Ray Peat's Newsletter

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Progesterone and ideas of "balance" in "hormone replacement therapy": The importance of inhibition

Because I came to progesterone research after involvement in other biological issues such as the study of the effects of nuclear fallout and ionizing radiation on the brain, rather than as a physician, I had no commitment to any of the ideas which had grown up with the pharmaceutical industry, and that have become so basic to the professions' understanding of the actions of drugs and hormones. For example, *receptors* are supposed to be part of our genetic constitution, making us able to respond to drugs, poisons, hormones, infections, allergens, nervous stimuli, odors, etc. A substance, by binding to its receptor, sets in motion a biological response. With stimuli such as odors and adrenalin, there is a certain logic to the situation—with prolonged stimulation, fatigue sets in, we adapt to a certain level of stimulation, and it then takes a larger amount of the stimulus to produce a response. The receptors are "desensitized."

But if a stimulus evoked, or increased the quantity of, its own receptor, *increasing* the tissue's sensitivity, there would be a tendency for things to get out of control. What could be the biological meaning of such a situation?

Imagine applying this principle to various kinds of receptors—any odor would tend to increase until it became overpowering, the heart would be accelerated by smaller and smaller stimuli, or would require stronger and stronger impulses from the vagal nerve to restrain it. **Allergy represents what happens when a stimulus creates increased sensitivity to itself;** autoimmunity and lymphoma could represent similar processes of positive-feedback, increasing responses to a given level of stimulation. Excitotoxicity, epilepsy, movement disorders, and mania are other examples of what happens when negative (inhibitory) feedback fails. (Estrogen's interactions with other excitatory processes, such as allergy, will be considered in other articles; see Kalogeromitros, et al., 1995; Ahmed, et al., 1989.)

Estrogen's action on many tissues increases the tissue's ability to bind estrogen; estrogen induces its own "receptor," in a self-stimulating, self-destabilizing process. This is unlike the behavior of other "receptors," such as the adrenalin receptor, which is inactivated by increased exposure to adrenalin. This unusual interaction between tissue and hormone requires careful examination.

For example, estrogen's immediate effect on a responsive tissue is to cause it to take up water, and to increase its ratio of sodium to potassium; these changes lead to depolarization-activation of nerve, muscle, and some glandular cells, and of initiation of growth and cell division in other cell types. If the stimulation to growth process continued unchecked, or even accelerated, it's obvious that form and proportion and organization would quickly be lost. Similarly with the other forms of stimulatiion—activated responses must not continue beyond the organism's need for them.

Estrogenic stimulation, like an allergic reaction, would tend to increase progressively, if it weren't for the antiestrogens. The antiinflammatory effect of the glucocorticoids on an allergic reaction, preventing anaphylactic shock, are analogous to the effects of the antiestrogens, blocking estrogenic stimulation. The analogy is especially interesting, when we consider that Selye characterized estrogen's effect as similar to the shock phase of the stress reaction, and that antihistamines are generally

antiestrogenic, and antiestrogens are generally antihistaminic.

Since the actual levels of estrogen increase (Musey, et al., 1987; also see Rodriguez, et al., 1993 and O'Rourke, et al., 1996) during a woman's reproductive years, and then often act almost unopposed during a time around menopause (Nencioni and Polvani, 1985), and tend to increase progressively in aging men, and in both sexes during stress, we need to know what our protective systems are, for interrupting estrogen's excitatory actions on a great variety of tissues.

One of progesterone's effects is to degrade and eliminate estrogen receptors (Brown and MacLusky, 1994; Medlock, et al., 1994; Okulicz, et al., 1993; Selcer and Leavitt, 1988). This is clearly an antiestrogenic action, and many people like to say the opposite, that progesterone induces estrogen receptors, simply because the idea suits their their doctrines of synergy, balance, and more basic ideas of genetic constitution, the nature of gender, etc. But the facts are so clear that they will have to look elsewhere for something to support their orientation.

Recently it has been found that estrogen receptors are degraded by proteasomes (Nawaz, et al., 1999; Alarid, et al., 1999). This could relate to the fact that unsaturated fatty acids promote the retention of estrogen in the cell, since unsaturated fatty acids often inhibit proteolytic enzymes.

