Preventing and treating cancer with progesterone

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

> "The energy of the mind is the essence of life."
> — Aristotle

All through the last century, as more and more resources were devoted to solving "the cancer problem," the death rate from cancer increased every year. Something was clearly wrong with the way the problem was being approached.

If you grind up a computer and dissolve it in acid, you can find out exactly what substances it was made of, but you won't learn from that information how the computer worked. Twentieth century biologists became fond of emulsifying cells and studying the soluble parts. By the end of the century, they had identified so many parts that the government was financing projects to use supercomputers to try to understand how the parts interacted.

If some essential information was lost in studying the parts, supercomputation isn't the way to find it. Even with infinite computing capacity, a description of the electrons on carbon and hydrogen atoms on amino acids in protein molecules won't lead to the reality of how those atoms would have functioned in the living state.

The image of a cell as a watery solution contained in an elastic membrane bag is still having a radically stupefying effect on biology and medicine. The idea that a cell can be understood by using a computer to model a network of interactions between genes and gene products is nothing more than a technologizing of the primitive understanding of life that was promulgated by the Weismann-Mendel-Morganist school. It was the dogmatic insistence of that genetic determinist school that cancer originated with a genetic mutation.

By the middle of the 20th century, that dogma had excluded the most important parts of biology from the schools and the journals. Ideas of a developmental field, cellular coherence, and holistic cooperativity were denounced as unscientific vitalism. Returning to the idea of a "cancer field" is an essential first step in thinking realistically about preventing and treating cancer, but that idea has hardly progressed since the 1930s.

In the last few years, interest in cloning and stem cells and tissue regeneration has revived interest in studying the factors that contribute to the spatial and temporal ordering of cell growth.

The idea of a developmental field was a fundamental part of embryology in the first half of the 20th century. It was an empirical idea, supported most commonly by evidence that diffusing substances and secreted materials governed the differentiation of cells and tissues, but the form-generating effects of bioelectric fields were also often demonstrated, and there was some evidence that tissue radiations played a role. The extracellular matrix secreted by cells served to transmit information between cells, but its form was regulated by cells, and its structure was a factor governing the cells' differentiation.

Experiments in amphibians showed that regeneration of organs had a reciprocal relationship with the development of cancer--a tumor could be turned into a tail, for example, if it was grafted onto the stump following amputation of the tail, but factors that weakened regeneration could cause a tumor to develop. In these experiments, the normal organism's morphogenetic or epimorphic field overrode the disordered developmental field of the tumor.

In the absence of overriding external influences, the disordered system of the tumor, in which cells emitted many products of their disordered metabolism, could interfere with the normal functions of the organism. All of the products of the injured cells, including their altered extracellular matrix, constituted the cancer field.

The recent recognition of the "bystander effect" of radiation exposure, in which cells that haven't been irradiated undergo genetic changes or death when they are exposed to irradiated cells, has provided an opportunity to return to the "field" idea in cancer, because the stress-induced factors emitted by irradiated cells are the same toxic factors emitted by cells undergoing carcinogenesis from other causes, such as over-exposure to estrogen.

H. J. Muller, one of T. H. Morgan's students and colleagues, studied the mutagenic effects of x-rays, and the genetic determinists argued that the random changes produced in the genetic material by ionizing radiation provided a model of the evolutionary process. Randomly altered genes and natural selection would explain everything, including cancer. Every time cells divide, their genes supposedly become more susceptible to random changes, so increased replication of cells would increase the risk of producing genetic changes leading to cancer. This idea is so simple and so widely believed that many people focus only on the rate of proliferation, and the random mutations that supposedly occur during proliferation, when they try to explain carcinogenesis. They feel that it's reasonable to discuss cancer without bothering to understand the physiology of the cell or the organism.

The organism can only be understood in its environments, and a cell can't be understood without reference to the tissue and organism in which it lives. Although the geneticists were at first hostile to the idea that nutrition and geography could have anything to do with cancer, they soon tried to dominate those fields, insisting that mutagens and ethnicity would explain everything. But the evidence now makes it very clear that environment and nutrition affect the risk of cancer in ways that are not primarily genetic.

Every tumor, like every person, has a uniqueness, but valid and practical empirical generalizations can be made, if we understand some of their properties and the conditions that govern their development and survival.

Percival Potts' observation of scrotal cancer in chimney sweeps eventually led to the study of soot carcinogenesis, and then to the study of the properties of the polycyclic aromatic hydrocarbons in soot. The similarities of those properties to estrogen's soon became apparent.

Over the decades, many studies have confirmed that prolonged, continuous exposure to estrogen is carcinogenic, and that progesterone offsets those effects.

Following the animal studies that showed that carcinogenesis by estrogen could be prevented or reversed by progesterone, studies of the endogenous hormones in women showed that those with a natural excess of estrogen, and/or deficiency of progesterone, were the most likely to develop uterine or breast cancers.

The Morganist school of genetic determinism moved into endocrinology with a doctrine that hormones act only through hormone receptors, proteins which activate certain genes.

Many researchers -- physical chemists, biochemists, cytologists, embryologists, reproductive and developmental biologists, gerontologists, physiologists, neurologists, endocrinologists -- were investigating estrogen's properties and actions, and had made great progress by the 1950s, despite the medical frauds being perpetrated by the estrogen industry (Rothenberg, 2005).

All of this complex and subtle work was of no interest to a small group of people who wanted to impose their genetic views onto biology.

The inventor of the estrogen receptor, Elwood Jensen, has written that the results of certain of his experiments "caused the demise of the transhydrogenation hypothesis and convinced all but the most diehard enzymologists that estradiol binds to a characteristic component of target cells to exert its physiological effect without itself being chemically altered." The hypothesis he referred to was just part of a large fairly systematic international effort.

How he did away with the opposition, who were studying the complex metabolic actions of estrogen, was by synthesizing isotope-labeled estradiol and estrone, and claiming to observe that they weren't metabolically altered, as they produced their hormonal effect. Since the experiment was extremely expensive, and required the cooperation of the Atomic Energy Commission, it wasn't easily repeated. However, many experiments have subsequently demonstrated that practically every tissue in the body (and plants and bacteria) metabolize the estrogens, causing estradiol to change into estrone, and estrone, into estradiol. Jensen's decisive and historically crucial experiment was false.

But it served its purpose, and (with help from the pharmaceutical industry and government granting agencies) marginalized the work of those "enzymologists" and everyone else who persisted in studying the complex actions of estrogen.

The enzyme that converts the weaker estrone into the stronger estradiol is an important factor in determining estrogen's effects on a particular tissue. Progesterone is able to regulate the cell's metabolism, so that the oxidative pathway, forming estrone from estradiol, predominates. Estrogen-dominated tissues are likely to have a balance in the direction of reduction rather than oxidation, increasing the amount of the active estradiol.

The immediate effects of estrogen and progesterone on cells, that occur long before genes can be activated, were simply ignored or denied by the promoters of the estrogen receptor doctrine. Some of these excitatory or antiexcitatory effects are probably structural changes, that involve the mobilization of calcium inside cells, and the activation or inhibition of reactions involving phosphoric acid. Although they have been known for many years, they are always referred to as "novel" or "non-classical" effects, and are called "membrane effects," because that's the only way the reductionists are able to identify changes that happen immediately throughout the cell.

