THE PROGESTERONE DECEPTION ♀

by Ray Peat, Ph.D.

In the 1930s, it was demonstrated that estrogen, even in small doses, produced abortions, and that when it is given early enough, even a very small dose will prevent implantation of the fertilized embryo. Progesterone was known, by the early 1940s, to protect against the many toxic effects of estrogen, including abortion, but it was also known as "nature's contraceptive," since it prevents pregnancy without harmful side-effects, by different mechanisms including prevention of sperm entry into the uterus. That is, progesterone prevents the miscarriages which result from excess estrogen,[1,2] but if used before intercourse, it prevents conception, and thus is a true contraceptive, while estrogen is an abortifacient, not a contraceptive.

In the 1950s, there was a search for chemicals which would prevent ovulation. According to Carl Djerassi,[3] drug companies were extremely reluctant to risk a religious backlash against their other products, and so hesitated to market contraceptives. Obviously, the induction of monthly abortions would have been even harder to sell.

According to Djerassi,[3] "Until the middle 1940s it was assumed that progesterone's biological activity was extremely specific and that almost any alteration of the molecule would diminish or abolish its activity." This would obviously discourage interest from the drug companies, who could patent a substance which they had chemically modified, but could not patent a simple natural substance. However, many substances—even non-steroidal chemicals—turned out to have estrogenic action.[4]

By 1942, Hans Selye had demonstrated that natural steroids retain their activity when administered orally. But every drug company with a steroid patent had a vested interest in having the public believe that the natural steroids cannot be conveniently used. The doctrine that natural steroids are destroyed by stomach acid appeared, was promoted, and was accepted. In the manufacture of progesterone, the precursor steroid is boiled in hydrochloric acid to free it from its glucose residue; no one seriously believed that stomach acid hurts progesterone, except the public.

The real issue is solubility. Hydrocortisone is reasonably soluble in water, but progesterone is extremely insoluble in water, and though it is vastly more soluble in vegetable oil than in water, it does not stay in solution at room temperature, even at the low concentration of 1 part in 1000 parts of vegetable oil.

When people speak of an allergy to progesterone (or even to penicillin) they generally are not aware of the presence of a very toxic solvent.[5] A few years ago, progesterone was often sold dissolved in benzyl benzoate; the PDR warned of possible allergic reaction "to progesterone." Now it is supposedly sold "dissolved in vegetable oil," with about 10% benzyl alcohol as a "bacteriostatic agent." "Bacteriostatic water" contains 0.9% to 1.9% benzyl alcohol, and can irreversibly harm nerves.[7] Awareness of benzyl alcohol's toxicity goes back to 1918, at least; it was proposed as an effective insecticide and found to be toxic to many animal systems. The "safe" systemic dose[7] is exceeded with an injection of 150 mg. of progesterone, yet the local concentration is far higher. It can cause a severe reaction even when used at a lower concentration, in bacteriostatic water.[5]

Other alcohols, including ethanol, have been used as solvents but since they (ethanol even more than benzyl alcohol) have an affinity for water, the solution decomposes in contact with tissue water.

In spite of the toxicity of the vehicle, several beneficial effects can be obtained with injected progesterone, in serious conditions such as epilepsy or cancer of the breast or uterus. Many researchers have commented on "the very obvious difficulty of giving very large amounts of progesterone."[8] Published comparisons of the efficiency of injections and suppositories show that suppositories are only about 6% as efficient as injections.[8] My comparisons of oral progesterone in tocopherol, with other forms and methods of administration, show a roughly similar efficiency for oral and injected progesterone, and about 1/20 the effect for suppositories. Crystals of progesterone are visible in the suppositories I have examined, and this material is obviously wasted.

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An old theory of vitamin E's mechanism of action in improving fertility was that it "spares progesterone."[9] It is established that some of the effects of vitamin E and progesterone are similar; for example, both prevent oxygen waste and appear to improve mitochondrial coupling of phosphorylation with respiration. I suspect that if they actually both work at the same mitochondrial site, then they must have a high mutual solubility. Knowing the long-standing problem of administering large doses of progesterone without a toxic solvent, I applied for and was granted a patent for the composition of progesterone in tocopherol. One of my reasons for publishing in the form of patents is that I have had many years of experience of having my discoveries taken up by others without acknowledgment. My dissertation research, which established that an estrogen excess kills the embryo by suffocation, and that progesterone protects the embryo by promoting the delivery of both oxygen and glucose, didn't strike a responsive chord in the journals, which are heavily influenced by funds from the drug industry.

According to a consultant for a major medical journal, the idea "...of dissolving progesterone, a fat soluble steroid hormone, in vitamin E which is then incorporated into chylomicrons absorbed via the lymphatics, and thus avoids the liver on the so-called first pass...is so simple it is amazing that the pharmaceutical companies have not jumped on it."