By reducing the cell's ability to bind estrogen, progesterone acts as an "estrogen repellant." But it also activates enzymes* which physically/chemically detoxify estrogen, converting it to a water-soluble sulfated form, in which it tends to be expelled from cells and to be excreted in the urine. On the systemic level, progesterone helps to activate the liver's detoxifying systems, in which other types of enzymes modify estrogen, reducing its activity and preparing it for excretion, in both the bile and the urine.

One way of looking at progesterone is that it is an antiestrogen. The estrogen industry doesn't like that concept, and prefers to think of progesterone as an estrogen *synergist*. But if its effect is to interrupt estrogen's excitatory actions, and to eliminate estrogen from the tissues, it is no more "synergic" with estrogen than the inhibitory impulses of the vagus nerve are synergic with the excitatory adrenergic influences. The FDA, in its service to industry, has classified progesterone as a "progestin," defining the category only in terms of an effect on the uterus. No other pseudoscientific concept exceeds this in its harmful consequences.

But to describe progesterone as an antiestrogen is meaningful only to the extent that we understand the nature of estrogenic stimulation.

Estrogen, as an easy derivative of testosterone, is deeply involved in the establishment of masculine features; even in mature women, estrogen excess (progesterone deficiency) can produce hirsutism and other masculine traits when it overstimulates the adrenal glands. As a goad (the term estrogen is based on *estrus*, gadfly, intense stimulus, goad), estrogen initiates activity in cells and systems; depending on the organism's resources, that stimulus will be restrained before it gets out of control.

Does the specific outcome of stimulation take its direction from estrogen, or rather from the ways in which estrogen is neutralized and detoxified? There are many antiestrogenic systems (e.g., thyroid, progesterone, testosterone, sulfation, methylation, glucuronidation, antiinflammatory factors, etc.) and the varied, specific nature of the organism's response to stimulation is probably sufficient to account for the different outcomes, such as masculinity or feminity, tumefaction or growth, alertness or mania.

How specific is estrogenic stimulation itself? Asphyxia, radiation injury, vitamin deficiencies, and other harmful stimuli, closely mimic the estrogenic excitation/shock response. (Boling, et al., 1939;Mandl and Zuckerman, 1956; Biskind, 1946.) Estrogenic activation, with the uptake of water and the loss of potassium (relative to intracellular sodium), is probably the simplest reaction a cell is capable of, and any specificity that can be found in the process is the result of pre-existing cellular conditions, or of defensive reactions of the organism. **Depending on its place in the life of an individual, estrogen can either masculinize or feminize, produce breasts or whiskers.**

Hydration cellular important

The similarity of radiation injury to estrogenic stimulation has led to studies showing some radiation protection from progesterone; similar protective actions of progesterone can be seen for other types of injury. Thyroid, and other antiestrogens, also have a wide spectrum of protective actions, against radiation, asphyxia, carcinogens, etc.

I think the only way to approach the *general nature* of cellular excitation is to see it in terms of the basic properties of the living material. Only something as general and basic as the cell's state of hydration, its "wetness," can account for the coherent way in which cells are activated, with related processes happening at all levels, from chromosomes, to mitochondria and enzymes, the structural protein meshwork of the cytoskeleton, and sensory functions.

Cells use something like metaphor or analogy (as previously discussed in relation to J. Cairns' work, and e.g., in observations such as those of Smith, et al., 1990) to achieve coordination over long distances, and a medium of coordination and cooperation is needed; cell water, with its rich structural potential, provides that medium.

What do these perspectives imply for medical practice?

First, that the issue of "estrogen defiiciency" must be weighed very carefully. 35 years ago, men were given estrogen "to protect them from heart attacks," and the treatment increased the incidence of heart problems; several new campaigns are underway to use estrogens to protect both men and women from heart attacks. The arguments for "cardioprotective" actions of estrogen are based on very peculiarly chosen "indicators," excluding from consideration estrogen's contributory role in diabetes, elevation of free fatty acids and triglycerides, in the tendency to clot, synergism with adrenalin in spasticity of blood vessels, and other conditions relevant to heart disease. Similar campaigns, contrary to facts, are being developed in "brain protection," and other imaginary benefits of estrogen. Consistently, it has been found that the "positive results" found among women who take estrogen aren't scientifically valid, since the groups were selected in such a way that the women who took estrogen were healthier to begin with than the women who didn't take estrogen.