Cellular excitation involves an increase of intracellular calcium and the activation of phosphorylating enzymes in cells. Some experiments suggest (Improta-Brears, et al., 1999) that the estrogen receptor mediates estrogen's ability to mobilize calcium (leading to the activation of cell division, mitosis). Whether or not it does, the recognition that estrogen activates calcium, leading to activation of the phosphorylation system, should "cause the demise of" the "classical estrogen receptor" doctrine, because the phosphorylation system alters the expression of genes, much as the estrogen receptor was supposed to do by its direct actions. **But before it alters the expression of genes, it alters the activities of enzymes.** When estrogen activates calcium and phosphorylation independently of the estrogen receptor, the situation is even worse for the Jensen dogma.

Progesterone's opposition to those early excitatory effects of estrogen are so basic, that there shouldn't be any difficulty in thinking of it as an antiestrogen, that stops cell division primarily by opposing the excitatory effects of estrogen and other mitogens. Progesterone's opposition to the calcium-activating and phosphorylating effects of estrogen affects everything in the cell, according to the cell's specific nature.

But the reductionists don't like "nongenomic" explanations of anything, even when they are triggered by the estrogen receptor rather than by a membrane-event. So, to argue that progesterone's opposition to estrogen is general, it's necessary to examine each of estrogen's actions, where those actions are clearly known, and to evaluate progesterone's effects on the same events.

When a cell is stimulated or slightly stressed, homeostatic mechanisms are activated that help it to return to its normal resting state. The mobilization of calcium and the phosphorylation system is followed by increased synthesis of cholesterol and the formation of glucose from glycogen. Cholesterol itself is protective, and in some cells it is massively converted into progesterone, which is even more effective in restoring homeostasis.

In the ovary, the enzymes that synthesize cholesterol, along with the production of progesterone, are activated by the

pituitary hormone, FSH, but also by estrogen. In the liver and uterus and vascular endothelium, which aren't specialized for the production of progesterone, stimulation by estrogen activates the enzymes to increase the formation of cholesterol.

When cells are injured or seriously stressed, instead of being able to directly recover their normal quiescence, they may instead mobilize their systems for growing and replicating, to replace damaged or destroyed cells.

Prolonged exposure to estrogen, that can't be offset by the homeostatic factors, such as progesterone, typically causes cells to enter a growth phase. (But so do other excitatory processes, such as ionizing radiation.)

One of the basic reactions to injury is to shift the cell away from oxidative metabolism to glycolytic metabolism, which is inefficient, but can support cell division. Chemical stains show that during cell division cells are in a reduced state, with abundant sulfhydryl groups including reduced glutathione and protein sulfhydryls. This shift in itself increases the formation of active estradiol from estrone.

In the inflamed or estrogen dominated cell, enzymes such as the cyclooxidases (COX), that convert arachidonic acid into prostaglandins, are activated. Beta-glucuronidase and sulfatases are activated, and these cause intracellular estrogen to increase, by removing the water soluble sulfate and glucuronate portions from estrogens that had been inactivated. The detoxifying enzymes that attach those molecules to estrogen are inactivated in the estrogen dominated cell. The prostaglandin formed from arachidonic acid stimulates the formation of the enzyme aromatase or estrogen synthetase, that converts androgens into estrogen.

Those processes, initiated by excitation or injury, increase the amount of estrogen in the cell, which intensifies the excitation.

Progesterone opposes all of those processes, decreasing the amount of estrogen in the cell by modifying the activities of those five types of enzyme.

Although many kinds of protein (including enzymes) bind estrogen, the protein that Jensen called "the estrogen receptor" is largely responsible for the ability of the uterus and breasts to retain high concentrations of estrogen. Various kinds of stimulation or stress (including heat and oxygen deprivation) cause its appearance, and estrogen itself increases the amount of the estrogen receptor in a cell. The estrogen receptor doesn't just "activate genes," as the Jensen dogma claimed. For example, the estrogen receptor directly binds and inactivates the "tumor suppressor" p53 protein, which otherwise would restrain the replication of damaged cells.

Progesterone causes the estrogen receptor to be eliminated. (Batra; Boling and Blandau; Resko, et al.)

Among the cell activating factors, other than estrogen, are proteins that are considered to be "oncogenes," because of their involvement in cancer. Several of these proteins are activated by estrogen, inhibited by progesterone. The term "oncogene" refers to any gene that contributes to the development of cancer, but it is so burdened by ideology that it shouldn't be used as if it had a simple clear meaning.

A variety of proteins promote cell activity and replication, under the influence of estrogen. The "composite transcription factor activating protein 1," AP-1 which integrates the effects of other transcription factors, is important in a variety of cell types, and its activity is increased by estrogen and decreased by progesterone.

When the "progesterone receptor" **lacks progesterone,** it has the opposite effect of progesterone, and this feature has been used propagandistically, by infecting cells with a virus carrying the progesterone receptor protein, and then suggesting that the disturbed functions of the cell reflect a potential effect of progesterone. The receptor, lacking progesterone, tells the cell that it has a progesterone deficiency, but too many molecular endocrinologists are trying to say that the receptor protein is the same as the progesterone.

The generality of the process of excitation/activation can be clearly seen in the effects of the nerve-inhibiting GABA and the nerve-exciting glutamate or NMDA. In cultured breast cancer cells, GABA inhibits growth, NMDA increases growth. As in the brain, progesterone supports the actions of GABA, and opposes those of NMDA or the excitatory amino acids, while estrogen in general promotes the effects of the excitatory amino acids, and opposes those of GABA.

Both the excitatory amino acids and a peptide that promotes inflammation, tumor necrosis factor (TNF), activate the enzyme which makes estrogen, aromatase. Estrogen, by activating NF kappaB, increases the formation of TNF, which in itself can promote the growth and metastasis of cancer. Various antiinflammatory agents, including aspirin, progesterone, testosterone, saturated fats, and glycine, can inhibit the production of NF kappaB.

An enzyme that has been thought of mainly in relation to the brain is catechol-O-methyl transferase, which is inhibited by estrogen (producing effects similar to cocaine), leading to brain excitation.The enzyme detoxifies catecholestrogen (Creveling, 2003), protecting cells from DNA damage (Lavigne, et al., 2001). When the activity of this enzyme is low, there is increased risk of breast cancer (Matsui, et al., 2000). Progesterone increases its activity (Inoue and Creveling, 1991, 1995).

Another enzyme system that affects the body's reactions to stress and modifies processes of inflammation and growth, the monoamino-oxidases, is affected oppositely by estrogen and progesterone. Estrogen's effects are partly mediated by increased formation of serotonin, progesterone's, by decreasing it. Histamine is another promoter of inflammation that is increased by estrogen, decreased by progesterone.

