# RU486, Cancer, Estrogen, and Progesterone

From the original article in 2007. Author: Ray Peat.

Recently many people have been disturbed by reading claims that progesterone can cause cancer, or diabetes, or autoimmune diseases, or heart disease, or Alzheimer's disease. A flurry of press conferences, and a few groups of "molecular biologists" working on "progesterone receptors," and the results of studies in which Prempro (containing a synthetic "progestin") increased breast cancer, have created great confusion and concern, at least in the English speaking countries.

Wyeth, the manufacturer of Prempro, has been highly motivated to recover their sales and profits that declined about 70% in the first two years after the Women's Health Initiative announced its results. When billions of dollars in profits are involved, clever public relations can achieve marvelous things.

Women and other mammals that are ***deficient*** in progesterone, and/or that have an excess of estrogen, have a higher than average incidence of cancer. Animal experiments have shown that administering progesterone could prevent cancer. Cells in the most cancer-susceptible tissues proliferate in proportion to the ratio of estrogen to progesterone. When the estrogen dominance persists for a long time without interruption, there are progressive distortions in the structure of the responsive organs--the uterus, breast, pituitary, lung, liver, kidney, brain, and other organs--and those structural distortions tend to progress gradually from fibroses to cancer.

As a result of the early studies in both humans and animals, progesterone was used by many physicians to treat the types of cancer that were clearly caused by estrogen, especially uterine, breast, and kidney cancers. But by the 1950s, the drug industry had created the myth that their patented synthetic analogs of progesterone were medically more effective than progesterone itself, and the result has been that medroxyprogesterone acetate and other synthetics have been widely used to treat women's cancers, including breast cancer.

Unfortunately, those synthetic compounds have a variety of functions unlike progesterone, including some estrogenic and/or androgenic and/or glucocorticoid and/or antiprogesterone functions, besides other special, idiosyncratic side effects. The rationale for their use was that they were "like progesterone, only better." The unpleasant and unwanted truth is that, as a group, they are seriously carcinogenic, besides being toxic in a variety of other ways. Thousands of researchers have drawn conclusions about the effects of progesterone on the basis of their experiments with a synthetic progestin.

The earliest studies of estrogen and progesterone in the 1930s had the great advantage of a scientific culture that was relatively unpolluted by the pharmaceutical industry. As described by Carla Rothenberg, the massive manipulation of the medical, regulatory, and scientific culture by the estrogen industry began in 1941. After that, the role of metaphysics, word magic, and epicycle-like models increasingly replaced empirical science in endocrinology and cell physiology.

As the estrogen industry began losing billions of dollars a year following the 2002 report from the Women's Health Initiative regarding estrogen's toxicity, and as it was noticed that progesterone sales had increased more than 100-fold, it was clear what had to be done--the toxic effects of estrogen had to be transferred to progesterone. For more than 50 years, progesterone was recognized to be antimitotic and anti-inflammatory and anticarcinogenic, but suddenly it has become a mitogenic pro-inflammatory carcinogen.

Science used to involve confirmation or refutation of published results and conclusions. A different experimenter, using the technique described in a publication, would often get a different result, and a dialog or disputation would develop, sometimes continuing for years, before consensus was achieved, though many times there would be no clear conclusion or consensus.

In that traditional scientific environment, it was customary to recognize that a certain position remained hypothetical and controversial until some new technique or insight settled the question with some degree of clarity and decisiveness. People who cherry-picked studies to support their position, while ignoring contradictory evidence, were violating the basic scientific principles of tentativeness and reasonableness. Contradictory, as well as confirmatory, data have to be considered.

But when a single experiment involves several people working for a year or more, at a cost of a million or more dollars, who is going to finance an experiment that "would merely confirm" those results? The newly developed techniques for identifying specific molecules are often very elaborate and expensive, and as a result only a few kinds of molecule are usually investigated in each experiment. The results are open to various interpretations, and most of those interpretations depend on results from other studies, whose techniques, results, and conclusions have never been challenged, either. There is no significant source of funding to challenge the programs of the pharmaceutical industry.