In the powder form, direct and intimate contact with a mucous membrane allows "lipid phase to lipid phase" transfer of progesterone molecules. Instead of bypassing the liver, much of the progesterone is picked up in the portal circulation, where a major part of it is glucuronidated and made water soluble for prompt excretion. Since this glucuronide form cross-reacts to some extent with ordinary progesterone in the assay process, and since 50% of the ordinary free progesterone is carried inside the red blood cells,[10] and 50% is associated with proteins in the plasma (while the glucuronide hardly enters the red blood cells at all), it is better to judge by clinical efficacy when comparing different oral forms. My comparisons show several times higher potency in the tocopherol composition than in powder form.

Since progesterone's use as a drug antedates the 1938 law requiring special federal approval, its legal status is similar to that of thyroid hormone. Unfortunately, for both thyroid and progesterone, there is a tendency to cut corners for the sake of a bigger profit margin.

For example, steroid acetates are generally a little cheaper than the simple natural steroid. Some people assume that an acetate or butyrate can be substituted for the steroid itself. This can cause dangerous reactions.

Medroxyprogesterone acetate is considered a progestagen, because it modifies the uterus in approximately the way progesterone does. However, it is luteolytic and lowers the ovaries' production of progesterone, while progesterone itself has a positive effect on the corpus luteum, stimulating progesterone synthesis. It is probably partly the acetate group in this molecule which makes it bind firmly to "receptors," yet causes it to block the enzymes which would normally be involved in progesterone metabolism. (I think testosterone, even, would be a safer "progestagen" than medroxyprogesterone acetate). Pregnenolone acetate similarly blocks the enzymes which normally metabolize pregnenolone.[11] In aspirin, for instance, it is the acetyl group which (by a free radical action) blocks an enzyme involved in prostaglandin synthesis.

Another place to cut costs is in the tocopherol. Tocopherol acetate does have "vitamin E activity," but since it is only about half as efficiently absorbed as the simple tocopherol,[12] it is a mistake to save a few dollars an ounce at the expense of losing half of the therapeutic effect. People who have compared natural progesterone in natural tocopherols with other compositions have insisted that the other compositions must not contain progesterone!

The taste of natural vitamin E is stronger

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than that of the synthetic forms, but since the mixture is absorbed by any tissue it contacts, including various parts of the bowel, it can be taken in a capsule. If a small amount of olive oil is used with it, absorption through the skin is very rapid. Many women use it vaginally, spread onto a diaphragm, to hold it in contact with the membranes. The efficiency of absorption by all routes is so high that patients should be warned against its anesthetic effect, until their dosage requirement is stabilized. Some physicians prefer concentrations higher than 10%, but the risk of accidental drunkenness or anesthesia is higher with the stronger solutions. It is an indication of the tocopherol solution's high availability that medical researchers such as Roy Hertz,[8] who thought they were administering maximal doses by combining injections with suppositories, never mentioned the problem of anesthetic effect from an overdose. Similarly, it is evidence of the extremely poor availability of the micropulverized progesterone that the researchers have administered hundreds of milligrams per day, without mentioning the symptoms of an overdose. Because of the difficulties involved in scientifically studying the clinical effectiveness of various formulations, I think the most practical way of evaluating the effectiveness of different progesterone formulations is to measure the amount extractable from the red blood cells, a few hours after the peak serum level has been reached. This will reasonably reflect the amounts reaching brain cells, adrenal glands, and the various other cells on which progesterone has its therapeutic action. ■

References

1. A. A. Gidley-Baird, et al., Failure of implantation in human *in vitro* fertilization and embryo transfer patients: the effects of altered progesterone/estrogen ratios in humans and mice, *Fertility and Sterility 45*(1): 69-74, 1986.
2. J.L. Yovich, et al., Early luteal serum progesterone concentrations are higher in pregnancy cycles, *Fertility and Sterility 44*(1): 185-189, 1985.
3. C. Djerassi, The making of the pill, *Science 84:* 127-129, 1984.
4. R. Kehl, *Les Glandes Endocrines*, Presses Universitaires de France, Paris, 1952.
5. J.A. Grant, et al., Unsuspected benzyl alcohol hypersensitivity. *N Engl J Med 306*(2): 108, 1982.
6. T.E. Feasby, et al., Neurotoxicity of bacteriostatic water, *N Engl J Med 308*(6): 966-7, 1983.
7. E. T. Kimura et al., Parenteral toxicity studies with benzyl alcohol, *Toxicol Appl Pharmacol 18:* 60-68, 1971.
8. A. White, ed., *Symposium on Steroids in Experimental and Clinical Practice*, The Blakiston Co., New York, 1951, p. 401.
9. A. Fraschini, *Il Metodo Biologico di Rinvigorimento*, Edizioni Minerva Medica, Milan, 1954.
10. E. Mulder, et al., Metabolism of free and conjugated steroids by intact and haemolysed mammalian erythrocytes, *Biochem. Biophys. Acta 260:* 290-297, 1972.
11. S. Lieberman, et al., A heuristic proposal for understanding steroidogenic processes, *Endocrine Reviews 5*(1): 128-148, 1984.
12. L.J. Machlin and E. Gabriel, Kinetics of tissue alpha-tocopherol uptake and depletion, following administration of high levels of vitamin E, p. 48 in *Annals of the N.Y. Academy of Science 393*, B. Lubin and L.J. Machlin, eds., New York, 1982.

