Estrogen, progesterone, and cancer: Conflicts of interest in regulation and product promotion

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

What is Cancer? (Johns Hopkins Univ.)

> The **term cancer** refers to a new growth which will invade surrounding tissues, metastasize (spread to other organs) and may eventually lead to the patient's death if untreated.
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> A tumor is not necessarily a cancer. The word tumor simply refers to a mass. For example, a collection of pus is by definition a tumor. A cancer is a particularly threatening type of tumor.
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> - **neoplasm** — An abnormal new growth of tissue that grows more rapidly than normal cells and will continue to grow if not treated. These growths will compete with normal cells for nutrients. This is a non-specific term that can refer to benign or malignant growths. A synonym for tumor.
> - **tumor** — The more commonly used term for a neoplasm. The word tumor simply refers to a mass. This is a general term that can refer to benign or malignant growths.
> - **benign tumor** — A non-malignant/non-cancerous tumor. A benign tumor is usually localized, rarely spreads to other parts of the body and responds well to treatment. However, if left untreated, benign tumors can lead to serious disease.
> - **malignant tumor** — Cancer. A malignant tumor is resistant to treatment, may spread to other parts of the body and often recurs after removal.
> - **cancer** — A malignant tumor (a malignant neoplasm).
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> http://pathology2.jhu.edu/pancreas/pc_overview.cfm

Issues that at first seem scientific too often turn out to be merely propagandistic. When a claim has no scientific value, it's necessary to directly attack that claim, but the propagandist hopes to (and often does) control the discourse, by resorting to techniques such as censorship, public relations, and financial-political power. The pharmaceutical industry uses all of those anti-scientific powers just as effectively as the military-industrial lobby does.

While Donald Rumsfeld answered the question, "where are the weapons of mass destruction?" by saying "We know where they are. They're in the area around Tikrit and Baghdad and east, west, south and north somewhat," the estrogen industry responds to the evidence that estrogen causes breast cancer, strokes, heart attacks, blood clots and Alzheimer's disease by saying "it's progesterone that is responsible."

To deal with the antiscientific fraudulent claims of the estrogen industry, it isn't necessary to search every square meter of Iraq, as it was with Rumsfeld's claim; it's enough to show that there is no science involved in their claims, by analyzing their experimental methods. But it's also important to examine some of the methods they have used to further their goals, despite the absence of any factual basis.

For more than 60 years, the estrogen industry has been using the techniques of public relations, including the placement of pseudoscientific articles in medical journals, to promote their sales. Recently, Carla Rothenberg documented a conspiracy of the estrogen industry in the 1940s to get medical and governmental approval of their products by shifting attention away from the clear evidence of estrogen's toxicity. Her paper competently reviews the subsequent history of "Hormone Replacement Therapy." http://leda.law.harvard.edu/leda/data/711/Rothenberg05.pdf

After 2002 when the Women's Health Initiative study announced some of the harmful effects of hormone treatment, resulting in a disastrous decrease in estrogen sales, the industry has intensified and diversified its public relations efforts, and has succeeded in recovering some of their lost market. Historically, whenever some of the claimed benefits of estrogen have been disproved, the industry shifts its emphasis to new, previously unmentioned "virtues" of the product. Hundreds of different benefits claimed for estrogen in prestigious medical journals have been proven false, but until 2002, the industry's profits grew steadily. Now, compensating for the annual loss of billions of dollars, they are highly motivated.

Dozens of toxic effects of estrogen were demonstrated and never refuted, but a variety of techniques of distraction and misdirection gradually emerged, to prevent the accumulated evidence of estrogen's toxicity (and/or ineffectiveness) from interfering with the campaigns to market it for the widest possible variety of conditions.

Since the WHI study involved the use of Prempro (PREMPRO™--conjugated estrogens and medroxyprogesterone acetate), the emphasis of the industry has been to divert attention from the toxic effects of estrogen, by blaming everything on "progesterone." An intense campaign is underway to assign all of estrogen's harmful effects to progesterone.

The pharmaceutical industry has a long history of lying about natural progesterone (and many other natural substances), to promote sales of their competing products. The price ratio of retail estrogen tablets to bulk estrogen can be 1000 to 1, while the ratio for progesterone products is often less than 10 to 1. With the increased use of progesterone (its sales in the US have increased more than 100-fold), the estrogen industry has had to develop new kinds of attack. A small shift of the market away from estrogen costs the drug industry hundreds of millions of dollars. The loss of estrogen sales following the 2002 WHI study, that convincingly demonstrated its toxicity, was huge, with the decreased sales of Wyeth alone amounting to billions of dollars. Wyeth has petitioned the FDA to prevent compounding pharmacies from selling the natural hormones.

People who have made a career of research that, according to them, reveals the "benefits" of estrogen have, in recent years, expanded their work to argue that it is progesterone, rather than estrogen, that causes diabetes, heart disease, dementia, and cancer.

The EPA currently has a document draft on the internet which, in relation to the evaluation of a carcinogenic herbicide, reviews the issue of the balance between estrogen and progesterone in the development of cancer in rats, and includes the observation that progesterone is not carcinogenic to rats, **and that it instead is protective against cancer, because of its antiestrogenic effects.**

Recently, stores in California have placed warnings near their progesterone-containing cosmetics, saying that the State of California "knows" progesterone to be a carcinogen.

Californians often talk about their state's having the world's sixth largest economy. The state accounts for 14% of the GDP of the U.S. If the state regulates a product made in Michigan, Texas, or France, the producer is very likely to change the product to suit California.

If an industry wants to control its competitors or potential competitors, an investment in California's regulatory system can pay huge rewards.