In the light of such imagined protective effects of estrogen, supplements are being recommended, either without any measurement of estrogen, or on the basis of finding a "low level" of estrogen, without taking any of the opposing or balancing factors into account. The idea of "estrogen deficiency," like that of "estrogen's protective action," is completely without scientific foundation.

Any idea of balance suggests that there could be an imbalance in either direction. The harm done by unopposed estrogenic stimulation is clear. Does an excess of progesterone occur, and if it does, is it harmful? Animal experiments, in particular, have made it clear that, at a certain level, and in the absence of interfering factors, progesterone's sedative action can reach the level of deep anesthesia. When Selye's lab technicians discovered this effect, they thought they had killed the animals, because of the animals' complete relaxation and unresponsiveness. There have been no publications of a similar effect in humans (largely because of editorial policies, rather than from a lack of experimental evidence), but if there were, the anesthetized condition would have to be characterized as being harmful only in the behavioral sense, since tissues aren't harmed. When tumors of the corpus luteum produce very large amounts of progesterone, anesthesia has never been a recognized consequence of such massive production of progesterone. Many years of animal and human study indicate that the health of the mother during pregnancy, and of the offspring, directly correspond to the amount of progesterone present. (Excess estrogen during pregnancy leads to fetal death, retardation, or subsequent health problems including breast cancer.)

Progesterone production increases tremendously during pregnancy, reaching hundreds of milligrams per day in late pregnancy, so it is hard to think of it in terms of a "hormone," as traditionally defined. Like serum albumin, I think progesterone should be thought of primarily as a physical/chemical protective substance. But, unlike albumin, its protective properties just seem

to increase with concentration, right up to the absorptive limits of the cells. (The biological protection, however, at the upper extreme, includes sedation and anesthesia, and isn't compatible with ordinary function, and so, outside of the context of pregnancy (in which sedation and anesthesia are appropriate), these can be thought of as "side effects." Since they are part of progesterone's intrinsic function, though, the idea of "side effect" has to be understood as "collateral to the intended pharmacological effect." I think the idea of "side effect" connotes a doctrine of "one substance-one effect," something the drug industry promotes.)

Progesterone's functions include antitoxic or catatoxic effects, antiswelling and antiinflammatory effects, antiglucocorticoid and antiprostaglandin effects. When it alleviates a problem, that doesn't mean that the problem was caused by a progesterone deficiency. About 30 years ago, I proposed that biological energy, differentiation, and respiratory function are integrated in such a way that certain things stabilize/increase them, or destabilize/weaken them. Radiation, anoxia, and aging cause many coherent and systematic changes in function, and some of the things that have been classified as hormones or nutrients produce similar changes. Estrogen, I suggested, was produced to take advantage of something very basic in the nature of life, to promote reparative or regenerative functions. Like radiation, hypoxia, and a variety of stressors and nutritional imbalances, estrogen causes cells to take up water, and to shift away from respiratory metabolism, going into the mitotic state.

Besides being an antiestrogen, progesterone is a neurosteroid, an antiexcitotoxin, an inhibitory modulator. But these effects in the nervous system have their parallels in the immune system, where it modulates the actions of many cells, protecting the thymus, restraining mast cell degranulation, inhibiting the shock reaction. It is an antitoxin, stabilizing cell structure and function. In the mitochondria, it preserves or restores respiratory efficiency. In.the circulatory system, it regulates heart action and vascular tone, preventing venous pooling of the blood and orthostatic hypotension, helping to keep the pulse pressure in the low range indicating efficient circulation.

Therapeutically, we can think in terms of what the organism is doing in response to its challenges, and support those processes of restoration, adaptation, inhibition, and reconstruction.

Because excitation or stress is a simple thing--it is any disturbance of the living state's quiescence--radiation damage, asphyxia, nutritional deficiencies, various poisons, carcinogens, and irritants can imitate the actions of estrogen. Or, looking at estrogen's meaning in evolution, we could say that estrogen imitates the natural menaces that life confronts, so that the processes of regeneration can be managed and integrated into the life plans of the organisms.

This means that antiestrogenic strategies are appropriate under a great variety of conditions. Whatever the challenge, a successful response will restore the organism to a new, high energy state of readiness.

Estrogen's excitatory function, acting briefly, is an integral part of the organism's preparation for reproduction, and it is involved, in an analogous way, in the response to injury, where its local release stimulates cell division. If stimulation has such generalized properties that noxious events and a natural hormone produce similar reactions, what kind of role does stimulation play elsewhere in the organism?

