 0.1ml of cream. The syringes hold a total of 3mls's, or 30 "lines" each of 0.1ml.

The other silver package has 9 syringes of Progesterone which have Purple caps and purple foil labeling. The Progesterone is in a cream base and the concentration is 25mg of Progesterone for each 0.1ml of cream. The syringes hold a total of 3ml's, or 30 "lines" each of 0.1ml
This is for the standard Wiley Protocol ™



On the back of each bag you will see **the dosing schedule** for each hormone separately day by day. For the first two weeks of your new cycle and forever after, you will take estrogen only during the first two weeks and progesterone ***and*** estrogen **together** during the second two weeks. The goal of the Wiley Protocol is to re-establish normal rhythmic cycles for estrogen and progesterone in your body by increasing and decreasing (multi-phasic) doses in the undulating rhythm actually documented in young women.

"BID" means twice a day (once in the morning and again in the evening)

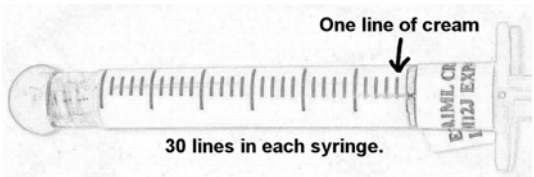
The basic Wiley Protocol dose schedule is also shown in the Appendix I on page 219 of the book "Sex, Lies, and Menopause", by T.S. Wiley.

How to Start the Wiley Protocol ™

If you are still having regular periods then DAY ONE is the first day of your period. Take the dose for DAY ONE.

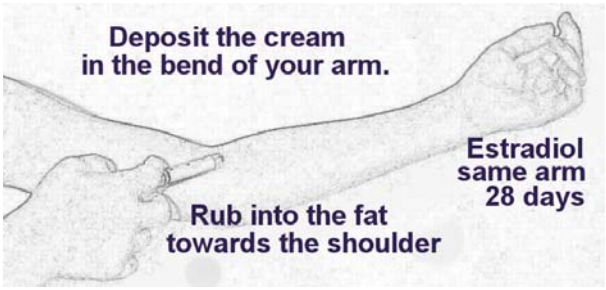
If you have stopped having periods, then DAY ONE for you is shown on the moon or Lunar Calendar which you can find online at the rhythmicliving.com website or maybe included in your hormones packets. The doses are also shown at the bottom of each day of this Lunar Calendar. Most months are not 28 days, so if you are on a Lunar Cycle, you will stop your progesterone on day 28, but continue your Estrogen through the "blank days" until you hit DAY ONE on the next Lunar Cycle.

Place the plunger on the palm of your hand and place your



first and second finger on the barrel.

Push plunger carefully. It can be sticky. It takes a few times to develop the skill to measure 1 line at a time.
Measure out 4 lines for your first application of estradiol. Make a dot of cream on your hand or arm for each line of hormone that you measure out to practice controlling the plunger in the syringe.



Deposit the cream in the bend of your arm and use your hand to work the cream into the bend and the fat at the back of your arm towards your shoulder and any fatty arm skin that is not sun damaged.
The larger the application area the better your absorption will be. Rub it in well until it all disappears.
Don't mix or layer over with other creams of any other kind.

You will do this with your estrogen on the ***same*** arm through out your 28 day cycle. Read the bag or book to see how many lines to apply for each application.

On day 14 begin to apply your progesterone to the opposite arm in the same way.

At the start of the next cycle you will switch arms. So you will use the opposite arm for estrogen and the opposite arm for progesterone, switching arms once a month thereafter.

Important Information about the Application of Your Hormone Cream

Do not bathe for 40 minutes to 1 hour after applying the hormones.

Do not exercise for two hours because, although you can't wash off the hormones after an hour, you may sweat them back out of your fat base.

You can also apply the hormones to the back of your knees and inner thighs, but stay consistent. You want to build up a deposit of hormones in the fat base. Either use your arms or your legs.