California has listed progesterone as a carcinogen under the Safe Drinking Water and Toxic Enforcement Act, called Proposition 65. The law doesn't prevent the sale of carcinogens, it simply requires a warning. Warnings are posted in grocery stores and restaurants, on sports equipment, in beauty parlors, on apartments and parking lots, but there is so little effort spent on realistic evaluation of risks that the effect of the law is to allow the major polluters to go unnoticed among the ubiquitous warnings. But California has other laws that encourage its lawyers to sue for "unfair business practices" when they believe Prop 65 has been violated. That has resulted in a culture of vigilantism with bounty-hunting lawyers, some of whom try to enforce Prop 65 even against companies that are clearly exempt.

California's regulatory board that lists progesterone as a carcinogen cites two bodies that have evaluated carcinogens, the US National Toxicology Program (NTP), and the UN's International Agency for Research on Cancer (IARC), as authoritative sources. One of those, the US National Toxicology Program (NTP) cites the other's, the IARC's, evaluation of progesterone as the basis for its own listing of progesterone, so the opinion of IARC has been very influential.

The IARC publications discussed the toxicity of several of the synthetic progestins, and concluded that some of them are possible human carcinogens. The (1987) entry for medroxyprogesterone acetate, for example, has three sections: "A. Evidence for carcinogenicity to humans (inadequate)," "B. Evidence for carcinogenicity to animals (sufficient)," and C., that it can damage chromosomes**.** Eight citations, besides two IARC monographs (1974 and 1979), are given as supporting evidence.

The entry for progesterone, oddly, has only two sections, **"**A. Evidence for carcinogenicity to animals (sufficient)**,"** and B, that it doesn't damage chromosomes. **There is no mention of human carcinogenicity at all.** Besides the IARC monographs, only one study is mentioned, a test in beagles (I'll comment on the competency of that study below). At the end of the whole section, which included eleven synthetics and progesterone, it concludes: "Overall evaluation" "**Progestins are possibly** carcinogenic to humans (Group 2B)," oddly **neglecting to distinguish progesterone from the synthetics.**

The corruption of the term "progestin" or "progestogen" by the industry and the drug regulators has been terribly consequential. The synthetic chemicals classified as progestins often have ***anti-progesterone*** actions, and shouldn't be called progestins at all, because they don't support gestation, contrary to what the term falsely implies. It is exactly their anti-progesterone/antigestational action that led to their use as contraceptives.

Since the 1987 review by IARC, it seems that their only other review of progesterone's carcinogenicity was of a single study in 1999, and that study clearly gave evidence that progesterone prevented cancer.

But California's board of "qualified experts" in the Office of Environmental Health Hazard Assessment (OEHHA) identify **progesterone** as known to cause cancer, and cites the group of studies listed by IARC in the medroxyprogesterone acetate report as their evidence. Rather than trying to clarify the confusions that exist in the IARC documents, this board has compounded the confusion.

In the transcript of the meeting, at which they decided to list progesterone as a carcinogen, they received testimony from only one outside expert, Richard Edgren, who answered the chairman's question, why don't you want progesterone listed, by saying, because it isn't a carcinogen. He said that the inclusion of a large number of non-carcinogenic materials "could vitiate the use of the list."

But the chairman had, early in Edgren's review of the shortcomings of animal studies of carcinogenesis, heard the word "metastasis," in connection with beagle dogs, and--although Edgren hadn't said that any metastatic cancer had been found in the progesterone test (it hadn't)--the committee's decision to list progesterone appears to have hinged on that word.

Edgren, referring to "**various synthetic and semi-synthetic progestogens**," said that administering them by injection "leads to the development of mammary nodules, some of which have the characteristics of malignant tumors, although these tumors rarely metastasize." A little later, Kilgore said "I mean, I heard you say that it was rare that it metastasized. I would say any kind of metastasizing is important." Edgren isn't quoted in the transcript as having attempted to explain that the malignant and metastatic cancers appeared only in beagles treated with synthetic progestins. At best, the behavior of the chairman and the committee, as reflected in that transcript, was erratic and confused, or more accurately, irrational.

The only biologist on the committee who spoke during the meeting, Dr. Spangler, expressed confusion and dissatisfaction with the evidence:

". . . in reviewing the information that was supplied to me regarding progesterone, I was confused and concerned by what appears to be a variety of discrepancies in the way the compound has been reviewed." "In one place, IARC says there is limited evidence; in another place, it says there is sufficient evidence. And NTP says there is sufficient evidence. And they cite as their sufficient evidence a variety of very convoluted experimental procedures, in which mouse mammary tumor virus positive mice were used in a study; and, in addition to that, some other carcinogen, some other potent carcinogen, was applied at the same time or after." "It was just very confusing. And I had a lot difficulty evaluating it."

The State's rules explicitly state that **all the relevant evidence** is to be presented to the committee for consideration, and that the evidence must show clearly, **by accepted scientific methods,** that **a material causes cancer (i.e., malignant tumors)** before it can be listed. What is clearly shown by the few papers provided to the committee is that their procedures were not followed at all. Providing publications that didn't even claim to have involved the development of cancer, and ignoring an immense amount of more relevant evidence, the committee, in a parody of legal process, didn't even get a randomly selected sampling of the relevant evidence.

In my correspondence with OEHHA, when I pressed for information regarding the criteria for selecting evidence, and the qualifications of the staff who had the responsibility of selecting "all relevant evidence," their response was that they lacked the resources to answer the question.

