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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

Hirsutisme = \uparrow testos \uparrow stimu surr
l'efficacité de la réponse (\uparrow inhibition) face à la stimu est très importante

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.

① 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.

② 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.

③ By reducing the cell's ability to bind estrogen, progesterone acts as an estrogen repellent. 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 pseudo-scientific 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, anti-inflammatory 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 femininity, 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.

Estro \uparrow = \uparrow H₂O \uparrow Na⁺ Intracell \downarrow K intracell

Alters \uparrow = \uparrow glucose adaptation, mucus, temperature

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 deficiency" 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

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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 catatonic effects, antismelling 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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progesterone withdrawal, and estrogen-dependent protein responses (Rp and oxytocin receptor) were obtained within 8 h. Thus, progesterone-induced down-regulation of nRe and estrogen-dependent proteins is rapidly reversed upon removal of hormone. The recovery response of Re, Rp, and oxytocin receptor to progesterone withdrawal can be blocked by cycloheximide treatment at 4 h, suggesting that receptor recovery involves protein synthesis. These results are consistent with the hypothesis that progesterone down-regulates the Re system by a selective action on nRe retention.

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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."

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