# Ray Peat's Newsletter

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## Edema, estrogen, and aging: A universal problem, and better therapies

Before talking about the harmful effects of edema, and of the things that cause edema, and of the things that can remedy the various edemas, I think it's necessary to look at a few recent events in the very long history of medicine's intervention in this problem of excessive tissue water. Otherwise, I don't think the great importance of edema, and its fundamentally "estrogenic" nature, will be clear. Aging, shock, hypertension, cancer, heart failure, and many other biological problems involve edema as a central factor, and relieving the edema is probably an essential part of solving those problems.

**Carbon dioxide and estrogen are important in the regulation of water, which is a major problem in stress and aging.**

Some people have defined "homeostasis" as maintaining a consistency in the things dissolved in the body's water. Physiologists have tried to explain how homeostasis is maintained, but they have had the greatest difficulty with understanding *the water itself,* and the things which allow the body to maintain the right amount of water in the various compartments of the body. ***Edema*** ("an abnormal collection of liquid") isn't a sophisticated concept, and is generally used interchangeably with "water retention" and "swelling."

Many people think of edema as an esthetic problem: They don't like the appearance of fat fingers, swollen ankles, puffy eyelids, and soggy-boggy tissues in other areas. Swollen breasts and uterus can cause pain, and often occur premenstrually along with more generalized water retention. Estrogen's role in edema is understood by many women, but therapies have generally been directed toward the water itself, with empirical diuretics, because edema's *causes* aren't explained in medical texts.

This is, to a great extent, the result of deliberate distortion by the drug industry of the issues involved. Beginning in the 1950s, the sale of new patented diuretics (replacing traditional diuretics) began in an atmosphere in which estrogen was being given to pregnant women, to prevent various complications of pregnancy (which in fact were caused by excessive estrogen). Excess estrogen as the cause of toxemia couldn't be discussed openly, and the diuretics were sold as additional tools for controlling pregnancy-associated water retention, weight gain, high blood pressure, and damage to the fetus. Pregnant women were also told to diet to limit weight gain, and to sharply limit their consumption of salt. Estrogen, diuretics, salt restriction, and dieting were demonstrably all harmful to pregnant women and their babies, but they were imposed by the pharmaceutical-medical establishment. (Besides their appalling promotion of the new diuretics "to prevent toxemia," the pharmaceutical industry presented the new chlorothiazide diuretics as the only drugs capable of correcting the "sodium problem," creating multiple unnecessary confusions.)

**Shock, pneumonia, and hypertension are among the consequences of edema.**

**Understanding edema is essential for understanding stress, for preventing stress-induced sickness, and for resuscitation**

Emphasis on diet and sodium restriction served to put the blame for pregnancy problems on the women who couldn't control their

appetites. Besides the medical obscurantism that didn't want to examine estrogen's role in toxemia of pregnancy, there was a mechanical conception of the causes of edema. Although no one could explain how a molecule could fling an atom of sodium out of a cell or across membranes such as the kidney tubules, "sodium pumps" were said to explain the different concentrations of sodium in different compartments, and water was said to passively "follow the sodium." This theory failed to explain how water could be retained while sodium was lost, or why osmotic pressure varied under certain conditions..

Physical chemists understood how water could be moved from one compartment to another, by the process of electro-osmosis, but cell physiologists still generally believe in their sodium pumps and give them responsibility for the distribution of water. Medical textbook discussions of edema have a pitiful-comical quality, because their elaborate Rube Goldberg machines* don't do what they are supposed to do, despite all their embarrassing *ad hoc* devices and convolutions.

Because of the abundance of oxygen in the world, most things are in a relatively oxidized state. Oxygen's name means "source of acid," and it creates acids because of its great affinity for electrons. Acidity is defined as a tendency to *accept electrons, or to release protons.* In water, it is common to speak only about the protons, and to think of acidity as an excess of protons, a low pH. Finely divided minerals such as clays and zeolites, and partly oxidized organic substances, have a strong tendency to absorb and bind water,because of the polar nature they have because of their oxygen content. It is extremely hard to completely dehydrate materials such as proteins and nucleic acids because of their polar, predominantly acidic, affinity for water.

*Rube Goldberg, who was educated as an engineer, described his cartoon machines as "symbols of man's capacity for exerting maximum effort to accomplish minimal results." He said "there are two ways to do things, the simple and the hard way, and a surprisingly large number of people prefer doing things the hard way."

Soluble alkaline materials, with a tendency to *release electrons or accept protons,* associate with the acidic groups, tending to produce a neutral pH. However, extremely water soluble chemicals don't have complete freedom to associate with their oppositely charged groups in materials that are insoluble in water; some enter, some are excluded. This principle can be demonstrated with drops of simple acidic organic liquids suspended in water containing ionized solutes: Their different solubility, combined with their chemical affinities, creates an equilibrium, in which the organic droplet has a negative electrical charge.

Dead cells, such as hair, behave in this way too, because this electrical and ionic behavior is normal for any acidic solid, or immiscible liquid phase. It is the failure to recognize ordinary physics and chemistry that has made Rube Goldbergian cell physiology seem plausible to so many people. Bioelectricity, and ionic selectivity, are fundamentally passive, near-equilibrium processes, that don't require any convoluted "special" apparatuses to explain them.

When oxidative metabolism enters the picture, new acids are being formed inside cells. Carbon dioxide formation is the essence of oxidative metabolism, along with the formation of metabolic water, from the interactions of carbon fuel, electrons, and oxygen. Even before carbon dioxide has covalently reacted with water, to form carbonic acid, it has a great affinity for electrons. This affinity, which predisposes it to react with water and amines, governs its non-covalent, adsorptive properties, but these are passed over by most physiologists. Carbon dioxide is chemically active in many ways, besides its contributions to bicarbonates and carbonates and carbamates and organic acids.