Edgren, who had argued that progesterone wasn't a carcinogen, didn't make a very good presentation of the case against the few studies that had been mentioned by NTP and IARC. Even if he had been able to do that, in the few minutes he had (six or seven different substances were on the agenda for consideration for listing during that meeting), it doesn't seem likely that the committee would have been interested.

In a letter he wrote to the committee before it met, Edgren said **"Careful evaluation of data from a properly conducted oral study is a prerequisite before the carcinogenicity of any chemical can be adequately evaluated."** The reason for that statement is that it had become clear in the 1970s and 1980s that the invasive introduction of anything into the body's tissues creates inflammation and a complex series of systemic stress reactions that affect the immune system, and that can lead to the development or promotion of cancer, no matter how inert and innocuous seeming the injected material might be. The people on the committee didn't even discuss that issue. Worse, the studies mentioned by IARC included some that hadn't met basic scientific standards of experimental design, failing to use proper experimental controls, including vehicle controls, and failing to describe the actual composition of the vehicle or solvent used for administering progesterone.

Every good high school science teacher or science student knows that the experimental variables have to be clearly defined. The United Nations' IARC, the US's NTP, and California's Panel of Qualified Experts chose to draw conclusions on some studies that don't meet any standards for testing carcinogens, such as those published by the US government. And while disregarding basic standards of experimental design, their review of the literature had an even more serious flaw--it "cherry-picked" the published evidence that they apparently preferred, ignoring the studies which, over a period of more than 20 years, showed that progesterone prevents and/or cures tumors. And in an extremely unrepresentative selection of studies on the subject of progesterone's carcinogenicity, the selected studies presented some clear evidence of some of progesterone's anticarcinogenic effects, along with some results that can't be interpreted clearly.

One of the early papers listed as evidence of progesterone's carcinogenicity in animals actually concluded that their experiments completely failed "to produce any beneficial effect by the administration of progesterone on the mammary cancer in mice," and cautioned that their results showed "the need for care in attempting to generalize results even in different strains of the same species and emphasizes the difficulty of attempting to carry over results obtained in experimental animals to human pathology." (Burrows and Hoch- Ligeti, 1946).

The work (demonstrations of the anti-tumor effect of progesterone) that they were not able to confirm had included explicit observations that **intermittent injections** of progesterone were not effective in preventing tumors or causing them to regress, and emphasized the importance of continuous exposure. Knowing that, the Burrows and Hoch-Ligeti publication appears to have been designed propagandistically to oppose the work that was demonstrating the anti-tumor actions of progesterone, since they--without explanation--used the already discredited method of giving periodic injections of progesterone dissolved in peanut oil.

Without reading the article, people seeing it included on the agencies' list of studies supposedly providing evidence of progesterone's carcinogenicity would assume that it provided such evidence. It didn't. If the agencies cite this study, why didn't they mention any of the numerous studies showing that progesterone prevents tumors or causes them to regress? The reason this study was done was to argue against the studies that had demonstrated progesterone's protective effects, so anyone reading it had to know of those other studies' existence, as well as knowing that this study itself provided no evidence at all of carcinogenicity.

Reproducibility is the essence of science, and the anti-tumor effects of progesterone were repeatedly demonstrated by different investigators. The single study by Burrows and Hoch-Ligetti has never been replicated, and the reason for its failure to show an anti-tumor effect was already explained by the other workers.

Since the 1920s, many studies had demonstrated that "spontaneous" cancers increase in proportion to the quantity of polyunsaturated fat (especially linoleic acid) in the diet. By the end of the 1960s, the carcinogenicity of vegetable oils, or at least their "co-carcinogenicity" or "tumor promoting" effects had become widely known, and one of the World Health Organization publications observed that progesterone carcinogenicity studies using vegetable oil as the vehicle couldn't be recognized as valid.

More recently, ethanol has been found to antagonize progesterone's anticancer and anti-proliferative actions.

Studies using implanted pellets or plastic tubes containing a solution of progesterone sometimes neglected to even mention the nature of the solvent used. Since implanted pieces of inert materials, such as disks of plastic, could be carcinogenic, it was recognized that a proper control for a hormone-containing pellet or tube would require the implantation of a pellet or tube without the hormone. Sometimes, instead of actually implanting the object, sham surgery, similar to that involved in implantation of the pellet, would be used, in recognition that the surgical trauma itself could have far reaching effects on the organism.

Any tissue damage or irritation causes the release of cytokines and mediators of inflammation, which are known to be involved in tissue growth and cancer. When injected, even plain water and other normally harmless things are carcinogenic.

The need for proper experimental controls when using implanted devices is shown by a study that analyzed the fibrotic tumors that had grown around implanted plastic tubes. Crystals of talc were found in the tumor, that were assumed to have originated from the surgical gloves used during the operation. Talc is now widely recognized as a carcinogen, and is suspected of causing ovarian cancer.

Overlooked variables are the reason for the essentiality of repeatability and confirmation in science.

In the 1970s, a new method for suspending or dissolving oily chemicals in water was being explored. A cyclic carbohydrate, cyclodextrin, makes it possible to wet substances that are insoluble in water, such as progesterone, even if the substance remains in a solid crystalline form. Several companies were promoting the use of these for the administration of hydrophobic drugs.

In 1976, D.W. Frank reported that the cyclodextrins produced nephrosis in rats. In 1978, a study by Perrin, et al., reported its toxicity to the kidneys. Twenty years later, Horsky and Pitha at NIH reported that the cyclodextrins can synergize with carcinogens, and in 1982 a group in Japan reported that cyclodextrins can increase the production of kidney cancers by another carcinogen (Hiasa, et al.). The intrinsic carcinogenicity of a more water soluble cyclodextrin, that was considered "more toxicologically benign," was found to cause pathological changes in lungs, liver, and kidney, and to increase the formation of tumors in the pancreas and intestines of rats (Gould and Scott, 2005).