The result is that the pronouncements of the principal investigator, and the repetitions of those conclusions in the mass media, create a culture of opinion, without the foundation of multiple confirmations that used to be part of the scientific process. The process has taken on many of the features of a cult, in which received opinions are repeatedly reinforced by the investment of money and authority. Newspaper reporters know that the team of investigators spent two years on their project, and the lead investigator wears a white lab coat during the interview, so the reporters don't notice that the investigators' conclusion is a non sequitur, supported by chains of non sequiturs.

The public gets most of its information about science from the mass media, and the increasingly concentrated ownership of the media contributes to the use of scientific news as an adjunct to their main business, advertising and product promotion. The pharmaceutical industry spends billions of dollars annually on direct-to-consumer advertising, so the big scientific news, for the media, is likely to be anything that will increase their advertising revenue.

Social-economic cults often simplify the thought processes required by the participants, by inventing a scapegoat. The

estrogen cult has decided that progesterone will be its scapegoat.

Hans Selye argued that steroid hormones should be named by their origin, or by their chemical structural names, rather than their effects, because each hormone has innumerable effects. To name a substance according to its effects is to predict and to foreordain the discoveries that will be made regarding its effects.

The common system of hormonal names according to their putative effects has allowed ideology and metaphysical ideas to dominate endocrinology. The worst example of metaphysical medicine was the use, for more than 50 years, of "estrogen, the female hormone" to treat prostate cancer, in the belief that "male hormones" cause the cancer, and that the female hormone would negate it. This word magic led to a vast psychotic medical endeavor, that has only recently been reconsidered.

Within the scheme of hormones understood according to their names, "hormone receptors" were proposed to be the mechanism by which hormones produced their effects. Each hormone had a receptor. If another substance bound more strongly than the hormone to its receptor, without producing the effects of the hormone, it was called an antihormone.

The industry of synthetic hormones used the ideology of unitary hormonal action to identify new substances as pharmaceutical hormones, that were always in some way said to be better than the natural hormones--for example by being "orally active," unlike natural hormones, supposedly. Physicians docilely went along with whatever the drug salesmen told them. If a drug was classified as a "progestin" by a single reaction in one animal tissue, then it had a metaphysical identity with the natural hormone, except that it was better, and patentable.

The natural hormones eventually were assigned any of the toxic properties that were observed for the pharmaceutical products "in their class." If synthetic progestins caused heart disease, birth defects, and cancer, then the "natural progestin" was assumed to do that, too. It's important to realize the impact of logical fallacies on the medical culture.

Like the hormones themselves, which metaphysically supposedly acted upon one receptor, to activate one gene (or set of genes), the antihormones came to be stereotyped. If a particular hormonal action was blocked by a chemical, then that substance became an antagonistic antihormone, and when its administration produced an effect, that effect was taken to be the result of blocking the hormone for which it was "the antagonist."

The "antiprogesterone" molecule, RU486, besides having some progesterone-like and antiestrogenic properties, also has (according to Hackenberg, et al., 1996). some androgenic, antiandrogenic, and antiglucocorticoid properties. Experiments in which it is used might have pharmaceutical meaning, but they so far have very little clear biological meaning.

Adding to the conceptual sloppiness of the "molecular biology" wing of endocrinology, the culture in which pharmaceutical products had come to dominate medical ideas about hormones allowed the conventional pharmaceutical vehicles to be disregarded in most experiments, both *in vitro* and *in vivo*. If progesterone was injected into patients mixed with sesame oil and benzyl alcohol, then it often didn't occur to animal experimenters to give control injections of the solvent. For *in vitro* studies, in a watery medium, oil wouldn't do, so they would use an alcohol solvent, and again often forgot to do a solvent control experiment.

The importance of the solvent was seen by an experimenter studying the effect of vitamin E on age pigment in nerves. It occurred to that experimenter to test the ethyl alcohol alone, and he found that it produced almost the same effect as that produced by the solution of alcohol and vitamin E. Workers with hormones often just assume that a little alcohol wouldn't affect their system. But when the effects of alcohol by itself have been studied, many of the effects produced by very low concentrations happen to be the same effects that have been ascribed to hormones, such as progesterone.

In some cases, the solvent allows the hormone to crystallize, especially if the solvent is water-miscible, and fails to distribute it evenly through the medium and cells as the experimenter assumed would happen, and so the experimenter reports that the hormone is not effective in that kind of cell, even though the hormone didn't reach the cells in the amount intended.