Expectations during the First Three Months

Changes are going to happen in your body while your hormones and receptors are adapting back to a normal rhythm. You might not or might not feel the minute changes of adaptation. There is an adjustment period as your system "wakes-up". Some side effects of this "wake-up call" that you might experience the first month and even later are: a slight headache during the second progesterone phase, nausea as your blood sugar normalizes, an odd taste in your mouth, dizziness, weight changes (water), hypoglycemia, and breast tenderness.

Your thyroid may have to adjust to having your hormones back so you might feel palpitations or vibrations in the morning or at night when you lie down to go to sleep. Should this occur, spread out the entire day's dose (lines for morning and night added together) throughout the day, for example, 2 lines an hour for five hours. Continue this method for at least three days before returning to BID scheduling. If this thyroid response still continues, you should call your doctor to discuss it and go to the user group to learn about other's experiences with this effect.

*These are normal transient effects that are a result of your body making adjustments as your hormones take effect and your receptors return***.**

If you have a history of heart problems please discuss this with your doctor.

During the first month you may not receive all the estrogen you are applying and probably may not receive much of the progesterone. By month two, the estrogen from the first month's dose will have made enough estrogen receptors in a closed loop to provoke progesterone receptors. By your second cycle the progesterone effect will be more pronounced because it will have progesterone receptors to read to.

By month three a full compliment of receptors should be up and running and then it is time to start adjusting the dose for your individual needs. **Blood testing is in order at this juncture to give your doctor the information to correlate your remaining symptoms with the amounts of hormone you are receiving.** Women who are already cycling when they start the Protocol might need to adjust earlier.

Until your hormones are in synchrony, sleeping patterns may still continue to be broken. To deal with this interval waking, (at 2am and 4am or 1am and 3am) some women use Tylenol PM or sublingual melatonin one hour before bed, but never more than two hours after sunset. This regimen may also be used to "get off" of other common sleep aids. Never use more than 3mg of melatonin in the winter and never more than 1 mg in the summer. Melatonin is a powerful over-the-counter hormone available in the United States.

There is an expanded Frequently Asked Questions on the web site as well as a link to the user group. Questions that are gathered there are submitted to T.S. Wiley. The user group and web page is an educational forum and you are advised to discuss all decisions about your health and dosage changes with your doctor.

Should you have an emergency situation contact your doctor.

About medications, supplements and herbs.

All medications, prescription or otherwise, available to the public work across hormone receptors to be effective, therefore, all medications, supplements, and herbs can have an effect on hormone receptors.

ALL herbs work across hormone receptors. For example, evening primrose oil, Vitex agnus castus Chastetree or berry, Black Cohosh, Estrovan, lignans, red clover and flax have hormonal effects and could interfere with your Wiley Protocol ™. Check the constituents of all "combination" products from healthfood stores and naturopathic and chiropractic practitioners.

Medications that are Contraindicated on the Wiley Protocol™

Arimidex
Anastrazole
Letrezole
Aromasin
Exemestane
Fosamax
Raloxifen
Tamoxifen

Discuss these drugs with your doctor before stopping them.
Down the line you may find you need less of certain conventional medications like anti-depressants, especially SSRIs and Lipitor. *Discuss this with your doctor.*

These products that have been seen to be no problem with the Wiley Protocol™

Magnesium
B-vitamins
Omega 3's and 6's
Lithium
Anti-psychotic drugs
Anti-epilepsy
Common sleep meds like Ambien, Tylenol PM, Melatonin, Resterol, Zantax, Zantac

Bleeding Out of Rhythm

Consult your doctor and the website for information about:
Bleeding before day 21 can be either a sign of too much or too little estrogen. On the basic Protocol™, too much is unlikely. Bleeding on or after day 21: try using 2-4 lines more of progesterone BID for one day only. If the bleeding continues, stop all progesterone and let your period happen. Call the next day DAY ONE. This earlier than normal bleeding indicates the need for 2 more lines of estradiol BID for your entire cycle beginning on this new DAY ONE, so you will make more progesterone receptors and your progesterone can hold the lining past DAY 21.