The interaction of energy and structure in the cell means that an energy deficit becomes excitatory. In the case of nutrition, this has been worked out in relatively great detail. Hypoglycemia, for example, causes a graded, progressive excitation, that first makes food appetizing, and then, if the excitation is continued and intensified, there is a more generalized arousal, and the image of the desired food becomes more generalized. Need and arousal mobilize various functional systems to satisfy the need. Pavlov, working on these issues, knew that it was essential to answer the question, "what stimulates the activities that we consider uniquely human?" The exploratory reflex is activated by novelty, by anything which isn't understood. The need/desire for freedom and understanding has the same basic pattern as

the other needs, and it has apparently evolved by differentiation from the basic sensitivity of the living material.

The relatively mild stimulation of novelty, when combined with meeting basic needs and preventing irrelevant, stressful stimulation, can be therapeutic. For example, in a digestive disturbance, therapeutic stimulation might be achieved by something as mild as beef broth, acting by intrinsic (unconditional) chemical processes, or by some simple alteration in the way the food is prepared, or a change in the mealtime atmosphere. The therapeutic effect of laughter, which is produced by surprise, can be seen in terms of a basic organismic process of organizing resources, creatively adapting to produce a new state of readiness.

In outline, a benign stimulation is one which can be met with adequate energy, with good humor, and with an adequate amount of progesterone and related chemical resources.

All of the information that has accumulated about estrogen in the last century leads to the view that it is the organism's means of producing a **momentary and localized imbalance,** goading cells into activity.

An important factor in the integration of this momentary imbalance into the life of the organism is the manner in which destabilizing excitation and the restoration of stability, e.g., estrogen and progesterone production, relate to each other. Estrogen stimulates the formation of progesterone, and progesterone lowers the concentration of estrogen. (Liu, et al., 1997)

Whether we consider pregnancy, or bone metabolism, or the health of the brain or the circulatory system, no situation has been identified in which the "balance of estrogen and progesterone" can be improved by the use of estrogen supplementation. But there is a tremendous amount of information showing that reproduction and the health of bones, brain, and circulatory system, and many other functions, can be improved by antiestrogenic approaches. The pharmaceutical industry is trying to exploit this information, by reclassifying their *antiestrogenic* drugs as "designer estrogens." But the body already has its proper array of antiestrogenic strategies, which can be supported in many safe and economical ways.

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J Neuroendocrinol 1995 Feb;7(2):119-25 Regulation of estrogen receptor and progesterone receptor messenger ribonucleic acid by estrogen in the brain of the whiptail lizard (Cnemidophorus uniparens). Young LJ, Nag PK, Crews D. "First we determined a dosage of 17 beta-estradiol 3-benzoate (0.5 micrograms) which reliably induced receptive behavior in ovariectomized C. uniparens. Then using in situ hybridization, we examined the effects of that dosage on the expression of estrogen receptor and progesterone receptor mRNA in the brain 24 h after injection. Estrogen treatment resulted in a **significant up-regulation of estrogen receptor mRNA expression in the ventromedial nucleus of the hypothalamus and torus semicircularis,** down-regulation of estrogen receptor mRNA expression in the lateral septum, and no change in the periventricular nuclei of the hypothalamus, the periventricular nucleus of the preoptic area, and the dorsal hypothalamus. **The same dosage resulted in increased progesterone receptor mRNA expression in the ventromedial nucleus of the hypothalamus and the periventricular nucleus of the preoptic area;** no significant changes in progesterone receptor mRNA expression were observed in the periventricular nuclei of the hypothalamus or the torus semicircularis, although the differences in progesterone receptor expression in the torus semicircularis approached statistical significance."

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chick oviduct, despite the basic differences in reproductive strategy between birds and mammals."

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a major impact on the interpretation of past and future experiments of this kind.