Estrogen's effects in the nervous system go beyond the production of cocaine-like hypomania, or chorea, or epilepsy, and include the activation of the basic stress hormones, increasing the formation in the hypothalamus of pro-opiomelanocortin (POMC), which is a precursor of ACTH to activate the adrenals, and endorphins ("endogenous opiates"), which stimulate growth processes. Both endorphins and ACTH can be found in tumors such as breast cancer. The ACTH stimulates the

production of cortisol, that protects against some of the immediate causes of inflammation and growth, but that contributes to the loss of resistance, and increases estrogen synthesis.

A protein called the sigma receptor, known for its role in cocaine's action, binds progesterone, and can inhibit the growth of cancer. Some anesthetics have similar effects on tumors, acting through this protein. The sigma receptor, in association with progesterone or pregnenolone, is protective against the excitatory amino acids.

The extracellular medium changes during the development of a tumor. Irritated hypoxic cells, and estrogen-stimulated cells, increase their production of collagen, and the increase of collagen interferes with normal cell functions. Progesterone reduces the formation of collagen, and probably contributes to its removal.

Naloxone or naltrexone, which blocks the actions of the endorphins and morphine, is being used to inhibit the growth of various kinds of cancer, including breast cancer and prostate cancer. Leptin (which is promoted by estrogen) is a hormone produced by fat cells, and it, like estrogen, activates the POMC-related endorphin stress system. The endorphins activate histamine, another promoter of inflammation and cell division.

Progesterone opposes those various biochemical effects of estrogen in multiple ways, for example by inhibiting the ACTH stress response, by restraining cortisol's harmful actions, and by inhibiting leptin.

Mediators of the radiation bystander effect include NO, TNF, COX, and prostaglandins. These are produced by other things that cause inflammation and injury, including estrogen.

Cell division, when it is part of the body's continuous renewal and adaptation, isn't a source of mutations or degeneration, but when it is induced by the mediators of inflammation produced in response to injury, it leads to inherited changes, loss of differentiated function, and eventually to genetic instability.

When cell division is so disturbed that the number of chromosomes becomes abnormal, the instability of these cells decreases their ability to survive, but when the causes of the inflammation persist, they will continue to be replaced by other abnormal cells. The toxic products of dying cells can reach a point at which the debris can't be removed, adding to the injury and inflammation. The damaged bystander cells spread their influence through a cancer field, injuring more cells.

One of the "field" effects of cancer is the stimulation of new blood vessel development, angiogenesis. Lactic acid stimulates the formation of new blood vessels, the secretion of collagen, and tumor growth. Low oxygen, nitric oxide, carbon monoxide, prostaglandins and other products of tissue stress can stimulate the growth of new blood vessels, at the same time that they stimulate tumor growth and impair oxidative metabolism. Several of these agents promote each other's activity.

Therapeutic thinking has been influenced by the doctrine of the mutant cell as the initiator of cancer, leading to the idea that only things which kill the cancer cells can cure cancer. But when the body stops activating the processes of inflammation and growth, normal processes of tissue repair have an opportunity to eliminate the tumor. Even the fibroblasts which normally secrete collagen can participate in its removal (Simoes, et al., 1984). Something as simple as eliminating lactate can change their functions.

Although the angiogenic action of lactate has been known for several decades, some researchers believed that a specific anti-angiogenic peptide could be found which would stop the growth of cancer cells. The interest in angiogenesis tacitly acknowledges that there is a cancer field, but the faith that cancer could be cured only by killing the mutant cells seems to have guided the search for a single antiangiogenic substance. Such a substance would be toxic to normal tissues, since blood vessels are constantly being renewed.

The more advanced a tumor is, the more numerous the growth-promoting factors are likely to be, and the weaker the body's ability becomes to control them.

The search for toxic factors to kill the cancer cells is unlikely to lead to a generally effective treatment. Even immunological approaches that think in terms of destroying a tumor might be misconceiving the nature of the problem. For example, the protein called "tumor necrosis factor" (TNF) or cachectin was discovered as a result of Lawrence Burton's work in the 1960s. He extracted proteins from the blood that could shrink some tumors in mice with amazing speed. In the right setting, TNF is involved in the destruction of tumors, but when other factors are missing, it can make them worse. Burton was focussing on factors in the immune system that could destroy cancer, but he ignored the basic problem of tissue degeneration that produces tumors which are complex and changing.

If the cancer-productive field is taken into account, all of the factors that promote and sustain that field should be considered during therapy.

Two ubiquitous carcinogenic factors that can be manipulated without toxins are the polyunsaturated fatty acids (PUFA) and estrogen. These closely interact with each other, and there are many ways in which they can be modulated.

For example, keeping cells in a well oxygenated state with thyroid hormone and carbon dioxide will shift the balance from estradiol toward the weaker estrone. The thyroid stimulation will cause the liver to excrete estrogen more quickly, and will help to prevent the formation of aromatase in the tissues. Low temperature is one of the factors that increases the formation of estrogen. Lactic acid, serotonin, nitric oxide, prostaglandins, and the endorphins will be decreased by the shift toward efficient oxidative metabolism.

Progesterone synthesis will be increased by the higher metabolic rate, and will tend to keep the temperature higher.

Thyroid hormone, by causing a shift away from estrogen and serotonin, lowers prolactin, which is involved in the promotion

of several kinds of cancer.

Vitamin D and vitamin K have some antiestrogenic effects. Vitamin D and calcium lower the inflammation-promoting parathyroid hormone (PTH).

Eliminating polyunsaturated fats from the diet is essential if the bystander effect is eventually to be restrained. Aspirin and salicylic acid can block many of the carcinogenic effects of the PUFA. Saturated fats have a variety of antiinflammatory and anticancer actions. Some of those effects are direct, others are the result of blocking the toxic effects of the PUFA. Keeping the stored unsaturated fats from circulating in the blood is helpful, since it takes years to eliminate them from the tissues after the diet has changed. Niacinamide inhibits lipolysis. Avoiding over-production of lipolytic adrenaline requires adequate thyroid hormone, and the adjustment of the diet to minimize fluctuations of blood sugar.

The endorphins are antagonistic to progesterone, and when they are minimized, progesterone tends to increase, and to be more effective. The drugs naloxone and naltrexone, which block the effects of the endorphins, have several remarkable effects that resemble progesterone's. Naltrexone has been successfully used to treat prostate and breast cancer.

Opiates are still commonly used for pain relief in cancer patients, despite the evidence that has accumulated for several decades indicating that they promote inflammation and cancer growth, while suppressing immunity and causing tissue catabolism, exacerbating the wasting that commonly occurs with cancer. Their use, rather than alternatives such as procaine, aspirin, and progesterone, is nothing but a medical fetish.

Stress and estrogen tend to produce alkalosis, while thyroid, carbon dioxide, and adequate protein in the diet help to prevent alkalosis.

Antihistamines and some of the antiserotonin drugs (including "dopaminergic" lisuride and bromocriptine) are sometimes useful in cancer treatment, but the safe way to lower serotonin is to reduce the consumption of tryptophan, and to avoid excessive cortisol production (which mobilizes tryptophan from the muscles). Pregnenolone and sucrose tend to prevent over-production of cortisol.

