Ray Peat's Newsletter

Folly is the cloke of knavery.

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Estrogen's Mechanisms in Aging and Cancer

Estrogen is an important factor in aging and cancer, but the fact of its toxicity is systematically obscured, discouraging proper treatments.

If we want to understand what estrogen is, we should know what it does, and how it does it. Despite the drug industry's weekly releases to the mass media, explaining the wonderful consequences of "selectively activating the estrogen receptor," it isn't clear what estrogen does. It is, however, perfectly clear that estrogen doesn't do the things the industry says it does.

The industry's basic story was that estrogen is "the female hormone," and that supplementing it makes all of the female functions better, including fertility and pregnancy.

But in reality, supplemental estrogen masculinizes, sterilizes, promotes prostate cancer, kills embryos and fetuses, breaks chromosomes, disorganizes cell division, mutates genes, causes seizures, and shifts metabolic patterns.

One of estrogen's relatively normal effects is to shift metabolism toward the production of more lactic acid, and less ATP. Examining these relatively simple effects offers very interesting insights into what estrogen is.

Changing the cell's energy economy through modulation of enzymes is an important alternative to special receptor-mediated actions. This approach is probably the only one that can account for the estrogenic actions of oxygen deprivation and irradiation with x-rays or ultraviolet rays.

The right food, the right activity, the right air and the right light, supported when necessary by the right hormone or drug, can change the basic energy metabolism.

The idea of "estrogen dominance" in menopause has been accepted by many people, but its application to therapy has been very limited. The ways in which nutrition and the thyroid hormone can lower estrogen production just aren't being discussed in the books that recognize the role of estrogen dominance in the menopause.

Gradually, a few people are recognizing that progesterone can be used for other situations in which estrogen causes sickness. The role of estrogen in epilepsy, depression, circulatory disorders, and migraine is starting to be recognized, because of the immediate effects of supplemental progesterone. But estrogen's role in emphysema, asthma, liver and gall-bladder disease, diabetes, arthritis, strokes, movement disorders, memory problems, multiple organ failure, and a variety of inflammatory conditions is being neglected, for reasons that are largely ideological.

In pregnancy, menstrual disorders, and menopause, the situation makes it easy to think of the sex hormones, and the idea of balancing two of them seems plausible. Katharina Dalton popularized the idea that the premenstrual disorder could be diagnosed by finding a monthly rhythm in the symptoms, and treated by taking progesterone premenstrually. That was an extremely important contribution, because it gradually made doctors realize that the "syndrome" wasn't just a matter of monthly water retention, as the journals had characterized it.

But when the sickness doesn't have a clear monthly rhythm, or isn't associated with menopause, or isn't cured by supplemental progesterone, or occurs in a man or child, estrogen's role can easily be overlooked. If a problem is caused by stress, or x-rays, or aging, or a genetic mutation, some people think estrogen and progesterone are irrelevant.

This is because of a medical culture and ideology. As long as that culture defines the issues, very simple approaches to "insoluble" health problems are going to be ignored.

If we learn to see the problems in terms of a general disorder of energy metabolism, we can begin to solve them.

A. The Issues

Before genes were known to be made of DNA, some people spoke of the nucleus as if it were the "brain of the cell," although many experiments showed that idea to be very misleading.

100 years ago the doctrine of Weismannism explained the development, from a single cell, of organisms with many different kinds of cell, by saying that all of the genes were contained in the first cell, but that as the fertilized egg divided, the genes were distributed, divided up so that each tissue received only the genes that it needed for its specific structure and function.

While this doctrine was in force, the development of tumors, which often produce cells with some of the characteristics of other tissues, was neatly explained as the growth of a fragment that was "displaced" during the embryo's growth: "an embryonal rest." Dermoid tumors or pilonidal cysts are still usually explained as displaced embryonic tissue. Many other things, especially aneurisms (some aneurisms, e.g., "berry aneurisms," resemble tumors), that appear at any point in life are commonly described as "congenital," because of the great and lingering influence of Weismannism, which held that developmental potential existed only in the "germ line" cells. These ideas persist in the medical culture because of the uncritical nature of medical training.

The doctrine, the culture, of Weismannism is behind the desire to say that the nucleus, with its genes, ***controls*** the cell.