In 1974, D. W. Frank and others at Upjohn had begun testing the effects of progesterone and medroxyprogesterone acetate in beagle dogs, using an "aqueous suspension." Their 1979 publication describing that four year study didn't mention the way in which the "aqueous solution" had been made, and didn't mention cyclodextrins at all. Frank's published observation during the beagle study that cyclodextrins are toxic to the kidneys suggests that someone at Upjohn had noticed a problem with the "wetting agent" that was already in use in the beagle study.

Another remarkable feature of the four year beagle study was that, of 140 dogs that began the intended 7 year study, 28 had died by the time they published the report, and none died of cancer, but the causes of death were not reported. The only experimental group in which there were no deaths by the end of four years was the low dose progesterone group. The dogs in the high dose progesterone group received weekly intramuscular injections of 1140 mg of progesterone suspended in 11.4 ml of "aqueous vehicle." 2345 ml of the vehicle was received by each dog during the four years. Only four dogs in that group were still alive at the time of publication, but the cause of death of the other 16 wasn't mentioned. Quarts of a toxic material that had never before been used in this way, injected into their muscles, and the unexplained deaths of so many animals, make this a unique experiment that is unlikely ever to be repeated.

Their failure to mention injection-site muscle damage is just another indication of the study's low quality.

At the time of the study, it had been known for many years that interference with the organism's detoxifying systems, especially the liver and kidneys, can contribute to the development of cancer. Although the study was planned to continue for 7 years to meet the FDA requirement, **none of the eight authors ever published again on a related topic**, and most of them **didn't publish again at all.**

When I tried to contact one of the authors, he didn't respond. I assume they were embarrassed by the shoddiness of their methods. Richard Edgren has commented, "I can't believe how fast and how completely they shut down. They fired people and retrained the rest for other areas."

But the regulatory agencies have tied their reputations to studies of that sort.

No malignant cancers were reported in this four-year beagle study. Beagles normally have a high incidence of cancer, especially mammary cancer. In a different study in which 172 beagles were treated with contraceptive hormones, nine of them developed malignant cancers, and of those, five metastasized. (This might be why the chairman of the committee was thinking about metastatic cancer, but if so, he was simply confused, because the issue they were considering was the listing of natural progesterone, which wasn't reported to have produced any malignant or metastatic tumors.)

Two other studies cited by the IARC and other agencies, by Jones and Bern, 1977, and Rebout and Pageaut, hardly seem appropriate studies to support the idea that progesterone is carcinogenic.

Jones' and Bern's paper described the production, 12 months after neonatal treatment with progesterone, of vaginal and cervical lesions, and mammary nodules, which are also referred to as tumors. "Progesterone alone induced cervical lesions in only 1 of 32 mice...and induced vaginal lesions in only 2 or 32 mice. Furthermore, progesterone given with either dose of estrogen to intact mice reduced the incidence of hyperplastic lesions, compared with intact groups treated with estrogen alone." They commented (page 74) that their results were "mammary tumor virus dependent," and that this might account for the production of "hyperplastic alveolar nodules as opposed to" tumors of possible ductal origin, that had been seen in other studies when the carcinogen DMBA was used.

In another 1977 publication, Jones, Bern, and Wong described changes seen when the mice were 1.5 to 2 years old. This later publication appears to clarify the meaning of nodules or tumors in the younger animals: **"Although mammary tumors were observed neither in control nor in progesterone-treated intact mice, many of the latter group possessed hyperplastic alveolar-like mammary nodules and other dysplasias."** Neither of these studies refers to the carcinogenicity of progesterone.

The 1977 study (at the University of California, Berkeley) was explicitly motivated by Jones' and Bern's concern with the risks of the medical practice of treating pregnant women with DES and a synthetic progestin, and they used mammary tumor virus-bearing mice, and they didn't continue the study to observe the incidence of actual cancers. (Their choice of infant rodents to study progesterone might be questioned, because of earlier work showing that **immature rat ovaries are able to convert progesterone to estrogens,** unlike the tissues of other animals or humans: Quattropani and Weisz, 1973; Weniger, et al., 1984, later reported similar results.)

Anyone working with mammary tumor virus-bearing mice in the 1970s should have been aware of the effects of sex hormones on the expression of virus and development of cancer in the infected mice, as studied by Strong, Figge, and others for about 40 years. Excess estrogen causes the virus to be expressed, progesterone opposes its expression.

Jones and Bern injected the newborn mice with 0.02 ml of sesame oil daily for five days, with or without estrogen and progesterone. A newborn mouse weighs a little over a gram. On a weight and volume basis, this would be like injecting an adult human with more than a quart of sesame oil daily for five days. The proportionate weight of progesterone in an adult human would be several grams per day.

This amount of progesterone is far more than the anesthetic dose. Since the authors didn't mention anesthesia, very little of the progesterone could have been absorbed, meaning that deposits of crystals would have remained in their tissues.

Tissue irritation from foreign bodies and from vegetable oil, even in relatively small amounts, can produce severe systemic reactions, because of the reactive production of nitric oxide, prostanoids, and a great variety of pro-inflammatory and tumor-promoting cytokines.

This study might have had the formal appearance of a scientific experiment, but the unfamiliarity of the men with the material they were using, their use of mice carrying the mammary tumor virus, and, more importantly, the extremely complex reactions produced when extraneous materials are injected into the tissues, make this a useless experiment. The value of Richard Edgren's statement about the need to test carcinogens orally, rather than by injection, is becoming clearer all the time, as the role of irritation in cancer development is being better understood.