In the breast, COX-2 converts arachidonic acid into prostaglandins, which activate the enzyme aromatase, that forms estrogen from androgens. Until the tissues are free of PUFA, aspirin and salicylic acid can be used to stop prostaglandin synthesis.

Thyroid is needed to keep the cell in an oxidative, rather than reductive state, and progesterone (which is produced elsewhere only when cells are in a rapidly oxidizing state) activates the processes that remove estrogen from the cell, and inactivates the processes that would form new estrogen in the cell.

Thyroid, and the carbon dioxide it produces, prevent the formation of the toxic lactic acid. When there is enough carbon dioxide in the tissues, the cell is kept in an oxidative state, and the formation of toxic free radicals is suppressed. Carbon dioxide therapy is extremely safe.

In the 1930s, primates as well as rodents had been used in experiments to show the carcinogenic effects of estrogen, and the protective effects of progesterone.

By 1950, the results of animal studies of progesterone's anticancer effects were so clear that the National Cancer Institute got involved. But the estrogen industry had already been conducting its campaign against progesterone, and had convinced most doctors that it was inactive when taken orally, and so was inferior to their proprietary drugs that they called "progestins." The result was that it was usually given by injection, dissolved in vegetable oil or synthetic solvents such as benzyl benzoate or benzyl alcohol, which are very toxic and inflammation-producing.

The NCI researchers (Hertz, et al., 1951) treated 17 women with visible cancers of the uterine cervix that had been confirmed by biopsies. They were given daily intramuscular injections of 250 mg of progesterone in vegetable oil. Although they described the treatment as "massive dosage with progesterone," it didn't prevent menstruation in any of the women who had been menstruating before the treatment began. During a healthy pregnancy, a woman produces more progesterone than that.

Their article includes some photographs of cervical tumors before treatment, and after 31 days, 50 days, and 65 days of progesterone treatment. The improvement is clear. The examining physicians described softening of the tumor, and stopping of bleeding and pain.

"In eleven of the 17 treated patients visible and palpable evidence of regressive alteration of the tumor mass could be demonstrated. This consisted of (a) distinct reduction in size of the visible portion of the cancer as well as reduction of the palpable extent of the mass, (b) reduction in vascularity and friability of the visible lesion with a clearly demonstrable epithelization of previously raw surfaces and (c) markedly increased pliability of the previously rigid and infiltrated parametria."

"In 10 cases there was associated with this type of gross change a reduction in, or complete cessation of vaginal bleeding and discharge."

"Only one of the 17 patients showed active progression of the carcinomatous process while under the progesterone administration. The six patients whose lesions failed to show clearly demonstrable regressive changes showed minor alterations in size and vascularity of insufficient degree to be convincing to all clinical observers concerned. Nevertheless, none of the lesions under study appeared to be accelerated by progesterone."

Observing very similar patients under similar conditions while they were waiting for surgery, but were not receiving progesterone, they saw no such regressions of tumors.

The photographs and descriptions of the changes in the tumors were remarkable for any cancer study, but to have been produced by a treatment that didn't even alter the patients' menstrual cycle, the reader might expect the authors to discuss their plans for further studies of such a successful method.

But instead, they concluded "We do not consider the regressive changes observed to be sufficient to indicate the use of progesterone as a therapeutic agent in carcinoma of the cervix."

(Their research was supported by a grant from the American Cancer Society.)

If the researchers had bothered to test progesterone on themselves or on animals, they would have discovered that it is fully active when taken orally, dissolved in oil, and that nontoxic saturated fats could have been used. Progesterone anesthesia was very well known at that time, so it would have been reasonable to use doses that were at least equivalent to the concentrations present during pregnancy, even if they didn't want to use doses that would approach the anesthetic level. The total daily doses could have been about ten times higher, if they had been given orally as divided doses.

The solvent issue continues to impede research in the use of progesterone for treating cancer, but the main problem is the continuing belief that "the cancer cell" is the problem, rather than the cancer field. Substances are tested for their ability to kill cancer cells *in vitro*, because of the basic belief that mutated genes are the cause of the disease. When progesterone is tested on cancer cells *in vitro,* the experimenter often sees nothing but the effects of the solvent, and doesn't realize that nearly all of the progesterone has precipitated in the medium, before reaching the cancer cells.

The cancer industry began a few years ago to combine chemicals for chemotherapy, for example adding caffeine to paclitaxel or platinum (cisplatin), or histamine to doxorubicin, but they do it simply to increase the toxicity of the chemical to the tumor, or to decrease its toxicity to the patient. Doctors sometimes refer to combined chemotherapy as a "shotgun approach," meaning that it lacks the acumen of their ideal silver bullet approach. If cancers were werewolves, the cancer industry's search for more refined killing technologies might be going in the right direction. But the genetic doctrine of cancer's origin is just as mythical as werewolves and vampires.

A safe physiological approach to cancer, based on the opposition of progesterone to estrogen, would be applicable to every type of cancer promoted by estrogen, or by factors which produce the same effects as estrogen, and that would include all of the known types of cancer. Estrogen acts even on cells that have no "estrogen receptors," but estrogen receptors can be found in every organ.

As estrogen's non-feminizing actions are increasingly being recognized to include contributions to other kinds of disease, including Alzheimer's disease, heart disease, and rheumatoid arthritis, the idea of the bystander effect, and the field of cellular degeneration, will eventually clear the way for a rational use of the therapeutic tools that already exist.

There are several types of drug---carbonic anhydrase inhibitors, to increase carbon dioxide in the tissues, lysergic acid derivatives, to block serotonin and suppress prolactin, anti-opiates, antiexcitotoxic and GABAergic agents, anesthetics, antihistamines, anticholinergics, salicylic acid derivatives---that could probably be useful in a comprehensive therapy for cancer, but their combinations won't be explored as long as treatments are designed only to kill.

Preventing or correcting disturbances in the morphogenetic field should be the focus of attention.

References

Biochem Biophys Res Commun. 1991 Mar 15;175(2):625-30. **Antitumor activity of naltrexone and correlation with steroid hormone receptors.** Abou-Issa H, Tejwani GA.

Contraception 1981 Apr;23(4):447-55. **Comparison of plasma and myometrial tissue concentrations of estradiol-17 beta and progesterone in nonpregnant women.** Akerlund M, Batra S, Helm G.

Obstetrics and gynecology New York 2001 vol.97 no.4 (Supplement) page S10. Topical progesterone cream has antiproliferative effect on estrogen-stimulated endometrium, Anasti, James N. Leonetti, H B. Wilson, K J.

Proc Natl Acad Sci U S A. 1996 Jun 11;93(12):6169-74. **Modulation of AP-1 activity by the human progesterone receptor in endometrial adenocarcinoma cells.** Bamberger AM, Bamberger CM, Gellersen B, Schulte HM.