Footnote:

There is recent evidence that steroid glucuronidation can occur right in the intestinal wall, which probably helps explain the efficacy of chylomicron transport vs. micropulverized form. C. Longcope et al., *J. Steroid Biochem*, 23;1065-70, 1985.

Ray F. Peat
P.O. Box 3427
Eugene, OR 97403

Letters to the Editor

AHMA and Legal Action

Editor:

While still quite new in the job (July, 1986) I have been sobered recently by reports from around the nation of holistic physicians facing medical board inquisitions and licensing challenges simply because they follow their consciences as scientists. I suggest to our membership that it is now time for us to take action — legally and legislatively.

Please consider:

Physician members of the AHMA all began as professionally trained allopaths. (Since all of our medical schools are essentially allopathic, being trained as an allopath is the only way to emerge with an M.D. or D.O. degree.)

But medicine is an art as well as a science. Many of the prevailing treatments of today are discarded as useless or even harmful tomorrow. Other beneficial treatments are lost or overlooked because they do not conform to the expectations of the prevailing medical orthodoxy. Medicine, like other practical arts, has it ideological adherents and its share of ideological wars.

Our members — caring, thorough scientists — have often become frustrated by the limitations of conventional medicine, and so have sought to achieve a broader medical education. They have studied additional treatment modalities that work, that make people better. They have explored the impact of diet and nutrition, homeopathy, acupuncture, the relationship between the mind and disease, and more.

Holistic medical practice is patient-centered, not disease-centered. Holistic practice takes into account a wider variety of possible explanations for the cause of a patient's problem, and many incorporate the use of substances familiar to the healing arts for centuries, regardless of whether they are in vogue in the medical establishment.

We can no longer sit idly by and let our pioneers be picked off by licensing authorities for purely political reasons. It is appropriate and timely indeed that the AHMA Executive Committee has recently sanctioned a broad strategy—including the establishment of a legal defense fund — to arrange defense of our members on licensing issues.

In Oregon, Dr. Anderson may score a legal victory that will set precedent in every state in the union. She has an unusually "pure" and clearcut case of harassment and abuse of power by a state administrative agency (the Medical Board).

The Oregon law, like that of several states, allows the Board to issue subpoenaes for patient records and otherwise impose summary disciplinary sanction against a physician, without (a) revealing any basis for the investigation, or (b) providing other protections of constitutional due process prior to imposing disciplinary sanction.

Dr. Anderson's counsel, Samuel A. Abady, is a medically knowledgeable advocate, seasoned through association with the Center for Constitutional law in New York. Most recently, he represented Dr. Emanuel Revici in a successful legal bid to win a new trial on a de-licensing matter in New York.

Mr. Abady has been able to raise several constitutional issues in Dr. Anderson's case. It is a certainty the case will go to the State Supreme Court of Oregon, and it may be appealed into the federal courts on constitutional grounds.

Dr. Lynn Anderson, a thorough, caring, careful scientist with an extensive practice in Medford, Oregon, is the second AHMA member in two months that we have heard about to have her license challenged by a medical board, solely because of her pioneering efforts as an holistic physician.

Walt Stoll, M.D., also a dedicated holistic pioneer, has been "invited" by the Kentucky Medical board to justify his holistic methodologies in a hearing before the Board, as they ponder whether to cite him for license violations.

These are not fly-by-night sellers of snake oil. Dr. Anderson was the *top* of her medical school class at Washington University. Walt Stoll, M.D., A.B.F.P., is nationally known for his research, teaching, publications and medical practice experience spanning 25 years. The popularity of Dr. Walt Stoll and Dr. Lynn Anderson among their patients is legend. Neither Dr. Anderson nor Dr. Stoll have ever been charged with malpractice. Both are scientists of the highest caliber, and true pioneers in the field of holistic medicine.

Alarmingly, both are well-known members of the Board of Trustees of the AHMA, contributing many hours of uncompensated time and out-of-pocket expense in the service of the national organization that represents their profession.

Unfortunately, medical licensing boards often see themselves as the guardian of orthodox medical practice. Now certainly, politics is a fact of life that we must live with. But we also happen to have constitutional rights in the United States that are there to provide protection for social pluralism, for minority viewpoints, and for reasonable freedom of choice among resident consumers.

The time has come for us to protect and demand those rights. And we have an opportunity...

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