In their second 1977 study, Jones, Bern and Wong reported that at the age of 1.5 to 2 years, nearly two thirds of the progesterone treated mice had genital tract lesions. In another study published in 1977 (Iguchi and Takasugi) neonatal mice were given the same daily amount of progesterone, but for ten days rather than five, **giving them twice the dose. These authors reported that there were no permanent changes in the vaginal and uterine epithelium. This study wasn't mentioned by any of the agencies, but it calls the results of the California study into question.**

In a 1973 study by Rebout and Pageaut, progesterone was administered in a pellet, **the composition of which was not mentioned, and there was no vehicle control at all.** Each mouse received 45 mg of progesterone. The average mouse weighs about 30 grams. Invasive squamous carcinomas were produced by the carcinogen 20-methylcholanthrene, and these were more numerous in the progesterone treated mice. Methylcholanthrene is an extremely hydrophobic, highly irritating hydrocarbon which has often been used to create experimental cancers. The method of administering the carcinogen isn't clearly described: "Local exposure of carcinogen ... in the cervical canal for 9 weeks ... induced one invasive carcinoma in the vagina-exocervix and five in the endocervix." It was introduced into the cervical canal, but in what form and how often isn't described. Methylcholanthrene has some estrogenic properties.

Estrogen increases the production of mucus in the cervix and vagina, and increases its water content and mobility. Abundant and fluid mucus has a cleaning action, eliminating bacteria and other material. Progesterone makes the mucus more viscous and less hydrophilic, and when it dominates the reproductive physiology, it effectively creates a plug in the cervix that prevents the entry of sperms.

The choice of the cervix and vagina suggests that the authors were "engineering" the experimental outcome, because the effect of progesterone on cervical mucus is very well known. To apply the irritant to an area where it would normally be washed away by the mucus, but where it is kept in place by hormonally altering the mucus, is really a way of manipulating how much exposure to the irritating chemical the tissue will receive. It's analogous to studying the "toxicity" of an antihistamine, by applying a toxin to the nasal membrane of a person with a cold, and then administering the antihistamine to stop the flow of mucus, allowing the membrane to fully absorb the applied dose of toxin.

A different chemical carcinogen, 7,12-dimethylbenz(a)anthracene was used in another 1973 study (Jabara, et al.), in combination with progesterone. In this experiment, the carcinogen was administered to rats in one dose by stomach tube, dissolved in corn oil. The progesterone was injected subcutaneously in 3 mg doses in corn oil three times per week. Unfortunately, there was no control group in which the corn oil was injected alone.

The progesterone was supposedly dissolved in the corn oil, one tenth ml per dose. That amount of progesterone (3% weight/volume) will dissolve in hot corn oil, but as the oil cools, the progesterone crystallizes and precipitates. That creates doubt regarding what the animals were actually receiving.

Corn oil is one of the most effective vegetable oil tumor promoters/carcinogens, and it's now considered improper to use it as a solvent for testing even oral carcinogens, since some chemicals that are carcinogenic in the oil are relatively harmless when administered without the corn oil. The animals got 2 ml of corn oil in the stomach feeding with the carcinogen. One of the

groups (group 5) received, in addition, more than 6 ml of corn oil in the injections. The experiment lasted only 135 days, and in the group that received only the carcinogen, the mortality was only 5%, and that death occurred shortly after the carcinogen was administered. All of the groups receiving the corn oil and progesterone injections had higher mortality, two with 25%, one with 37.5% mortality. Despite the **unexplained general problem with prematurely dying rats,** the authors found that "The relative incidence rates indicated that **pretreatment with progesterone inhibited tumorigenesis,** except in the group (5) in which progesterone treatment was continued for the duration of the experiment." Without progesterone, it is almost certain that the additional corn oil injected would have ***increased*** tumorigenesis in all experimental groups.

Without that vehicle control group, the experiment can just as well be described as a test of corn oil, rather than of progesterone. If you claim to be testing the capacity of a substance to promote tumors, it shouldn't be administered in a standard tumor promoter.

A 1968 publication by Glucksmann and Cherry was included in the documents offered as evidence of progesterone's carcinogenicity. Unfortunately, they neglected to identify the vehicle used for giving twice weekly intramuscular injections of 1 mg of progesterone, and they didn't have a vehicle control for the progesterone injections. At that time, the most common vehicle was a mixture of 9% benzyl alcohol and oil, usually sesame or peanut oil. Benzyl alcohol by itself is quite toxic, and was responsible for the death or brain damage of thousands of babies in hospitals, even in the small amounts that remained as residue in tubing after they had been rinsed with "bacteriostatic water," which contains 0.9% benzyl alcohol, and which is still used as the vehicle for many injections, such as penicillin and vitamin B12. The antitoxic (or "catatoxic") action of progesterone greatly reduces the toxicity of benzyl alcohol.

In discussing the effects of hormones on the induction of sarcomas, Glucksmann and Cherry comment that "The rate of induction of sarcomas in intact rats was slowed down slightly by treatment with progesterone and not significantly increased in spayed animals...."

In their Discussion section, they mention several previous studies in relation to their own results, and comment, regarding other studies, that "The effect of progesterone on the type of induced cervical cancer in mice consists in increasing the columnar component of mixed carcinomas in castrates **. . .** without materially affecting the induction period and tumour yield. Thus the experimental evidence in rats and mice **is not as clearly antitumorigenic** as that of Lipschutz (1950) for guinea pigs and the clinical observations (Ulfelder, 1962; Jolles, 1962)."