J Gynecol Obstet Biol Reprod (Paris). 1990;19(3):269-74. **[The in vivo effect of the local administration of progesterone on the mitotic activity of human ductal breast tissue. Results of a pilot study]** Barrat J, de Lignieres B, Marpeau L, Larue L, Fournier S, Nahoul K, Linares G, Giorgi H, Contesso G. **"Mean mitotic activity was significantly lower in progesterone treated group (0.04/1,000 cells) than in placebo (0.10/1,000 cells) or in estradiol (0.22/1,000 cells) treated groups. High concentration of progesterone sustained in human breast tissue in vivo during 11 to 13 days does not increase, but actually decreases mitotic activity in normal lobular epithelial cells."** Randomized Controlled Clinical Trial

Clin Endocrinol (Oxf) 1979 Dec;11(6):603-10. **Interrelations between plasma and tissue concentrations of 17 beta-oestradiol and progesterone during human pregnancy.** Batra S, Bengtsson LP, Sjoberg NO

Endocrinology 1976 Nov; 99(5): 1178-81. **Unconjugated estradiol in the myometrium of pregnancy.** Batra S.

J Steroid Biochem 1989 Jan;32(1A):35-9. **Tissue specific effects of progesterone on progesterone and estrogen receptors in the female urogenital tract.** Batra S, Iosif CS.

Lancet. 1989 Oct 28;2(8670):1008-10. **Saturation of fat and cholecystokinin release: implications for pancreatic carcinogenesis.** Beardshall K, Frost G, Morarji Y, Domin J, Bloom SR, Calam J.

FASEB J. 2006 Oct;20(12):2009-16. **Therapeutic levels of aspirin and salicylate directly inhibit a model of angiogenesis through a Cox-independent mechanism.** Borthwick GM, Johnson AS, Partington M, Burn J, Wilson R, Arthur HM.

Br J Cancer. 2002 Oct 7;87(8):876-82. **The association of breast mitogens with mammographic densities.** Boyd NF, Stone J, Martin LJ, Jong R, Fishell E, Yaffe M, Hammond G, Minkin S.

Eur J Pharmacol. 1995 May 15;278(2):151-60. **Sigma binding site ligands inhibit cell proliferation in mammary and colon carcinoma cell lines and melanoma cells in culture.** Brent PJ, Pang GT.

Fertil Steril 1995; 63(4):785-91. **Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo.** Chang KJ, et al. The effect of transdermal estradiol (1.5 mg), transdermal progesterone (25 mg), and combined transdermal estradiol and progesterone (1.5 mg and 25 mg) on human breast epithelial cell cycles was evaluated in vivo. Results demonstrated that **estradiol significantly increases cell proliferation, while progesterone significantly decreases cell replication below that observed with placebo.** Transdermal progesterone was also shown to reduce estradiol-induced proliferation.

Br J Cancer. 1997;75(2):251-7. **Type I insulin-like growth factor receptor gene expression in normal human breast tissue treated with oestrogen and progesterone.** Clarke RB, Howell A, Anderson E. "The epithelial proliferation of normal human breast tissue xenografts implanted into athymic nude mice is significantly increased from basal levels by oestradiol (E2), but not progesterone (Pg) treatment at serum concentrations similar to those observed in the luteal phase of the human menstrual cycle." "The data indicate that the IGFR-I mRNA is up-regulated by two to threefold compared with untreated levels by 7 and 14 days E2 treatment. **In contrast, 7 or 14 days Pg treatment down-regulates the receptor mRNA to approximately half that of untreated levels,** whereas combination E2 and Pg treatment produced a twofold increase in IGFR-I mRNA levels compared with untreated tissue."

Brain Res. 2006 Dec 18;1126(1):2-26. **Functional significance of the rapid regulation of brain estrogen action: Where do the estrogens come from?** Cornil CA, Ball GF, Balthazart J.

Am J Epidemiol. 1981 Aug;114(2):209-17. **Breast cancer incidence in women with a history of progesterone deficiency.** Cowan LD, Gordis L, Tonascia JA, Jones GS. "Women in the PD [progesterone deficiency] group had 5.4 times the risk of premenopausal breast cancer as compared to women in the NH group." "Women in the PD group also experienced a 10-fold increase in deaths from all malignant neoplasm compared to the NH group."

Growth. 1975 Dec;39(4):475-96. **Cancer-related aspects of regeneration research: a review.** Donaldson DJ, Mason JM.

Int J Cancer. 1992 May 28;51(3):416-24. **Capacity of adipose tissue to promote growth and metastasis of a murine mammary carcinoma: effect of estrogen and progesterone.** Elliott BE, Tam SP, Dexter D, Chen ZQ. **"Estrogen can stimulate growth of SPI in adipose tissue sites, whereas progesterone inhibits growth."**

Breast Cancer Res Treat. 2002 Jul;74(2):167-76. **Regulation of MCF-7 breast cancer cell growth by beta-estradiol sulfation.** Falany JL, Macrina N, Falany CN.

Br J Cancer 1981 Aug;44(2):177-81. **Morphological evaluation of cell turnover in relation to the menstrual cycle in the "resting" human breast.** Ferguson DJ, Anderson TJ

Eur J Cancer. 1992;28A(6-7):1143-7. **Fatty acid composition of normal and malignant cells and cytotoxicity of stearic, oleic and sterculic acids in vitro.** Fermor BF, Masters JR, Wood CB, Miller J, Apostolov K, Habib NA.

Fertil Steril. 1998 May;69(5):963-9. **Estradiol and progesterone regulate the proliferation of human breast epithelial cells.** Foidart JM, Colin C, Denoo X, Desreux J, Beliard A, Fournier S, de Lignieres B. "Exposure to progesterone for 14 days reduced the estradiol-induced proliferation of normal breast epithelial cells in vivo." Randomized Controlled Trial

Mol Cell Biochem 1999 Dec;202(1-2):53-61. **Bcl-2, survivin and variant CD44 v7-v10 are downregulated and p53 is upregulated in breast cancer cells by progesterone: inhibition of cell growth and induction of apoptosis.** Formby B, Wiley TS."This study sought to elucidate the **mechanism by which progesterone inhibits the proliferation of breast cancer cells."** "The results demonstrated that progesterone does produce a strong antiproliferative effect on breast cancer cell lines containing progesterone receptors, and induced apoptosis. **The relatively high levels of progesterone utilized were similar to those seen during the third trimester of human pregnancy."**

Ann Clin Lab Sci 1998 Nov-Dec;28(6):360-9. **Progesterone inhibits growth and induces apoptosis in breast cancer cells: inverse effects on Bcl-2 and p53.** Formby B, Wiley TS.

Cancer Lett 1999 Jul 1;141(1-2):63-71. **Progestins suppress estrogen-induced expression of vascular endothelial growth factor (VEGF) subtypes in uterine endometrial cancer cells.** Fujimoto J, Sakaguchi H, Hirose R, Ichigo S, Tamaya T.

Mol Cell Biol. 2006 Oct;26(20):7632-44. **TReP-132 Is a Novel Progesterone Receptor Coactivator Required for the Inhibition of Breast Cancer Cell Growth and Enhancement of Differentiation by Progesterone.** Gizard F, Robillard R, Gross B, Barbier O, Revillion F, Peyrat JP, Torpier G, Hum DW, Staels B.

Am J Physiol. 1982 Oct;243(4):H619-27. **NAD/NADH: redox state changes on cat brain cortex during stimulation and hypercapnia.** Gyulai L, Dora E, Kovach AG.