To see more answers to many frequently asked questions go to the website thewileyprotocol.com
Discuss the educational material with your doctor before you make decisions about your health.

Consultation with your pharmacist

Your pharmacist is only allowed to answer questions *about your order*, to tell you where and how to apply the cream, the production and contents of the cream and hormones, your insurance, compounding information, and business matters pertaining to your order.

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By month 3 and every six months after that you are urged to get your blood tested.

Blood testing is done on day 12 and day 21.
There are cream application issues with regard to blood testing so here are two options for getting blood work done in regard to applying your cream. Stick with one. Morning or afternoon, either before you apply or 3 hr after.

These are abstracts of journal science published in molecular biology on the mechanisms of fetal oncogenes and compounded hormones by T.S. Wiley.

1: Ann Clin Lab Sci. 1998 Nov-Dec;28(6):360-9. Links

Progesterone inhibits growth and induces apoptosis in breast cancer cells: inverse effects on Bcl-2 and p53.

- **Formby B**,
- **Wiley TS**.

Sansum Medical Research Institute, Santa Barbara, CA 93105, USA.

Progesterone inhibits the proliferation of normal breast epithelial cells in vivo, as well as breast cancer cells in vitro. But the biologic mechanism of this inhibition remains to be determined. We explored the possibility that an antiproliferative activity of progesterone in breast cancer cell lines is due to its ability to induce apoptosis. Since p53 and bcl-2 genetically control the apoptotic process, we investigated whether or not these genes could be involved in the progesterone-induced apoptosis. We found a maximal 90 percent inhibition of cell proliferation with T47-D breast cancer cells after exposure to 10 microM progesterone for 72 hours. Control progesterone receptor negative MDA-231 cancer cells were unresponsive to these two concentrations of progesterone. After 24 hours of exposure to 10 microM progesterone, cytofluorometric analysis of T47-D breast cancer cells demonstrated 43 percent had undergone apoptosis without signs of necrosis. After 72 hours of exposure to 10 microM progesterone, 48 percent of the cells had undergone apoptosis and 40 percent demonstrated "leaky" membranes. Untreated cancer cells did not undergo apoptosis. Evidence proving apoptosis was also demonstrated by fragmentation of nuclear DNA into multiples of oligonucleosomal fragments. After 24 hours of exposure to either 1 microM or 10 microM progesterone, the expression by T47-D cancer cells of bcl-2 was down-regulated, and that of p53 was up-regulated as detected by semiquantitative RT-PCR analysis. These results demonstrate that progesterone at a concentration similar to that seen during the third trimester of pregnancy exhibited a strong antiproliferative effect on at least two breast cancer cell lines. Apoptosis was induced in the progesterone receptor expressing T47-D breast cancer cells.

PMID: 9846203 [PubMed - indexed for MEDLINE]

: Mol Cell Biochem. 1999 Dec;202(1-2):53-61. SpringerLink FULL-TEXT ARTICLE Links

Bcl-2, survivin and variant CD44 v7-v10 are downregulated and p53 is upregulated in breast cancer cells by progesterone: inhibition of cell growth and induction of apoptosis.

- **Formby B**,
- **Wiley TS**.