Comparing this study to that of Burrows and Hoch-Ligetti, the dose of 2 mg per week per rat is lower, on a body-weight basis, than the earlier study's dose of 1 mg per week in mice, but the greater frequency came a little closer to the continuous treatment that Lipschutz said was necessary. This could account for the fact that some of their results were intermediate between those of the Lipschutz group and those of Burrows and Hoch-Ligetti.

In Glucksmann's and Cherry's results, progesterone retarded one type of tumor and appeared to promote another (an epithelial tumor, which wasn't described as malignant or cancerous), but if the progesterone was dissolved in a tumor promoting solvent, it's impossible to ascribe the effect to progesterone. Vegetable oil applied to epithelium that has been exposed to a carcinogen such as the DMBA they used will typically increase the growth of the tumors. Without information about the vehicle, it's impossible to interpret that part of their results clearly, but anyway, they didn't describe any carcinogenic effect of progesterone; they did, however, describe a clearly **anticarcinogenic** action.

A 1962 study, by Capel-Edwards, et al., was intended to compare the effects of prolonged administration of high doses of progesterone with the known toxic effects of synthetic progestagens. They didn't find any malignant tumors, so the study can't be taken as evidence of the carcinogenicity of progesterone. The vehicle used for dissolving the progesterone consisted of benzyl alcohol, ethanol, and ethyl oleate. Some of the solutions contained more than 10% progesterone. When this sort of solution interacts with water in the tissues, it causes the progesterone to crystallize out of solution. The authors reported that "subcutaneous tissue reactions developed at injection sites," and that these "occurred in all animals, including controls, and were apparent for several days after the injection." These injection-site lesions sometimes developed into "sterile abscesses which eventually ulcerated and healed." The only dog that died during the study was in the control group, and although there were "a number of pathologic findings," the exact nature of that dog's sickness couldn't be determined. The injections were given daily, for **a total of 518 injections in each animal,** and each injection contained as much as 4 ml of the vehicle. Almost an ounce per week of this material, combined with the massive irritation produced by crystallization at hundreds of injection sites, would be the most likely explanation for the various inflammatory changes they saw, including osmotic fragility of red blood cells, and as much as a 50% enlargement of liver and kidneys.

Although some of the basic ideas about canine physiology that were held when the Capel-Edwards study was designed have been found to be mistaken, and the toxicity of their vehicle can now be seen, and they didn't conclude that progesterone was carcinogenic, their study wasn't the worst of those that have been presented as evidence of progesterone's carcinogenicity.

When an experimenter doesn't yet have a clear hypothesis, it's reasonable to do some exploratory tests, just to get an orientation to the possibilities so that it's possible to form a well defined hypothesis, before designing an experiment that will test the hypothesis. Sometimes an experimenter and journal editors will allow a merely exploratory experiment to be published. If they don't draw inappropriate conclusions from the ambiguous results, the publication can be justified, simply because it might stimulate others to investigate the subject more thoroughly.

But often editors allow the author to draw conclusions from the experiment that are not directly implied by the data, especially when those conclusions support the editor's prejudices. A conclusion may be consistent with, though not implied by, the results of the experiment. These publications may be effective propaganda, but they aren't good science.

But California's OEHHA identifies those eight publications as "the relevant evidence that clearly shows through scientifically

valid testing according to generally accepted principles that progesterone causes cancer."

In 2004, the agency was petitioned to remove progesterone from the list. In the document rejecting that petition, they mentioned that IARC in 1999 had reviewed newer evidence confirming the carcinogenicity of progesterone. After months of asking the man in charge of rejecting the petition to identify that very important new data, I hadn't received an answer, so I wrote to IARC, and the man in charge there responded:

"The IARC (1999) review is actually an IARC Monographs volume (Vol.72) . . . . This volume focuses on contraception and post-menopausal therapy. Progesterone is not used for these indications and, hence, after a quick search in the book I found only one reference that clearly reports an experiment with progesterone." [*Wednesday, October 04, 2006 12:44 AM]*

That article *(Grubbs CJ, Peckham JC & McDonough KD (1983) Effect of ovarian hormones on the induction of 1-methyl-1-nitrosourea-induced mammary cancer. Carcinogenesis 4(4):495-497)* **reported that progesterone reduced the incidence of mammary cancers caused by a carcinogen administered in vegetable oil.**

I don't think it's possible that anyone could read articles like this, **that don't even claim to show that progesterone causes cancer,** and conclude that they provide evidence of progesterone's carcinogenicity. **The choice of "evidence" seems to have been a selection of titles of unread articles.** And even the title of the 1999 IARC volume would have suggested to most people that it wasn't a review of progesterone.

The lack of vehicle controls in some of the studies, the use of an unnamed vehicle in one beagle study, and the use of tumor-promoting vehicles in most if not all of the studies, means that no scientifically competent or valid studies have been cited by IARC, NTP, or the California state bureaucracy, OEHHA, to support California's claim that they know progesterone is a carcinogen.

In their 2004 document, OEHHA mentioned 17 articles that had been submitted regarding progesterone's protective effects. Some of these were identified**;** two were egregiously misrepresented in a single sentence**:**

Plu-Bureau, et al., were said to have reported "no association between breast cancer risk and progesterone topically applied for the treatment of mastalgia and benign breast disease..." What Plu-Bureau, et al., said immediately following that was "Although the **combined treatment of oral progestogens with percutaneous progesterone significantly decreased the risk of breast cancer (RR = 0.5; 95% confidence interval 0.2-0.9) as compared with nonusers,** there was no significant difference in the risk of breast cancer in percutaneous progesterone users versus nonusers among oral progestogen users." (RR means "relative risk," or "risk ratio," and 0.5 means a 50% reduction in risk.)