J Hepatol 1994 Dec;21(6):1127-34 **The adverse influence of pregnancy upon sulphation: a clue to the pathogenesis of intrahepatic cholestasis of pregnancy?** Davies MH, Ngong JM, Yucesoy M, Acharya SK, Mills CO, Weaver JB, Waring RH, Elias E.. "Sulphation of oestrogens and monohydroxy bile acids is important in attenuating their cholestatic potential. Thus, impairment of sulphation could lead to retention of cholestatic compounds and precipitate intrahepatic cholestasis in susceptible individuals." "During in vivo studies utilising paracetamol as a metabolic probe, the proportion of paracetamol sulphate and sulphate: glucuronide ratio **were decreased in those with elevated oestrogens,** whether the rise in oestrogens was endogenous, in pregnancy (paracetamol sulphate $p < 0.05$; paracetamol sulphate:glucuronide ratio $p < 0.01$), or exogenous, with the contraceptive pill (paracetamol sulphate $p = 0.2$; paracetamol sulphate:glucuronide ratio $p < 0.001$)." "An imbalance of sulphation with glucuronidation provoked by high circulating oestrogen levels may be contributory in the pathogenesis of cholestasis of pregnancy."

Clin Exp Allergy 1995 May;25(5):461-6. **Influence of the menstrual cycle on skin-prick test reactions to histamine, morphine and allergen.** Kalogeromitros D, Katsarou A, Armenaka M, Rigopoulos D, Zapanti M, Stratigos I Department of Dermatology, University of Athens, A. Sygros Hospital, Greece. **"Results indicate a significant increase in weal-and-flare size to histamine, morphine, and parietaria on days 12-16 of the cycle, corresponding to ovulation and peak oestrogen levels.** This was observed in both atopic and non-atopic women. Differences in skin reactivity to histamine and morphine between the groups were not significant. Therefore, in women, the phase of the menstrual cycle is another factor that may influence skin-test results."

J Autoimmun 1989 Aug;2(4):543-52. **Estrogen induces the development of autoantibodies and promotes salivary gland lymphoid infiltrates in normal mice.** Ahmed SA. Aufdemorte TB, Chen JR, Montoya AI, Olive D, Talal N.

Neuroscience 1993 Dec;57(3):861-71. **Synergistic action of estradiol and myelin basic protein on mast cell secretion and brain myelin changes resembling early stages of demyelination.** Theoharides TC, Dimitriadou V, Letourneau R, Roznieckl JJ, Vliagoftis H, Boucher W Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA 02111. **"Mast cells are known for their participation in immediate and, more recently, delayed hypersensitivity reactions. They have been found in the meninges and certain brain areas where they are strictly perivascular, in close apposition to neurons, and they are activated by direct nerve stimulation or by neuropeptides. Intracranial mast cells contain many vasoactive substances which can increase the permeability of the blood-brain barrier, proteolytic enzymes which can degrade myelin in vitro, as well as chemotactic molecules** which can attract inflammatory molecules in vivo. Connective tissue mast cells, with which intracranial mast cells share many characteristics, contain cytokines which can cause inflammation directly. **Multiple sclerosis is a human demyelinating disease of unknown etiology, with a high prevalence in women which results in penetration of blood-borne immune cells within the brain parenchyma and subsequent destruction of myelin. Here, we report that 17 beta-estradiol and myelin basic protein, a major suspected immunogen in multiple sclerosis, had a synergistic action on inducing mast cell secretion."**

Am J Obstet Gynecol 1987 Aug;157(2):312-317. **Age-related changes in the female hormonal environment during reproductive life.** Musey VC, Collins DC, Musey PI, Martino-Saltzman D, Preedy JR. "We studied the effects of age, independent of pregnancy, by comparing serum hormone levels in two groups of nulliparous, **premenopausal women aged 18 to 23 and 29 to 40 years. We found that increased age during reproductive life is accompanied by a significant rise in both basal and stimulated serum follicle-stimulating hormone levels. This was accompanied by an increase in the serum level of estradiol-17 beta and the urine** levels of estradiol-17 beta and 17 beta-estradiol-17-glucosiduronate. The serum level of estrone sulfate decreased with age. Serum and urine levels of other estrogens were unchanged."

T. Nencioni and F. Polvani, **"Rationale for the use of calcitonin in the prevention of post-menopausal osteoporosis,"** in Calcitonin, A. Pecile, editor, Elsevier Science Publ., 1985.

C. C. Johnston, et al., "Age-related bone loss," pages 91-100 in U. S. Barrel, editor, Osteoporosis II, Grune and Stratton, N. Y., 1979. **Johnston (1979) found that progesterone (but not estrone, estradiol, testosterone, or androstenedione) was significantly lower in those losing bone mass most rapidly.**