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Progesterone inhibits the proliferation of normal breast epithelial cells in vivo, as well as breast cancer cells in vitro. But the biologic mechanism of this inhibition remains to be determined. We explored the possibility that an antiproliferative activity of progesterone in breast cancer cell lines is due to its ability to induce apoptosis. Since p53, bcl-2 and survivin genetically control the apoptotic process, we investigated whether or not these genes could be involved in the progesterone-induced apoptosis. We found a maximal 90% inhibition of cell proliferation with T47-D breast cancer cells after exposure to 10 microM progesterone for 72 h. Control progesterone receptor negative MDA-231 cancer cells were unresponsive to 10 microM progesterone. The earliest sign of apoptosis is translocation of phosphatidylserine from the inner to the outer leaflet of the plasma membrane and can be monitored by the calcium-dependent binding of annexin V in conjunction with flow cytometry. After 24 h of exposure to 10 microM progesterone, cytofluorometric analysis of T47-D breast cancer cells indicated 43% were annexin V-positive and had undergone apoptosis and no cells showed signs of cellular necrosis (propidium iodide negative). After 72 h of exposure to 10 microM progesterone, 48% of the cells had undergone apoptosis and 40% were annexin V positive/propidium iodide positive indicating signs of necrosis. Control untreated cancer cells did not undergo apoptosis. Evidence proving apoptosis was also demonstrated by fragmentation of nuclear DNA into multiples of oligonucleosomal fragments. After 24 h of exposure of T47-D cells to either 1 or 10 microM progesterone, we observed a marked down-regulation of protooncogene bcl-2 protein and mRNA levels. mRNA levels of survivin and the metastatic variant CD44 v7-v10 were also downregulated. Progesterone increased p53 mRNA levels. These results demonstrate that progesterone at relative high physiological concentrations, but comparable to those seen in plasma during the third trimester of human pregnancy, exhibited a strong antiproliferative effect on breast cancer cells and induced apoptosis.

PMID: 10705995 [PubMed - indexed for MEDLINE]

Hyaluronidase can modulate expression of CD44.

- **Stern R**,
- **Shuster S**,
- **Wiley TS**,
- **Formby B**.

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CD44 is a family of transmembrane glycoproteins with multiple isoforms generated by alternative exon splicing of a single gene. CD44 and its variants are expressed on a wide variety of cells including cancer cells. The mechanisms by which splice variant exons are selected are unknown. The presence of hyaluronan in the environment of the cell appears to influence that selection process. The expression of particular splice variants of CD44 as well as the simultaneous presence of hyaluronan is important for motility, invasion, and the metastatic spread of some tumors. The influence of hyaluronidase digestion on the expression of CD44 in human cancer cell lines was examined. CD44 isoforms containing alternatively spliced exons were sensitive to hyaluronidase digestion in all lines examined, but differences between cell lines were observed. Expression of CD44s, the standard form, was resistant to digestion in two of three cell lines. A tentative model was formulated proposing that CD44 isoforms containing splice variants are unstable, requiring the continuous presence of ligand for expression. CD44s is relatively more stable, not requiring the continuous presence of hyaluronan. Additionally, a number of new CD44 variant isoforms, not previously observed, were identified. Copyright 2001 Academic Press.

PMID: 11339835 [PubMed - indexed for MEDLINE]

These are experiments by other scientists using compounded progesterone for brain injury:

J Neurosurg. 2000 May;92(5):848-52. Links

Neuroprotective effect of postischemic administration of progesterone in spontaneously hypertensive rats with focal cerebral ischemia.

- **Kumon Y**,
- **Kim SC**,
- **Tompkins P**,
- **Stevens A**,
- **Sakaki S**,
- **Loftus CM**.

Department of Neurosurgery, The University of Oklahoma Health Sciences Center, Oklahoma City, USA. ykumon@m.ehime-u.ac.jp

OBJECT: Exogenous progesterone has been shown to reduce brain edema and ischemia-induced cell damage and to improve physiological and neurological function during the early stage of focal cerebral ischemia. In the present study, the authors assessed the neuroprotective potential of progesterone during the late stage of ischemia in a transient middle cerebral artery (MCA) occlusion model in the rat. METHODS: Forty-eight male spontaneously hypertensive rats were randomly assigned to six groups. Progesterone was dissolved in dimethyl sulfoxide (DMSO). In four groups of rats, the dissolved progesterone (4 mg/kg or 8 mg/kg) was administered for 2 or 7 days after ischemia. In two control groups DMSO was administered for 2 or 7 days after ischemia. Occlusion of the MCA was induced by insertion of an intraluminal suture, and reperfusion was accomplished by withdrawal of the suture. Treatment was initiated on reperfusion, which followed 2 hours of MCA occlusion, and continued once a day. Lesion volume, neurological deficit, and body weight loss were measured 2 or 7 days after ischemia, depending on the animal group. Treatment with a high dose of progesterone (8 mg/kg) resulted in reductions in lesion size, neurological deficits, and body weight, compared with control rats. CONCLUSIONS: Administration of progesterone to male rats 2 hours after MCA occlusion reduces ischemic brain damage and improves neurological deficit even 7 days after ischemia.