Cowan, et al. (1981), according to the OEHHA document, reported "reduced premenopausal breast cancer in women who had a history of progesterone deficiency." What they actually said was "These women were categorized as to the cause of infertility into 2 groups, those with endogenous progesterone deficiency (PD) and those with nonhormonal causes (NH). Women in the PD group **had 5.4 times the risk of premenopausal breast cancer** as compared to women in the NH group. This excess risk could not be explained by differences between the 2 groups in age at menarche or age at menopause, history of oral contraceptive use, history of benign breast diseases, or age at 1st birth. **Women in the PD group also experienced a 10-fold increase in deaths from all malignant neoplasm** compared to the NH group."

Ending the paragraph that mentioned those studies, the California document continues: "However, there is also evidence that progesterone may have a mitogenic effect. For example, Soderqvist et al. (1997) found that in breast cells of healthy women, cell proliferation was correlated with serum progesterone levels, thereby suggesting a proliferative action of progesterone."

Such a suggestion is not made by that "correlation." The authors said, "Our objective was to assess proliferation in normal breast epithelial cells from healthy women during the follicular and luteal phases of the menstrual cycle." At the beginning of the luteal phase, **both** estrogen and progesterone normally rise several-fold, so the small increase in proliferative rate also correlates with estrogen levels. A "defective luteal phase" is common, in which the ratio of estrogen to progesterone is high, and in that case progesterone's well established antiproliferative, differentiative effect will be overridden by estrogen's proliferative stimulation.

The state's reviewers didn't comment on the studies which showed that progesterone, besides inhibiting proliferation, also inhibits an "oncogene" which is associated with cancer, rather than just with proliferation. Instead, they cited a meaningless "correlation" as if it were some kind of argument against progesterone's anticancer effects. The authors of this document don't seem to know very much about the biology of cancer, but maybe they know too much about the issue of the proliferation of breast epithelium.

In a paragraph "rebutting" the petitioner's point that "This new research supports that exogenous progesterone actually ***reduces*** the risk of breast cancer in humans," the authors don't mention that point at all, but instead refer to cancer treatment and to the various claims relating to progesterone's carcinogenicity, ending with the mention of "studies that suggest progesterone stimulates cell proliferation (e.g., Soderqvist et al., 1997)." Apparently the authors had no answer to the petitioners' point, and preferred to talk about proliferation of breast cells.

Nearing the end of the document, the authors say "The NCI also reports on other studies of estrogens with **progestins,** which would suggest that **progesterone** increases the risk of human breast cancer," and then quotes comments on studies of estrogens with (synthetic) progestins. The authors cite two more studies with synthetic progestins, and then say "As discussed above, the mammary gland was a main target site in animal cancer bioassays providing the basis for the IARC and NTP identification of progesterone as carcinogenic." (The preceding discussion had mentioned the 4 year beagle study--which ended the careers of the researchers--and a 1993 publication by Kordon, et al., which had no control group for reference, and instead compared progesterone with different doses of medroxyprogesterone acetate, finding that the fewest tumors occurred in the progesterone group.*)

The techniques of distortion, diversion and evasion in this document are so obvious that any college composition teacher would have returned it to the student for revision. The document says much more about its authors than about its subject.

I think this bureaucratic behavior is understandable only if you know the composition of the group that is responsible for the progesterone listing, because the proliferation of breast cells has become an important issue for the group around USC professor Malcolm Pike.

Around 1980, Malcolm Pike, a statistician from South Africa, working in epidemiology, began arguing that the use of oral contraceptives prevented cancer. This epidemiologist, unfamiliar with steroid physiology except as it filtered through the oral contraceptive industry, decided that progesterone was the primary cause of breast cancer, by ***stimulating*** cell division and increasing the tissue density of the breast.

This line of reasoning gained adherents in the USC Keck School of Medicine, despite an overwhelming amount of contrary evidence, accumulated over more than 50 years, that progesterone protects against breast cancer, partly by ***inhibiting*** cell division, and that increased breast density is significantly associated with breast mitogens, such as serum insulin-like growth factor-I (IGF), prolactin, and estrogens, rather than with progesterone.

Breast mitogens correspond to both breast density and the risk of breast cancer (Boyd), but progesterone (antimitogen) corresponds to factors associated with **low risk** of breast cancer**.** Progesterone may reduce breast density by inhibiting some growth factors, including IGF, NO (nitric oxide), VEGF (vascular endothelial growth factor), bcl-2 (a protein that inhibits apoptosis), polyamines, and prostaglandins.

Much of the research at USC's Keck School has been generously funded by pharmaceutical companies with huge interest in estrogen-related products. The medical school website has articles by their faculty that give the impression that they are often more concerned with the fate of the estrogen market than with the science they claim to be doing. For example, commenting on the WHI evidence showing that estrogen helps to cause Alzheimer's disease, professor B.E. Henderson said "I continue to believe that estrogen therapy may help reduce a woman's risk of developing Alzheimer's disease **. . . ."** I noticed that there were hundreds of other estrogen-related items on the USC website.

The medical school, some of its professors, government agencies, and private companies are involved in some very complex, overlapping activities that give the impression of what used to be called "conflicts of interest."

The Keck School (a private institution), and the company, Balance Pharmaceuticals, Inc., controlled by three of their professors, participate in the business promotion organization operated by the State of California, Larta Institute, which manages Project T2, which is part of a "commercialization" system, involving awards of federal government money**:** "The organization will provide the awardees with assistance in all aspects of commercialization, including business development, funding and capital acquisition, **government regulatory processes,** intellectual property protection, licensing strategies, and merger and acquisition opportunities. SBIR Phase II is the research and development stage of the well-known program, with award sizes typically starting at $750,000 each." "Working with one of the Federal government's largest and most important agencies to assist SBIR awardees on the cusp of commercialization is a natural extension of everything we've done for the past ten years," said Larta Institute CEO Rohit Shukla.