Drug Metab Dispos. 1995 Mar;23(3):430-2. **Induction of catechol-O-methyltransferase in the luminal epithelium of rat uterus by progesterone: inhibition by RU-486.** Inoue K, Creveling CR.

Hertz R, Cromer J.K., Young J.P. and Westfall B.B., pages 366-374, in ***Symposium on Steroids in Experimental and Clinical Practice,*** Abraham White, Blakiston, 195.

Cancer Res. 2005 Jul 15;65(14):6450-8. **Progesterone receptor in non-small cell lung cancer--a potent prognostic factor and possible target for endocrine therapy.** Ishibashi H, Suzuki T, Suzuki S, Niikawa H, Lu L, Miki Y, Moriya T, Hayashi S, Handa M, Kondo T, Sasano H. "Cell proliferation was inhibited by progesterone in these progesterone receptor-positive NSCLC cells in a dose-dependent manner, which was inhibited by progesterone receptor blocker. Proliferation of these tumor cells injected into nude mice was also dose-dependently inhibited by progesterone, with a concomitant increase of p21 and p27 and a decrease of cyclin A, cyclin E, and Ki67. Results of our present study suggested that progesterone receptor was a potent prognostic factor in NSCLCs and progesterone inhibited growth of progesterone receptor-positive NSCLC cells. Therefore, progesterone therapy may be clinically effective in suppressing development of progesterone receptor-positive NSCLC patients."

Naunyn Schmiedebergs Arch Pharmacol. 1986 Aug;333(4):368-76. **Effect of progesterone on the metabolism of noradrenaline in rabbit uterine endometrium and myometrium.** Kennedy JA, de la Lande IS.

Agressologie 1971;12(2):105-112. **[The inhibiting effect of atmospheres oxygenated without CO2 on the respiration of rat tissue slices (brain, liver). Physiopathological implications].** Laborit H, Lamothe C, Thuret F

Am J Respir Crit Care Med. 2004 Jan 1;169(1):46-56. **Hypercapnic acidosis attenuates endotoxin-induced acute lung injury.** Laffey JG, Honan D, Hopkins N, Hyvelin JM, Boylan JF, McLoughlin P.

**Endocrinology. 1996 Apr;137(4):1505-6.*

[Comment on: Laidlaw, et al., Endocrinology. 1995 Jan;136(1):164-71.] ***Experiments on proliferation of normal human breast tissue in nude mice do not show that progesterone does not stimulate breast cells.*** *Pike MC, Ursin G, Spicer DV. Letter*

*Endocrinology. 1995 Jan;136(1):164-71. **The proliferation of normal human breast tissue implanted into athymic nude mice is stimulated by estrogen but not progesterone.** Laidlaw IJ, Clarke RB, Howell A, Owen AW, Potten CS, Anderson E. "We conclude that E2 is sufficient to stimulate human breast epithelial cell proliferation at physiologically relevant concentrations and that P does not affect proliferation either alone or after E2 priming."

Agressologie 1971;12(2):105-112. **[The inhibiting effect of atmospheres oxygenated without CO2 on the respiration of rat tissue slices (brain, liver). Physiopathological implications].** Laborit H, Lamothe C, Thuret F

Endocrinology. 1995 Jan;136(1):164-71. **The proliferation of normal human breast tissue implanted into athymic nude mice is stimulated by estrogen but not progesterone.** Laidlaw IJ, Clarke RB, Howell A, Owen AW, Potten CS, Anderson E.

Int J Cancer. 2005 Nov 20;117(4):561-8. **Gene regulation profile reveals consistent anticancer properties of progesterone in hormone-independent breast cancer cells transfected with progesterone receptor.** Leo JC, Wang SM, Guo CH, Aw SE, Zhao Y, Li JM, Hui KM, Lin VC.**"Progesterone consistently suppressed the expression of genes required for cell proliferation and metastasis and increased the expression of many tumor-suppressor genes."**

Fertil Steril. 2003 Jan;79(1):221-2. **Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium.** Leonetti HB, Wilson KJ, Anasti JN. Randomized Controlled Trial

Prostate. 1995 Apr;26(4):194-204. **Growth inhibition of androgen-insensitive human prostate carcinoma cells by a 19-norsteroid derivative agent, mifepristone.** Lin MF, Kawachi MH, Stallcup MR, Grunberg SM, Lin FF. "Mifepristone, also known as RU 486, is a 19-norsteroid derivative. Currently, mifepristone is being tested in clinical trials on meningioma and breast cancer."**"The results demonstrated that while both DHT and Dex alone had essentially no effect on cell growth, progesterone alone resulted in a 20% growth inhibition, while mifepristone had more than 60% inhibition with a 16-day exposure. At an equal concentration, the degree of growth inhibition of PC-3 cells by mifepristone or progesterone was partially diminished by simultaneous exposure to Dex."**

Am J Pathol. 2003 Jun;162(6):1781-7. **Progesterone induces cellular differentiation in MDA-MB-231 breast cancer cells transfected with progesterone receptor complementary DNA.** Lin VC, Jin R, Tan PH, Aw SE, Woon CT, Bay BH.

Endocrinology. 2003 Dec;144(12):5650-7. **Distinct molecular pathways mediate progesterone-induced growth inhibition and focal adhesion.** Lin VC, Woon CT, Aw SE, Guo C.

Int J Cancer. 2005 Nov 20;117(4):561-8. **Gene regulation profile reveals consistent anticancer properties of progesterone in hormone-independent breast cancer cells transfected with progesterone receptor.** Leo JC, Wang SM, Guo CH, Aw SE, Zhao Y, Li JM, Hui KM, Lin VC.

Int J Biometeorol. 1987 Sep;31(3):201-10. **Effects of chronic normobaric hypoxic and hypercapnic exposure in rats: prevention of experimental chronic mountain sickness by hypercapnia.** Lincoln B, Bonkovsky HL, Ou LC.

J Steroid Biochem Mol Biol. 2000 Jun;73(3-4):171-81. **Progesterone effect on cell growth, ultrastructural aspect and estradiol receptors of normal human breast epithelial (HBE) cells in culture.** Malet C, Spritzer P, Guillaumin D, Kuttenn F. "On a culture system of normal human breast epithelial (HBE) cells, we observed an inhibitory effect on cell growth of a long-term P treatment (7 days) in the presence or absence of E2, using two methods...." "Cells exhibited a proliferative appearance after E2 treatment, and returned to a quiescent appearance when P was added to E2." "Moreover, the immunocytochemical study of E2 receptors indicated that **E2 increases its own receptor level whereas P and R5020 have the opposite effect, thus limiting the stimulatory effect of E2 on cell growth.** In the HBE cell culture system and in long-term treatment, P and R5020 appear predominantly to inhibit cell growth, both in the presence and absence of E2."

Horm Res. 1987;28(2-4):212-8. **Antiestrogen action of progesterone in breast tissue.** Mauvais-Jarvis P, Kuttenn F, Gompel A. "Most data indicate that progesterone and progestins have a strong antiestrogen effect on breast cell appreciated by the decrease of estradiol receptor content, the decrease of cell multiplication and the stimulation of 17 beta-hydroxysteroid activity which may be considered as a marker of breast cell differentiation dependent of progesterone receptor."