The people who like to think that the "genes control the cell" have built their more modern understanding of human and mammalian biology on ideas that were developed in the 1950s and 1960s for explaining the responses of bacteria to different kinds of food. In bacteria, there is no distinction between nucleus and cytoplasm, and their DNA isn't arranged in chromosomes. Their appropriate adjustments to changes in their environment were explained in terms of regulatory molecules that activate and inhibit specific

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genes. (As I have mentioned before, the work of John Cairns [Cairns and Foster, 1991] and others has shown that there is something fundamentally wrong with this idea, even for explaining bacterial physiology.)

These ideas were applied to explaining the more complex processes that regulate cells that contain a nucleus. The gene-***discarding*** details of Weismannism were dropped, in favor of a new doctrine, in which genes were bound up and inactivated, except when they were specifically activated according to the specific needs of a tissue.

Hormone receptors were seen as analogs of the regulatory molecules in bacteria. The receptors that the drug companies talk about are almost always understood in terms of the bacterial regulatory model, in which a protein binds to a drug or a signal substance, and then moves into the nucleus where it binds to specific genes. (In this scheme, the hormone is said to be "providing information" to the cell, regulating the "information in the genes.")

In neurology, receptors have been used to explain why all nerves don't respond in the same way to molecules such as adrenaline, acetylcholine, and dopamine. During development certain of their genes were activated, producing the receptors that allow them to respond only to certain substances.

The two kinds of receptor belonged to two different cultures--endocrinologists simply believed that nerves didn't have estrogen receptors, and neurologists believed that the relevant gene expression was taken care of before birth. Both of these cultures have turned out to be radically mistaken.

Because of the idea that activation of genes by receptors had to explain everything, estrogen was said to act only through its "receptor protein," and for decades most biologists simply denied that estrogen could have essentially instantaneous effects on cells, the way nerve transmitters do. As hundreds of "impossible" facts piled up, the scientific/medical establishment bent a little, and decided that there was another estrogen receptor, which would account for the immediate actions of estrogen. The alpha and beta estrogen receptors are now familiar entities, if we believe what is being said by many medical endocrinologists.

But estrogen does many things, and some of them clearly don't involve either the "alpha" or "beta" receptor proteins. Rather than making it easier to understand all of estrogen's effects, another "receptor" is just another distraction, making it easier to ignore some of the unexplained facts.

What began as a reductionist attempt to explain everything in terms of chance and mechanistic materialism, has resulted in an infinite tangle of assumptions and wild interpretations.

What, specifically, is wrong with the idea that a hormone binds to and activates a receptor protein which then activates certain genes?

First, it has been asserted for more than 30 years that this is the only way a hormone can work. A few years ago, the single estrogen receptor was supplemented by another receptor. In mice which have been mutated to lack these receptors, there are still responses to estrogen, and so a "receptor X" has been proposed. As long as a cell or organism can respond to something, it will be claimed that there is a receptor for it.

Second, the "classical hormone receptor" idea claims that the receptor/response system is highly specific, and is activated by a highly specific binding of the hormone to the receptor, and of the complex to the gene.

Third, the doctrine claims to be so important that other processes of regulation and differentiation of cells are forgotten or treated as if they were trivial.

The first objection is really an objection to the medieval way of thinking, in which every reaction has to be reified, turned into a concrete object. This attitude seems to be useful in getting funding.

The second false claim has been amply disproved--the range of things which can activate estrogen receptors is great, and the evidence that falsifies the claim has existed longer than the identity of the estrogen molecule has been known.

The third point will be settled by anyone who investigates the massive amount of research demonstrating that cell physiology and structure are thoroughly dependent on processes that occur after the genes have produced their product, messenger RNA. The stabilization and degradation of the RNA, and its rearrangement and splicing, are clearly very closely connected with the cell's nature and function.