These are four of the common sources of error about progesterone: (1) Saying that progesterone has produced an effect which was produced by a different substance. (2) Saying that progesterone is the cause of a certain effect, if an "anti-progesterone" chemical prevents that effect. (3) Saying that progesterone caused something, when in fact the solvent caused it. And (4) saying that progesterone fails to do something, when progesterone hasn't been delivered to the system being studied.

Many years ago, experimenters who wanted to minimize the problems involved in administering progesterone in toxic solvents found that, with careful effort, progesterone could be transferred to a protein, such as albumin, and that the albumin-progesterone complex could be washed to remove the solvent. In this form, the progesterone can be delivered to cells in a form that isn't radically different from the form in which it naturally circulates in the body. Apparently, the labor involved discourages the widespread use of this technique.

Although the industry's early generalizations about estrogen and progesterone, defining them as "the female hormone" and "the pregnancy hormone," were radically mistaken, some useful generalizations about their effects were gradually being built up during the first few decades in which their chemical and physiological properties were studied.

Estrogen's name, derived from the gadfly, accurately suggests its role as an excitant, getting things started. Progesterone's name, relating to pregnancy, is compatible with thinking of it as an agent of calming and fulfillment. But these properties show up in every aspect of physiology, and the special cases of female estrus and pregnancy can be properly understood only in the larger context, in which, for example, progesterone is a brain hormone in both sexes and at all ages, and estrogen is an essential male hormone involved in the sperm cell's function and male libido.

Progesterone can, without estrogen, create the uterine conditions for implantation of an embryo (Piccini, 2005, progesterone

induces LIF; Sherwin, et al., 2004, LIF can substitute for estrogen), and it has many other features that can be considered apart from estrogen, such as its regulation of salts, energy metabolism, protein metabolism, immunity, stress, and inflammation, but without understanding its opposition to estrogen, there will be no coherent understanding of progesterone's biological meaning.

Both estrogen and progesterone are hydrophobic molecules (progesterone much more so than estrogen) which bind with some affinity to many components of cells. Certain proteins that strongly bind the hormones are called their receptors.

Cells respond to stimulation by estrogen by producing a variety of molecules, including the "progesterone receptor" protein. When progesterone enters the cell, binding to these proteins, the estrogenic stimulation is halted, by a series of reactions in which the estrogen receptors disintegrate, and in which estrogen is made water soluble by the activation of enzymes that attach sulfate or a sugar acid, causing it leave the cell and move into the bloodstream, and by reactions that prevent its reentry into the cell by inactivating another type of enzyme, and that suppress its *de novo* formation in the cell, and that oxidize it into a less active form. Progesterone terminates estrogen's cellular functions with extreme thoroughness.

A recent publication in *Science* ("Prevention of Brca1-mediated mammary tumorigenesis in mice by a progesterone antagonist," Poole, et al., Dec. 1, 2006), with associated press conferences, reported an experiment in which a special kind of mouse was prepared, which lacked two tumor-suppressing genes called BRCA and p53.

One of the functions of the BRCA gene product is to repair genetic damage, and another function is to (like progesterone) suppress the estrogen receptor and its functions. Estrogen, and some environmental carcinogens, can suppress the BRCA gene product. Estrogen can also turn off the tumor suppressor protein, p53. So it is interesting that a group of experimenters chose to produce a mouse that lacked both the normal BRCA and p53 genes. They had a mouse that was designed to unleash estrogen's effects, and that modeled some of the features of estrogen toxicity and progesterone deficiency.

This mouse, lacking an essential gene that would allow progesterone to function normally, probably affecting progesterone's ability to eliminate the estrogen receptor, also lacked the tumor suppressor gene p53, which is required for luteinization (Cherian-Shaw 2004); **in its absence, progesterone synthesis is decreased, estrogen synthesis is increased.**

(Chen, Y, et al., 1999**:** BRCA represses the actions of estrogen and its receptor, and, like progesterone, activates the p21 promoter, which inhibits cell proliferation. Aspirin and vitamin D also act through p21.)

The mutant BRCA gene prevents the cell, even in the presence of progesterone, from turning off estrogen's effects the way it should. The antiestrogenic RU486 (some articles below), which has some of progesterone's effects (including therapeutic actions against endometrial and breast cancer), appears to overcome some of the effects of that mutation.