Biochem Biophys Res Commun 1982 Jan 29;104(2):570-6. **Progesterone-induced inactivation of nuclear estrogen receptor in the hamster uterus is mediated by acid phosphatase.** MacDonald RG, Okulicz WC, Leavitt WW.

Cancer Lett. 2005 Apr 18;221(1):49-53. **Effects of progesterone on ovarian tumorigenesis in xenografted mice.** McDonnel AC, Van Kirk EA, Isaak DD, Murdoch WJ.

Int J Cancer. 2004 Nov 1;112(2):312-8. **Endogenous sex hormones and subsequent breast cancer in premenopausal women.** Micheli A, Muti P, Secreto G, Krogh V, Meneghini E, Venturelli E, Sieri S, Pala V, Berrino F.

J Clin Endocrinol Metab 2000 Sep;85(9):3442-52. **Progesterone withdrawal up-regulates vascular endothelial growth factor receptor type 2 in the superficial zone stroma of the human and macaque endometrium: potential relevance to menstruation.** Nayak NR, Critchley HO, Slayden OD, Menrad A, Chwalisz K, Baird DT, Brenner RM.

Endocrinology 1981 Dec;109(6):2273-5. **Progesterone-induced estrogen receptor-regulatory factor in hamster uterine nuclei: preliminary characterization in a cell-free system.** Okulicz WC, MacDonald RG, Leavitt WW **In vitro studies have demonstrated a progesterone-induced activity associated with the uterine nuclear fraction which resulted in the loss of nuclear estrogen receptor.**

Mol Endocrinol. 1991 May;5(5):709-17. **Progestins induce down-regulation of insulin-like growth factor-I (IGF-I) receptors in human breast cancer cells: potential autocrine role of IGF-II.** Papa V, Hartmann KK, Rosenthal SM, Maddux BA, Siiteri PK, Goldfine ID.

Gynecol Endocrinol. 1999 Jun;13 Suppl 4:11-9. **Biological effects of progestins in breast cancer.** Pasqualini JR, Ebert C.

Gynecol Endocrinol. 2001 Dec;15 Suppl 6:44-52. **Biological effects of progestins in breast cancer.** Pasqualini JR, Ebert C, Chetrite GS.

J Steroid Biochem Mol Biol. 2005 Feb;93(2-5):221-36. **Recent insight on the control of enzymes involved in estrogen formation and transformation in human breast cancer.** Pasqualini JR, Chetrite GS.

Cancer Epidemiol Biomarkers Prev. 2002 Apr;11(4):361-8. **Steroid hormone levels during pregnancy and incidence of maternal breast cancer.** Peck JD, Hulka BS, Poole C, Savitz DA, Baird D, Richardson BE. "**When estrogen-to-progesterone ratios were evaluated, there was an indication of a modest increased incidence of breast cancer for those with high total estrogens and high estrone levels relative to progesterone.**"

Br J Urol. 1990 Mar;65(3):268-70. **Erythrocyte stearic to oleic acid ratio in prostatic carcinoma.** Persad RA, Gillatt DA, Heinemann D, Habib NA, Smith PJ.

Int J Cancer. 2006 Nov 9; **Inflammation and IGF-I activate the Akt pathway in breast cancer.** Prueitt RL, Boersma BJ, Howe TM, Goodman JE, Thomas DD, Ying L, Pfiester CM, Yfantis HG, Cottrell JR, Lee DH, Remaley AT, Hofseth LJ, Wink DA, Ambs S.

Biology of reproduction 15, 153-157, 1976, **Sex steroids in reproductive tract tissues: Regulation of estradiol concentrations by progesterone**. Resko JA, Boling JL, Brenner RM and Blandau RJ.

Carla Rothenberg, **History of hormone therapy,** http://leda.law.harvard.edu/leda/data/711/Rothenberg05. pdf. 2005.

J Clin Endocrinol Metab 1996 Apr;81(4):1495-501. **Characterization of reproductive hormonal dynamics in the perimenopause.** Santoro N, Brown JR, Adel T, Skurnick JH. "Overall mean estrone conjugate excretion was greater in the perimenopausal women compared to that in the younger women [76.9 ng/mg Cr (range, 13.1-135) vs. 40.7 ng/mg Cr (range, 22.8-60.3); P = 0.023] and was similarly elevated in both follicular and luteal phases. Luteal phase pregnanediol excretion was diminished in the perimenopausal women compared to that in younger normal subjects (range for integrated pregnanediol, 1.0-8.4 vs. 1.6-12.7 microg/mg Cr/luteal phase; P = 0.015)." "We conclude that **altered ovarian function in the perimenopause can be observed as early as age 43 yr and include hyperestrogenism, hypergonadotropism, and decreased luteal phase progesterone excretion.** These hormonal alterations may well be responsible for the increased gynecological morbidity that characterizes this period of life."

Cancer Res. 1984 Feb;44(2):841-4. **High testosterone and low progesterone circulating levels in premenopausal patients with hyperplasia and cancer of the breast.** Secreto G, Recchione C, Fariselli G, Di Pietro S.

Gen Comp Endocrinol. 1988 Dec;72(3):443-52. **Progesterone down-regulation of nuclear estrogen receptor: a fundamental mechanism in birds and mammals.** Selcer KW, Leavitt WW.

Clin Exp Obstet Gynecol 2000;27(1):54-6. **Hormonal reproductive status of women at menopausal transition compared to that observed in a group of midreproductive-aged women.** Sengos C, Iatrakis G, Andreakos C, Xygakis A, Papapetrou P. "**CONCLUSION: The reproductive hormonal patterns in perimenopausal women favor a relatively hypergonadotropic hyper-estrogenic milieu.**"

J Natl Cancer Inst Monogr. 1994;(16):85-90. **Menstrual timing of treatment for breast cancer.** Senie RT, Kinne DW.

J Neurosci. 2001 Aug 1;21(15):5723-9. **Progesterone blockade of estrogen activation of mu-opioid receptors regulates reproductive behavior.** Sinchak K, Micevych PE.

J Clin Pathol. 2005 Oct;58(10):1033-8. **Proliferating fibroblasts at the invading tumour edge of colorectal adenocarcinomas are associated with endogenous markers of hypoxia, acidity, and oxidative stress.** Sivridis E, Giatromanolaki A, Koukourakis MI.

Neuroscience. 1991;42(2):309-20. **Progesterone administration attenuates excitatory amino acid responses of cerebellar Purkinje cells.** Smith SS.