There might turn out to be many interesting "repressors" and "activators" of specific genes, that conform to the standard bacterial model, but that hasn't been what the drug industry wants us to believe. They have an interest in selling the idea that hormones and drugs have a specific ability to "unlock" certain genes. Estrogen might no longer unlock the "femininity genes," but it is supposed to unlock the genes that protect the bones, heart, and brain. The "estrogen receptor" no longer has anything at all to do with femininity. It is found in every organ of both men and women. When a mutant mouse was produced that lacked an estrogen receptor, testicular edema was one of the most noticeable problems. (There might be reason to think this indicates an *increased* activity of estrogen in the absence of the receptor: See Sowerbutts, et al., 1986).

The conversion of estrogen, in the early 1960s, from something that "increased fertility" to something that prevents fertility, started a process that convinced the industry that they should concentrate their sales effort on women who are already infertile. That probably saved the industry from extinction, since the use of estrogen during pregnancy caused not only miscarriages, but also birth defects and cancer and other diseases in the children. But the present claims that estrogen activates specific genes that protect the aging tissues will eventually sound as foolish as the idea of "femininity genes" does now.

Without the receptor doctrine, the introduction of new drugs might require evidence of actual health benefits.

The facts of hormonal control of cell function are much more interesting than the simple receptor dogma.

B. Some Evidence

Within the last few years, a new technique (reverse transcriptase-polymer chain reaction) has made it possible to detect very small amounts of RNA, to show in a very clear way whether certain genes in a single cell are active.

Y. Kimoto has applied the test to several very different types of cell. Some genes involved in energy production and the basic maintenance systems are known to be active in all sorts of cells, but other genes, such as those that are responsible for the highly specialized functions of mature tissues, are believed to be inoperative in tissues with a different kind of specialization. He showed that all of the 25 types of RNA, for making very different kinds of protein, were present in each type of cell. ***"These findings strongly suggest that every cell can express every mRNA. Beneath the cell differentiation there may exist a DNA-->RNA basal constant flow...."***

If all of the organism's genes are always active in every cell, then the question is clearly "what really governs the cell's differentiation, and the varying expression of the genes' protein products?"

When a cell doesn't need a particular kind of RNA, it is degraded almost instantly. When it is pressured to adapt in a certain direction, the RNA for making the adaptive proteins becomes very stable, and accumulates.

A similar process occurs with proteins, degrading them quickly, or protecting them. In many enzymes, a vitamin or other coenzyme binds to the protein and stabilizes it.

If the enzymic activity is changed in the presence of a hormone, many people have assumed that new proteins with different functions were produced by activation of genes, but in many cases, hormones (like vitamins) directly alter the functions of enzymes.

In the 1960s, Engel and his collaborators showed that estrogen binds to several enzymes, and that the association of estrogen with the enzyme alters the cell's chemistry, including the balance between oxidation and reduction. These enzymes could very properly be called "estrogen receptors," because they mediate the cell's response to estrogen. But the general atmosphere was such that only receptors which moved into the nucleus and bound to a gene could be accepted. Everything had to be explained by the prestigious bacterial model.

Nevertheless, in the 1960s and earlier there were other people who could demonstrate that basic changes in the cell's chemistry altered the expression of genes. C.D. Cone, Jr., showed that osmotic forces and the cell's surface electrical potential, which he manipulated by adjusting the ratio of sodium to potassium, could powerfully activate the genes. He demonstrated that even the nuclei of brain cells could be stimulated to undergo mitosis, duplicating their DNA as a result of a simple change of the salt balance.

Around 1985, stress (high temperature, or deprivation of oxygen or glucose, for example) was found to alter gene expression in a systematic way. **It turned out that estrogen activates these same "stress proteins."**

This was particularly interesting, since many years earlier it was demonstrated that many kinds of stress imitated the function of estrogen. Suffocation or x-ray exposure (of the brain, or ovary, or any part of the body) would trigger the lordosis reaction, for example. More recently, it has been noticed that a moderate x-ray exposure of the brain can bring on premature puberty in girls. And irradiation (x-rays, gamma rays, or ultraviolet rays) synergizes in other ways with estrogen, for example in causing cancer.

The estrogen receptor, even without any estrogen, will still move into the nucleus and bind to the genes, under the stress of oxygen deprivation. This is consistent with the idea that estrogen is doing something to the cell that resembles the changes produced by the other stressors. Under more objective circumstances, the "estrogen receptor" might have been identified as just another of the components in a stress response.