Besides the issue of giving public money to private groups to commercialize ideas, many of which were developed using government-funded research, adding assistance with &ququot;government regulatory processes" to the help given to private corporations should arouse suspicions. The idea of "privatization" is given a new dimension**:** It's all for the insiders, without the usual lip-service paid to "competition."

On California's committee that chooses chemicals to put on their list of "known carcinogens" is Juliet Singh, who is the chief executive of **Trans Pharma Corporation**, a company that is developing transdermal drug delivery systems, for example for giving hormones by applying them to the skin. Under California's law, chemicals on the carcinogen list may to sold as drugs without a warning.

On the committee with Singh are Anna Wu and Thomas Mack, who co-authored several papers with Malcolm Pike, who was the most visible promoter of the campaign against progesterone, and who with two other USC professors controls Balance Pharmaceuticals, Inc., which is being promoted by Larta Institute, and that's planning to market a contraceptive based on the idea of suppressing progesterone. Three USC professors are on California's carcinogen committee, more than from any of the other universities in the state.

In a jury trial, I think this would look like a tainted jury.

Comparing the California agency's parody of legitimate process in this instance with its reconsideration in 2002 of its listing of saccharin as a carcinogen is illuminating. In that case, there was at least a pretense that the staff had made an attempt to provide "all relevant scientific evidence" for the committee to review, as specified by the agency's regulations. And in its decision, the State's Qualified Experts made a point of declaring, according to the language of the law, that in the opinion of the state's qualified experts it had not been "clearly shown through scientifically valid testing according to generally accepted principles to cause cancer." The Committee found that, in this case, it had to use a "'weight of evidence' approach to evaluate the body of information available...."

Unfortunately, the committee allowed some bizarre speculations about calcium phosphate to outweigh the fact that saccharin is a mild carcinogen, and in evaluating the rat experiments they were in such a hurry to remove saccharin from the list that they neglected to notice that calcium phosphate precipitation isn't unique to rat urine, but very commonly occurs in human urine. Their decision to remove it from the list rested on that non-fact.

Although the agency cited 150 studies, and went through the formality of describing some of them in their document, anyone

reading the document justifying the delisting of saccharin, and the document rejecting the delisting of progesterone, will find it hard to see a principle of law that could justify removing a carcinogen from the list, because of uncertainty regarding the mechanism by which it causes cancer, and keeping progesterone on the list, despite overwhelming evidence that it protects against cancer, and a great amount of evidence regarding the mechanisms through which the protection occurs.

The committee of experts who "weighed" speculations about calcium phosphate in the 2002 saccharin document, chose not to consider, either in 1987 or 2004, any of the hundreds of empirical studies showing progesterone's protective anticancer effects. The committee "considered" approximately half of all research publications on saccharin and cancer, and fewer than 1% of those relating to progesterone and cancer. Something other than scientific objectivity must explain those differences.

The agency in charge of those processes of evaluating evidence of carcinogenicity declines to identify the people who made those possibly biased, certainly bizarre, selections of articles, or to list their qualifications for being in the crucial position of deciding what evidence would be provided to the Scientific Advisory Panel. And in the list of studies that the committee did receive, are two (Kwapien, et al., and Yager and Yager) that are about completely different chemicals, that the agency still identifies as evidence of progesterone's carcinogenicity.

Many progesterone products have been taken off the market because of California's warning signs and labels, and as a result many women are having to rely on their physicians for progesterone. Too many physicians know only what the pharmaceutical companies want them to know about progesterone and other hormones that had been available for decades in places such as health food stores.

An article in JAMA (Marcia Stefanick, April 11, 2006) was summed up by Stefanick in a way that seems designed to encourage physicians to return to prescribing estrogen**:** "In the estrogen and progestin trial those women who got on the active pills, we saw an increase in breast cancer within five years. In the case of estrogen only, we not only do not see an increase by 7 years, but there's actually a suggestion of a decrease." That is a serious misrepresentation of the study.

The recently reported (December 15, 2006) decline of breast cancer incidence, coinciding with the great decrease in the use of menopausal estrogen treatments, also coincided with an increased use of natural progesterone, but if the lawyers, bureaucrats, and agents of the estrogen industry succeed in convincing the public that progesterone is carcinogenic, its use will decline, and breast cancer incidence could be expected to increase again.

The studies that show cancer prevention by progesterone have, over the years, failed to resonate in the medical culture. The confusion created by classifying the antiprogestational, carcinogenic synthetics as "progestins" is largely responsible for the failure to understand the protective nature of progesterone.

If the evidence showing that progesterone prevents or cures cancer could be weighed against the evidence purporting to show that it is carcinogenic, I think it would be clear that something like a cultural-commercial misogyny has been at work. The novelty of the newer misogyny is that it is so often led, or at least figureheaded by women.

*Note: Compare the results of Kordon, et al., 1993, with the later results of Aldaz, et al.:

Kordon, et al., reported 58% of the animals had tumors in the group receiving low dose MPA pellets, 98% in the high dose MPA group.

Aldaz, et al., 1996, wrote "The synthetic progestin medroxyprogesterone acetate (MPA) was postulated by some authors to increase mammary tumor incidence in various rodent models. However, controversy exists regarding the role of MPA in experimental and human carcinogenesis." **"MPA by itself did not produce any mammary tumors."**

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