It might have been proper to describe the engineered mouse that lacked both the BRCA and the p53 genes as a mouse in which the effects of estrogen excess and progesterone deficiency would be especially pronounced and deadly. To speak of progesterone as contributing to the development of cancer in that specially designed mouse goes far beyond bad science. However, that study makes sense if it is seen as preparation for the promotion of a new drug similar in effect to RU486, to prevent breast cancer.

The study's lead author, Eva Lee, quoted by a university publicist, said "We found that progesterone plays a role in the development of breast cancer by encouraging the proliferation of mammary cells that carry a breast cancer gene." But they didn't measure the amount of progesterone present in the animals. They didn't "find" anything at all about progesterone. The "anti-progesterone" drug they used has been used for many years to treat uterine, ovarian, and breast cancers, in some cases *with* progesterone, to intensify its effects, and its protective effects are very likely the result of its antiestrogenic and anti-cortisol effects, both of which are well established, and relevant. In some cases, it acts like progesterone, only more strongly.

"Other more specific progesterone blockers are under development," Lee notes. And the article in *Science* magazine looks like nothing more than the first advertisement for one that her husband, Wen-Hwa Lee, has designed.

According to publicists at the University of California, Irvine, "Lee plans to focus his research on developing new compounds that will disrupt end-stage cancer cells. The goal is a small molecule that, when injected into the blood stream, will act as something of a biological cruise missile to target, shock and awe the cancerous cells." "In this research, he will make valuable use of a breast cancer model developed by his wife." "She developed the model, and I will develop the molecule," Lee says. "We can use this model to test a new drug and how it works in combination with old drugs."

"Previously we blamed everything," Lee says of his eye cancer discovery. "We blamed electricity, we blamed too much sausage - but in this case it's clear: It's the gene's fault."

The things that these people know, demonstrated by previous publications, but that they don't say in the *Science* article, are very revealing. The retinoblastoma gene (and its protein product), a specialty of Wen-Hwa Lee, is widely known to be a factor in breast cancer, and to be responsive to progesterone, RU486, and p21. Its links to ubiquitin, the hormone receptors, proteasomes, and the BRCA gene are well known, but previously they were seen as linking estrogen to cell proliferation, and progesterone to the inhibition of cellular proliferation.

By organizing their claims around the idea that RU486 is acting as an antiprogesterone, rather than as a progesterone synergist in opposing estrogen, Eva Lee's team has misused words to argue that it is progesterone, rather than estrogen, that causes breast cancer. Of the many relevant issues that their publication ignores, the absence of measurements of the actual estrogen and progesterone in the animals' serum most strongly suggests that the project was not designed for proper scientific purposes.

They chose to use techniques that are perfectly inappropriate for showing what they claim to show.

In the second paragraph of their article, Poole, et al., say "Hormone replacement therapy with progesterone and estrogen, but not estrogen alone, has been associated with an elevation risk in postmenopausal women." Aside from the gross inaccuracy of saying "progesterone," rather than synthetic progestin, they phrase their comment about "estrogen alone" in a way that suggests an identity of purpose with the estrogen industry apologists, who have been manipulating the data from the WHI estrogen-only study, clearly to lay the blame on progesterone. (Women who took estrogen had many more surgeries to remove mammographically abnormal breast tissue. This would easily account for fewer minor cancer diagnoses; despite this, there were more advanced cancers in the estrogen group.)

While the Poole, et al., group are operating within a context of new views regarding estrogen, progesterone, and cancer, they are ignoring the greater part of contemporary thinking about cancer, a consensus that has been growing for over 70 years**:** All of the factors that produce cancer, including breast cancer, produce inflammation and cellular excitation.

Progesterone is antiinflammatory, and reduces cellular excitation.

Even within their small world of molecular endocrinology, thinking in ways that have been fostered by computer technology, about gene networks, interacting nodes, and crosstalk between pathways, their model and their arguments don't work. They have left out the complexity that could give their argument some weight.