PMID: 10794300 [PubMed - indexed for MEDLINE]

1: Pharmacol Biochem Behav. 2003 Sep;76(2):231-42. ELSEVIER FULL-TEXT ARTICLE Links

Behavioral effects and anatomic correlates after brain injury: a progesterone dose-response study.

- **Goss CW**,
- **Hoffman SW**,
- **Stein DG**.

Department of Psychology, Emory University, Atlanta, GA 30322, USA.

Evidence suggests that progesterone enhances functional recovery in rats after medial frontal cortical contusions; however, a high dose of progesterone exacerbates tissue loss in a stroke model when administered chronically (7-10 days) prior to injury [Stroke 31 (2000) 1173)]. This study attempts to determine progesterone's dose-response effects on behavioral performance and GABA-A receptor expression following a cortical contusion. Male rats received injections of 0, 8, 16, or 32 mg/kg progesterone in 22.5% 2-hydroxypropyl-beta-cyclodextrin following cortical impact. Lesion 8 mg/kg and lesion 16 mg/kg groups displayed less thigmotaxis in the Morris water maze (MWM) than 0 and 32 mg/kg groups and were not significantly impaired relative to shams on other water maze measures. Increased variability in the 32 mg/kg group during somatosensory neglect testing was the only evidence indicating that a high dose of progesterone was disruptive to a few animals. These results suggest that low and moderate doses of progesterone are optimal for facilitating recovery of select behaviors and that postinjury progesterone treatment permits a wider dose range than preinjury treatment. Progesterone did not affect lesion size, but a strong negative correlation was observed between thalamic GABA-A receptor density and water maze performance. Future studies could explore causes for this relationship.

PMID: 14592674 [PubMed - indexed for MEDLINE]

1: Exp Neurol. 2006 Aug;200(2):378-85. Epub 2006 Jun 22. ELSEVIER FULL-TEXT ARTICLE Links

Tapered progesterone withdrawal promotes long-term recovery following brain trauma.

- **Cutler SM**,
- **Vanlandingham JW**,
- **Stein DG**.

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We previously demonstrated that after traumatic brain injury (TBI), acute progesterone withdrawal (AW) causes an increase in anxiety behaviors and

cerebro-cellular inflammation compared to tapered progesterone withdrawal (TW). Our current study investigates the behavioral and cellular effects of AW two weeks after termination of treatments to determine the longer-term influence of withdrawal after injury. Adult, male Sprague-Dawley rats received either bilateral frontal cortex contusion (L) or sham (S) surgery. Rats were injected at 1 and 6 h post-injury, then every 24 h for six days. Vehicle (V)-treated rats were given 9 injections of 22.5% cyclodextrin, whereas AW rats received 9 injections of 16 mg/kg progesterone and TW rats received 7 injections of P at 16 mg/kg, followed by one at 8 mg/kg and one at 4 mg/kg. On day 8, sensory neglect and locomotor activity tests were initiated. Animals were killed 22 days post-TBI and the brains prepared for either molecular or histological analysis. Western blotting revealed increased brain-derived neurotrophic factor (BDNF) and heat shock protein 70 (HSP70) in TW vs. AW animals. P53 was increased in VL animals, whereas all progesterone-treated groups were equivalent to shams. TW animals had markedly decreased sensory neglect compared to AW animals and increased center time in locomotor activity assays. In addition, lesion reconstruction revealed a decreased lesion size for TWL over AWL over VL animals. Glial fibrillary acidic protein (GFAP) immunofluorescent staining followed this pattern as well. In conclusion, after TBI, AW affects select behaviors and molecular markers in the chronic recovery period.