Cancer Causes Control. 2004 Feb;15(1):45-53. **Serum levels of sex hormones and breast cancer risk in premenopausal women: a case-control study (USA).** Sturgeon SR, Potischman N, Malone KE, Dorgan JF, Daling J, Schairer C, Brinton LA. **"For luteal progesterone, the RR for the highest versus lowest tertile was 0.55 (0.2-1.4)."**

Biomed Pharmacother 1984;38(8):371-9. **Breast cancer and oral contraceptives: critique of the proposition that high potency progestogen products confer excess risk.** Sturtevant FM A recent report by Pike et al. from the U. S. A. concluded on the basis of epidemiologic evidence that an increased risk of breast cancer was manifested by young women who had used combination oral contraceptives (OC) with a high "potency" of progestogen over a prolonged period. This conclusion is criticized in the present article, centering on three cardinal defects in the Pike study: (1) The assigned potencies of OC's are fiction and were derived from out-dated delay-of-menses data; (2) Well-known risk factors for breast cancer were ignored; (3) The method assumed no error of recall of OC brand, dose and duration of use occurring many years before telephone interviews. Noting that others have not been able to confirm these findings, it is concluded that there is no scientific basis for accepting the suggestion of Pike et al.

Cancer Res. 2004 Nov 1;64(21):7886-92. **Reduction of human metastatic breast cancer cell aggressiveness on introduction of either form a or B of the progesterone receptor and then treatment with progestins.** Sumida T, Itahana Y, Hamakawa H, Desprez PY.

Endocr Relat Cancer 1999 Jun;6(2):307-14. **Aromatase overexpression and breast hyperplasia, an in vivo model--continued overexpression of aromatase is sufficient to maintain hyperplasia without circulating estrogens, and aromatase inhibitors abrogate these preneoplastic changes in mammary glands.** Tekmal RR, Kirma N, Gill K, Fowler K "To test directly the role of breast-tissue estrogen in initiation of breast cancer, we have developed the aromatase-transgenic mouse model and demonstrated for the first time that increased mammary estrogens resulting from the overexpression of aromatase in mammary glands lead to the induction of various preneoplastic and neoplastic changes that are similar to early breast cancer." "Our current studies show aromatase overexpression is sufficient to induce and maintain early preneoplastic and neoplastic changes in female mice without circulating ovarian estrogen. Preneoplastic and neoplastic changes induced in mammary glands as a result of aromatase overexpression can be completely abrogated with the administration of the aromatase inhibitor, letrozole. Consistent with complete reduction in hyperplasia, **we have also seen downregulation of estrogen receptor and a decrease in cell proliferation** markers, suggesting aromatase-induced hyperplasia can

be treated with aromatase inhibitors. Our studies demonstrate that **aromatase overexpression alone, without circulating estrogen, is responsible for the induction of breast hyperplasia and these changes can be abrogated using aromatase inhibitors.**"

Ann N Y Acad Sci 1986;464:106-16. **Uptake and concentration of steroid hormones in mammary tissues.** Thijssen JH, van Landeghem AA, Poortman J "For estradiol the highest tissue levels were found in the malignant samples**. No differences were seen in these levels between pre- and postmenopausal women despite the largely different peripheral blood levels."** "Striking differences were seen between the breast and uterine tissues for the total tissue concentration of estradiol, the ratio between estradiol and estrone, and the subcellular distribution of both estrogens. **At similar receptor concentrations in the tissues these differences cannot easily be explained."** "**Lower concentrations of DHEAS and DHEA were observed in the malignant tissues compared with the normal ones and the benign lesions.**"

Cancer. 1983 Jun 1;51(11):2100-4. **Elevated serum acute phase protein levels as predictors of disseminated breast cancer.** Thompson DK, Haddow JE, Smith DE, Ritchie RF.

Crit Care Med. 2003 Nov;31(11):2705-7. **Carbon dioxide: a "waste product" with potential therapeutic utilities in critical care.** Torbati D.

J Steroid Biochem Mol Biol 2000 Jun;73(3-4):141-5. **Elevated steroid sulfatase expression in breast cancers.** Utsumi T, Yoshimura N, Takeuchi S, Maruta M, Maeda K, Harada N. In situ estrogen synthesis makes an important contribution to the high estrogen concentration found in breast cancer tissues. Steroid sulfatase which hydrolyzes several sulfated steroids such as estrone sulfate, dehydroepiandrosterone sulfate, and cholesterol sulfate may be involved. In the present study, we therefore, assessed steroid sulfatase mRNA levels in breast malignancies and background tissues from 38 patients by reverse transcription and polymerase chain reaction. The levels in breast cancer tissues were significantly increased at 1458.4+/-2119.7 attomoles/mg RNA (mean +/- SD) as compared with 535.6+/-663.4 attomoles/mg RNA for non-malignant tissues (P<0.001). Thus, increased steroid sulfatase expression may be partly responsible for local overproduction of estrogen and provide a growth advantage for tumor cells.

Fed Proc. 1980 Jun;39(8):2533-8. **Influence of endogenous opiates on anterior pituitary function.** Van Vugt DA, Meites J.

Clin Endocrinol (Oxf) 1978 Jul;9(1):59-66. **Sex hormone concentrations in post-menopausal women.** Vermeulen A, Verdonck L. "Plasma sex hormone concentrations (testosterone, (T), androstenedione (A), oestrone (E1) and oestradiol (E2) were measured in forty post-menopausal women more than 4 years post-normal menopause." **"Sex hormone concentrations in this group of postmenopausal women (greater than 4YPM) did not show any variation as a function of age,** with the possible exception of E2 which showed a tendency to decrease in the late post-menopause."

J Steroid Biochem 1984 Nov;21(5):607-12. **The endogenous concentration of estradiol and estrone in normal human postmenopausal endometrium.** Vermeulen-Meiners C, Jaszmann LJ, Haspels AA, Poortman J, Thijssen JH The endogenous estrone (E1) and estradiol (E2) levels (pg/g tissue) were measured in 54 postmenopausal, atrophic endometria and compared with the E1 and E2 levels in plasma (pg/ml). The results from the tissue levels of both steroids **showed large variations and there was no significant correlation with their plasma levels. The mean E2 concentration in tissue was 420 pg/g, 50 times higher than in plasma and the E1 concentration of 270 pg/g was 9 times higher.** The E2/E1 ratio in tissue of 1.6, was higher than the corresponding E2/E1 ratio in plasma, being 0.3. **We conclude that normal postmenopausal atrophic endometria contain relatively high concentrations of estradiol and somewhat lower estrone levels.** These tissue levels do not lead to histological effects.

J Natl Cancer Inst Monogr. 2000;(27):67-73. **Endogenous estrogens as carcinogens through metabolic activation.** Yager JD.

Regul Pept. 2003 Jul 15;114(2-3):101-7. **Inhibition of cytosolic phospholipase A2 mRNA expression: a novel mechanism for acetylsalicylic acid-mediated growth inhibition and apoptosis in colon cancer cells.** Yu HG, Huang JA, Yang YN, Luo HS, Yu JP, Meier JJ, Schrader H, Bastian A, Schmidt WE, Schmitz.

Brain Res. 1999 Aug 28;839(2):313-22. **Opioid growth factor and organ development in rat and human embryos.** Zagon IS, Wu Y, McLaughlin PJ.

J Biol Chem. 2005 Apr 29;280(17):17480-7. Epub 2005 Feb 22. **A novel antiestrogenic mechanism in progesterone receptor-transfected breast cancer cells.** Zheng ZY, Bay BH, Aw SE, Lin VC.