The medical mainstream has recognized for 30 years that progesterone protects the uterus against cancer; that was the reason for adding Provera to the standard menopausal hormonal treatment. The new claim that natural progesterone causes breast cancer should oblige them to explain why the hormone would have opposite effects in different organs, but the mechanisms of action of estrogen and progesterone are remarkably similar in both organs, even when examined at the molecular level. If "molecular endocrinologists" are going to have interpretations diametrically opposed to classical endocrinology (if black is to be white, if apples are to fall up), they will have to produce some very interesting evidence.

Cancer is a malignant (destructive, invasive) tumor that kills the organism. The main dogma regarding its nature and origin is that it differs genetically from the host, as a result of mutations. Estrogen causes mutations and other forms of genetic instability, as well as cancer itself. Progesterone doesn't harm genes or cause genetic instability.

The speculative anti-progesterone school has put great emphasis on the issue of cellular proliferation, with the reasoning that proliferating cells are more likely to undergo genetic changes. And synthetic progestins often do imitate estrogen and increase cellular proliferation. People like the Lees are asserting as an established fact that progesterone increases cellular proliferation.

A paper by Soderqvist has been cited as proof that progesterone increases the proliferation of breast cells. He saw more mitoses in the breasts during the luteal phase of the menstrual cycle, and said the slightly increased mitotic rate was "associated with" progesterone. Of course, estrogen increased at the same time, and estrogen causes sustained proliferation of breast cells, while progesterone stimulation causes only two cell divisions, ending with the differentiation of the cell. (Groshong, et al., 1997, Owen, et al., 1998)

One of the ways that progesterone stops proliferation and promotes differentiation is by keeping the retinoblastoma protein in its unphosphorylated, active protective state (Gizard, et al., 2006) The effects of estrogen and progesterone on that protein are reciprocal (Chen, et al., 2005). It's hard for me to imagine that the Lees don't know about these hormonal effects on Wen-Hwa's retinoblastoma gene product.

The inactivation of that protein by hyperphosphorylation is part of a general biological process, in which activation of a cell (by injury or nervous or hormonal or other stimulation, including radiation) leads to the activation of a large group of about 500 enzymes, phosphorylases, which amplify the stimulation, and cause the cell to respond by becoming active in many ways, for example, by stopping the synthesis of glycogen, and beginning its conversion to glucose to provide energy for the adaptive responses, that include the activation of genes and the synthesis or destruction of proteins. Another set of enzymes, the phosphatases, remove the activating phosphate groups, and allow the cell to return to its resting state.

The "molecular" endocrinologists and geneticists are committed to a reductionist view of life, the view that DNA is the essence, the secret, of life, and that it controls cells through its interactions with smaller molecules, such as the hormone receptors.

The idea of hormone receptors can be traced directly to the work of Elwood Jensen, who started his career working in chemical warfare, at the University of Chicago. Jensen claims that an experiment he did in the 1950s "caused the demise" of the enzymic-redox theory of estrogen's action, by showing that uterine tissue can't oxidize estradiol, and that its only action is on the genes, by way of "the estrogen receptor." But the uterus and other tissues do oxidize estradiol, and its cyclic oxidation and reduction is clearly involved in some of estrogen's toxic and excitatory effects.

For some reason, the military is still interested in hormone receptors. Lawrence National Weapons Laboratory (with its giant "predictive science" computer) is now the site of some of the anti-progesterone research.

Molecular biologists have outlined a chain of reactions, starting at the cell surface, and cascading through a series of phosphorylations, until the genes are activated. The cell surface is important, because cells are always in contact with something, and their functions and structure must be appropriate for their location. But the reductionist view of a network of phosphorylating enzymes ignores some facts.

Glycogen phosphorylase was the first enzyme whose activity was shown to be regulated by structural changes, allosterism. The active form is stabilized by phosphorylation, but this process takes seconds or minutes to develop, and the enzyme

becomes active immediately when the cell is stimulated, for example in muscle contraction, within milliseconds. This kind of allosteric activation (or inactivation) can be seen in a variety of other enzymes, the cold-labile enzymes. A coherent change of the cell causes coordinated changes in its parts. These processes of enzymic regulation are fast, and can occur throughout a cell, practically simultaneously. Strict reductionists don't like to talk about them. "Network analysis" becomes irrelevant.