PMID: 16797538 [PubMed - indexed for MEDLINE]

Slides of Recurrence Rates of Cancer Patients on the Wiley Protocol

Clinical Characteristics

•67 women on hormone therapy identified

•54 women Wiley Protocol

–Premenopausal = 2

–Postmenopausal = 52

•Natural = 22

•Surgical = 24

•Chemo induced = 5

•Other = 1

Clinical Characteristics: Age

20 - 29 = 2

30 - 39 = 2

40 - 49 = 12

50 - 59 = 25

60 - 69 = 8

70 - 80 = 5

Years Duration

Years	# women
•>0.5	8
•1+	9
•2+	18
•3+	13
•>4	6

Clinical Characteristics

•Invasive Breast Cancer	28
•Stage I	10
•Stage II	12
•Stage III	2
•Stage IV	4
•Non-invasive Breast Cancer	5

Receptor Status

- •Invasive
  - —ER + 24/28
  - —ER - 4/28
- •Non-Invasive
  - —ER + 4/5
  - —ER - 1/5

Clinical Characteristics

- Non-Hodgkin's Lymphoma 4
- Colorectal 2
- Ovarian 2
- Post BMT 1
- Lung 1
- Leukopenia 3
- No cancer + FHx, hematological 8

WP Data

- Average length of use: 2.2 years as on October 2006

–Ranges 6 mo to 4.5 years

- Blood levels and tests
- Dose Adjustments

–28/54

- Compliance
- Drop out

Wiley Protocol AE's

- Pulmonary embolism

–71y.o. after 3 years; cont'd WP

•Breast cancer

–57 y.o. recurrence resected- continued

–59 y.o. new cancer opposite breast after 2 years

•(present at time of initiation)

Adverse Events

60 y.o. breast cancer mass removed- no nodes taken

Started WP 1 year later

Axillary mass 1 years after WP

Restaged- only axilla 2 nodes present at 2nd surgery

Ovarian Cancer IIIc

–49 y.o. 2.5 years on WP

Wiley Protocol Concerns

•Fibroids: for better, stable, or worse-

•Endometrial thickening or cancers - 0

•Cardiac events, stroke, or DVT -0

•Gallbladder disease -3 surgery -2

•Serum levels:

–progesterone levels- accuracy?

–Low day 12 E2

•Hypermetabolism

•Seasonal controlled by light/food/ stress

Benefits

•Bone density

•Lipids

•Perimenopausal symptoms

•Headache

•Mood and psyche

•Deep sleep and dreams

•Incontinence

•Vaginal dryness

•Libido

•Skin

Skin

Lipids

Wiley Protocol Issues

•Labor intense for patient and MD

–Need for patient education and selection

•Not reaching “target” levels

–Absorption / metabolism/ compounding variations

•Early bleeding (day 22 menses)

–Either not enough day 1-21 E2 or P4 sharp fall off

•Symptoms in between doses-

–Raise or change to TID x 3 days

• Dose adjustments- frequent

•Progesterone > estradiol

Wiley Protocol Issues

•Minor:

–Allergic skin reaction

•Base variation

–Thin vs. adipose sufficient

–Denser Breast tissue on mammography

•Most, but not all

–Lack of insurance coverage if not at registered pharmacies

–Weight gain- < 5lbs

–Breast tenderness- over in 3 months

Conclusions about the WP

•Provides definite relief of vasomotor and menopausal symptoms

•Very effective for new bone mineralization

•Stabilizes or minimally improves lipid profile

•Improves of mood and quality of sleep

•Has similar effects of other reported E2

•Has promising future with further study

•Short term use in high risk oncology population does not appear to be detrimental

—***Clinical trials needed*** !!!