Heat shock can increase the number of estrogen receptors (Marin, et al., 2001). Estrogen, too, generally increases the quantity of the estrogen receptor protein.

Testosterone, thyroid, cortisone are known to stabilize certain RNAs, causing the expression of gene products without necessarily doing anything directly to the gene. The overwhelming emphasis in research now seems to be on the factors that regulate the stability of RNA, rather than on the simpler bacterial model of gene activation.

In 1996, many people spoke of the original estrogen receptor as if it moved "from the membrane" through the cytoplasm to the nucleus, because of a habit of thinking of the cell surface as a "membranous barrier." But the protein that they identified as their estrogen receptor was in the cytoplasm.

For more than 30 years, people had been noticing that estrogen had many effects that were practically instantaneous, for example causing cells to take up water and alter their electrical behavor. Cone's work demonstrated that the cell's water content and electrical behavior could activate the nucleus, so I didn't see the need for having separate explanations for regulating water, ions, electrical potentials, and genetic expression.

But the Other Major Dogma of cell biology has been that "the plasma membrane" regulates everything. When people heard about estrogen's or progesterone's or the thyroid hormone's instantaneous actions, they thought it must be a membrane-controlled response.

V.D. Ramirez and his collaborators began talking about the reality of a second estrogen receptor, the beta receptor, or membrane-associated receptor. (The original "gene activating receptor" has now become the alpha receptor.)

Their definition of "membrane" was very standard: First you homogenize the tissue, and then centrifuge it, and certain layers of the sludge are called membranes. That's because of the tradition in which membranes served to enclose the "watery" cytoplasm, so naturally they were the part that wasn't watery, i.e., they were the insoluble lump left after homogenization and centrifugation.

But they identified several proteins that estrogen stuck to: **ATPase (regulating energy and salt and water), and GAPDH, the rate controlling enzyme of glycolysis. Estrogen activates this enzyme, and physiologically estrogen activates the glycolytic pathway, increasing the production of lactic acid as it shifts metabolism away from mitochondrial oxidation, lowering the cell's ATP production, and shifts the use of oxygen functions, such as producing nitric oxide, the free radical which is a common mediator for all the harmful forms of radiation, and for oxygen deprivation.**

This particular enzyme interests me, because of its function in controlling glycolysis, but also because it is inactivated by cold, along with other important enzymes involved in the estrogen reaction. In 1971 I proposed that estrogen activated this enzyme by altering the "structural temperature" of the cell water, something which paralleled C.D. Cone, Jr.'s sodium/electrical effects, that is, it would be a holistic shift in the way the insoluble ("membrane") proteins behaved, making them more insoluble or hydrophobic.

But Ramirez's group, like Engel's, was suggesting that the binding of estrogen to the enzymes, changing their activity, was the regulatory principle, which doesn't make too much difference, since the various interpretations end up causing the same metabolic shifts, toward the metabolism of stress, or cancer, or estrogen dominance. The shift of metabolism toward lactic acid production and lower energy production will also cause some holistic changes, such as changing the redox balance, possibly increasing the pH, and lowering the energy charge. However, I think a change in the cell's hydrophobicity or structural temperature would also make coherent changes in the stability of RNA as well as of proteins.

The activation of the other enzyme, ATPase, in Ramirez's experiments, is even more supportive of the idea that estrogen is modifying the cell water, lowering its order the way increased temperature would. In the mitochondrion, the enzyme that synthesizes ATP (ATP synthetase) will also destroy ATP, if conditions are changed.

The three main conditions that cause the enzyme to destroy ATP are prolonged standing after separating the mitochondria from the cells, freezing the mitochondria and then slowly thawing them (messing them up more thoroughly than when they are rapidly thawed), and treating them with estrogen.

Destroying the cell's ATP at a high rate is an important factor in forcing the cell to get its energy from glycolysis, producing lactic acid.

All of the stages involved in the development of cancer are promoted by estrogen. For example, the local acidification produced by lactic acid production promotes invasiveness, by activating proteolytic enzymes.