While a cell in general is activated by a wave of phosphorylation, certain processes (including glycogen synthesis) are blocked. When BRCA1 or retinoblastoma protein is hyperphosphorylated, its anti-estrogenic, anti-proliferative functions are stopped. The communication between cells is another function that's stopped by injury-induced phosphorylation.

Estrogen generally activates phosphorylases, and inactivates phosphatases. Progesterone generally opposes those effects.

Phosphorylation is just one of the regulatory systems that are relevant to the development of cancer, and that are acted on oppositely by estrogen and progesterone. To reduce the explanation for cancer to a gene or two or three may be an attractive idea for molecular endocrinologists, but the idea's simplicity is delusive.

Each component of the cell contributes complexly to the cell's regulatory stability. Likewise, a drug such as RU486 complexly modifies the cell's stability, changing thresholds in many ways, some of which synergize with progesterone (e.g., supporting the GABA system), others of which antagonize progesterone's effects (e.g., increasing exposure to prostaglandins).

There are other proteins in cells, besides the "hormone receptors," that bind progesterone, and that regulate cell functions globally. The sigma receptor, for example, that interacts with cocaine to excite the cell, interacts with progesterone to quiet the cell. The sigma receptor is closely related functionally to the histones, that regulate the activity of chromosomes and DNA, and progesterone regulates many processes that control the histones.

The GABA receptor system, and the systems that respond to glutamic acid (e.g., the "NMDA receptors") are involved in the inhibitory and excitatory processes that restrain or accelerate the growth of cancer cells, and progesterone acts through those systems to quiet cells, and restrain growth.

The inhibitor of differentiation, Id-1, is inhibited by progesterone, activated by estrogen (Lin, et al., 2000). Proteins acting in the opposite direction, PTEN and p21, for example, are activated by progesterone, and inhibited by estrogen.

The inflammatory cytokines, acting through the NFkappaB protein to activate genes, are generally oppositely regulated by estrogen and progesterone.

Prostaglandins, platelet activating factor, nitric oxide, peroxidase, lipases, histamine, serotonin, lactate, insulin, intracellular calcium, carbon dioxide, osmolarity, pH, and the redox environment are all relevant to cancer, and are affected systemically and locally by estrogen and progesterone in generally opposing ways.

About ten years ago, Geron corporation announced that it was developing products to control aging and cancer, by regulating telomerase, the enzyme that lengthens a piece of DNA at the end of the chromosomes. Their argument was that telomeres get shorter each time a cell divides, and that after about 50 divisions, cells reach the limit identified by Leonard Hayflick, and die, and that this accounts for the aging of the organism. Cancer cells are immortal, they said, because they maintain active telomerase, so the company proposed to cure cancer, by selling molecules to inhibit the enzyme, and to cure aging, by providing new enzymes for old people. However, Hayflick's limit was mainly the effect of bad culture methods, and the theory that the shortening of telomeres causes aging was contradicted by the finding of longer telomeres in some old people than in some young people, and different telomere lengths in different organs of the same person.

But it's true that cancer cells have active telomerase, and that most healthy cells don't. It happens that telomerase is activated by cellular injury, such as radiation, that activates phosphorylases, and that it is inactivated by phosphatases. Estrogen activates telomerase, and progesterone inhibits it.

Molecular endocrinology is very important to the pharmaceutical industry, because it lends itself so well to television commercials and corporate stock offerings. Monsanto and the Pentagon believe they can use reductionist molecular biology to predict, manipulate, and control life processes, but so far it is only their ability to damage organisms that has been demonstrated.

Besides the early animal studies that showed experimentally that progesterone can prevent or cure a wide variety of tumors, the newer evidence showing that progesterone is a major protective factor against even breast cancer, would suggest that dishonest efforts to protect estrogen sales by preventing women from using natural progesterone will be causing more women to develop cancer.

The recent report that the incidence of breast cancer in the United States fell drastically between 2002 and 2004, following the great decline in estrogen sales, shows the magnitude of the injury and death caused by the falsifications of the estrogen industry--a matter of millions of unnecessary deaths, just in the years that I have been working on the estrogen issue. The current campaign against progesterone can be expected to cause many unnecessary cancer deaths (e.g., Plu-Bureau, et al., Mauvais-Jarvis, et al.), while distracting the public from the culpability of the estrogen industry.

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