The mere presence of lactic acid in the blood displaces carbon dioxide, with many harmful consquences (all of which are seen in the estrogen dominant state). Carbon dioxide is in effect our basic protection against free radical damage. (Boljevic, et al., 1996.) Carbon dioxide is generally thought to be a major factor in regulating the balance of water in the body. For example, hyperventilation increases capillary leakiness, and causes fluid to leak out into the tissues. Estrogen decreases carbon dioxide by causing hyperventilation and increased lactic acid production. **Estrogen systemically increases capillary leakiness.** (Cho, et al., 1999; Ziylan, et al., 1990; Reid, et al., 1983; Merlen, 1982.) **The capillary leakiness is corrected by progesterone.** (Lagrue, et al., 1983.)

The idea that estrogen increases the structural temperature of cell water, even while the real temperature might be decreasing, would be consistent with the fact that the "heat shock" or stress proteins are expressed under estrogen's influence. And when, under the influence of estrogen or the unsaturated fatty acids, cells take up more water, they also take up a little sodium. This reduces the organizing influence of the cell's proteins on the water, and this is what increases its structural temperature. When the nervous system, responding to estrogen, "sets the thermostate lower," there is a slight restoration of the cell's water and protein interactions, but metabolic processes are slowed at the lower temperature.

Estrogen, like radiation and oxygen deprivation, increases formation of the nitric oxide (NO) free radical, which has so many harmful effects, ranging from damaging DNA to poisoning mitochondria. One of the consequences of increasing NO formation (and estrogen) is the activation of an enzyme (heme oxygenase) which produces carbon monoxide, in the process of breaking down the heme molecule (which is needed for respiratory enzymes, among other essential functions). In previous newsletters I have discussed the reasons for thinking that endogenously produced carbon monoxide could explain the gradual development of cancer, since it stabilizes cells in the primitive anti-respiratory condition.

Any injury that an organism can survive is likely to activate the defensive systems, increasing the organism's ability to survive a subsequent stress (e.g., Meerson, et al., 1991), and this seems to explain why estrogen treatment sometimes has a protective effect. In a healthy menstrual cycle, estrogen's dominance is present for just a few hours, and this short stimulus serves to stimulate compensatory production of progesterone. Ever since Lipshutz's experiments in the 1940s, it has been known that it is the prolonged, uninterrupted action of estrogen that is profoundly harmful, not the brief cyclical exposures.

It's the prolonged shock-like state that contributes to the degenerative diseases, which typically begin with a sort of diabetes, an inability to use glucose for energy because of the accumulation of too much of the wrong kind of fat.

C. Protective Measures

The avoidance of stress is the basic principle for preventing the development of the estrogen-dominant state. Since darkness is itself a stress, generally increased exposure to strong light that is rich in the long-wave part of the spectrum, yellow to red, is protective, since these frequencies restore enzymes damaged by stress. Avoiding ionizing radiation whenever possible is very important, and this includes especially medical/dental x-rays, which are almost always unnecessary.

The polyunsaturated fats, toxic heavy metals, and inappropriate amounts of certain amino acids, such as tryptophan, cysteine, leucine, and

glutamate, increase our sensitivity to stress of all sorts, including radiation, and so should be avoided as far as possible. Coconut oil or palm kernel oil (which is even more saturated than coconut oil, with a generous supply of the short fatty acids) should be used regularly, since it isn't possible to avoid the toxic unsaturated fats entirely. (Generally, starchy food should be avoided, for several reasons: Persorption, obesity, and the nature of the foods that contain them.)

Many drugs that are currently popular decrease stress resistance. A few drugs are protective in the short term, but are toxic if used for a long time. Aspirin protects against some of the worst stressors, including the polyunsaturated fats, so despite its mild toxicity, long term studies usually show that it decreases sickness and mortality. Antibiotics, though they are toxic in themselves, also have powerful antistress effects.

In stress, magnesium and sodium are lost rapidly, so the diet should contain foods such as fruits and meats that contain significant amounts of magnesium. Added sodium helps to spare magnesium.

Occasional use of liver, to assure a generous supply of vitamins and trace minerals, is safer than using chemical supplements. Niacin and thiamine help to correct some of the metabolic distortions created by stress or estrogen.

The specifically antiestrogenic hormones, thyroid (especially T3), pregnenolone, and progesterone, can compensate to some extent for exposure to any of the stressors, including ionizing radiation.

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