Both spontaneously, and enzymically, carbon dioxide combines with water. Formed inside the respiring cell, it is constantly leaving the cell as carbonic acid, bicarbonates, and carbonates. As it streams out of the cell, any positively charged group, such as a calcium ion, that it takes along will enter extracellular fluids with the carbonate or bicarbonate ion, approximately as a pair with equal positive and negative charges, but the removal of the alkaline metal ion will tend to restore the proteins' acidic nature, which had been

Acidity: accept electrons or libir protons

approximately neutralized by the passive interaction of acids and alkalis. The proteins, and the cells, will be electrically charged to a higher degree by respiration; nerve cells will show a voltage of about a tenth of a volt, while red blood cells, that don't produce energy by respiration, show an electrical potential of less than 1/400 of a volt. **This is partly a mnemonic device for visualizing the general scheme in which equilibrium conditions interact with dynamic metabolic processes.** The adsorptive effects of carbon dioxide, and a great variety of other chemical effects, modulate the cell's structure and function so that it retains far more potassium than sodium, and is able to excrete calcium while binding magnesium. But this simplified picture of carbon dioxide's effects on minerals makes it possible to understand the fact that the blood's pH is higher than the cell's, and many other mysteries, without resort to special hypothetical devices. The alkaline metals that have been mobilized from respiring cells in association with carbonic acid remain alone in the blood when carbonic acid turns into gaseous carbon dioxide and leaves the blood in the lungs. Protons, if we have to talk about them, are left in the cells, and subtracted from the blood, by the reactions of carbon dioxide, but the conventions for talking about the blood's alkalinity relative to the cells omit the background conditons: The intrinsic acidity of the cell substance, and forces exerted by the cell substance on the dissolved substances.

Myxedema, or mucous-edema, is a classical feature of hypothyroidism, but it's not always noticed, because it can occur in different tissues to different degrees. The protein that forms the mucoid jelly is partly made up of ordinary blood proteins, including albumin; transthyretin, the protein that carries thyroid hormone and vitamin A, is sometimes increased, and some connective tissue glycoproteins contribute to its bulk. Similarly to the way that mucus protects the lining of the intestine from irritants, there is probably a protective aspect to the accumulation of myxedema in stressed tissues, where it has a cushioning effect.

Starting with either hypothyroidism or hyperestrogenism, or both, since they tend to occur together, there are many pathways that lead to the excessive accumulation of water in tissues. In hypothyroidism, the adrenergic nervous system tends to overactive, and adrenalin production is sustained at a high level even when there isn't any external reason for it, since it is needed to maintain adequate blood sugar and energy, in the inefficient metabolic state of hypothyroidism.

**Adrenalin mobilizes free fatty acids from tissues, including fat and muscle tissues. Estrogen itself produces elevated free fatty acids. When the free fatty acids are unsaturated, they cause edema, by making blood vessels leaky, and by making cells take up extra water; this can cause brain swelling, stiffening of the heart muscle, and thickening of the lining of blood vessels, eventually obstructing them.**

Hypothyroidism suppresses respiration as a source of energy, so little carbon dioxide is produced, and lactic acid is formed even when there is no noticeable stress. This in itself resembles hyperventilation, since loss of carbon dioxide is the defining feature of hyperventilation, but the presence of abnormally high adrenergic activity, and of free fatty acids, stimulates further hyperventilation, exacerbating the loss of carbon dioxide. Decreasing the carbon dioxide impairs respiration even more, leading to increased lactic acid production, and that stimulates more adrenergic activity, and so on, in a vicious circle. Unsaturated fats also suppress respiratory production of carbon dioxide, and block the entry of glucose into cells.

Estrogen excess suppresses the liver's ability to synthesize albumin, and when this is combined with the leakage of albumin into the tissues (where it is slowly destroyed) and into the urine, the blood loses its ability to retain sodium, much of which is associated with albumin. Carbon dioxide, some of which is produced in the kidneys, helps to retain sodium, and this is probably the reason that hypothyroid people have difficulty retaining a normal amount of sodium (producing *hyponatremia*).

Both animal and human studies have shown that estrogen lowers the osmolarity of the serum and other body fluids, creating a more "diluted"

liquid. Some evidence suggests that it acts at different points to decrease the sodium (and albumin) in the blood, and to allow it to enter tissue cells, or to be lost in the intestine or urine. Although this dilutional effect of estrogen on the blood is small, it certainly increases the tendency of water to enter cells. Especially when combined with lactic acid and unsaturated fatty acids,

Since a hypotonic solution imitates the effects of estrogen, and things that cause tissue leakiness, such as cholera toxin, act like estrogen in the uterus, the edema itself produced by estrogen seems to be a central part of its normal physiological action. Histamine and serotonin and other inflammatory factors released by estrogen are known to contribute to its ability to produce edema. The excess nitric oxide produced under the influence of estrogen probably contributes to some edematous, inflammatory, and degenerative conditions. Since these effects of estrogen on tissue water are considered to be nongenomic, and independent to some extent of the normal estrogen receptors and response elements, any tissue is probably susceptible to estrogen-induced swelling, as well as to the swelling produced by unsaturated fats and carbon dioxide deficiency. Part of the toxicity of unsaturated fats could be their requirement of energy to be oxidized (S. Clejan and H. Schulz, 1986), but they reduce the efficiency of energy production in a variety of other ways.. In shock (whatever the cause), tissues become edematous, as water moves out of the blood stream. The weight of organs increases tremendously as a result of shock. In severe stress. shock, and estrogen poisoning, the production of energy is impaired by the swelling itself, though it may have been low energy production that allowed the shock-state to develop.

If estrogen can cause edema in any tissue, then antiestrogens, such as progesterone, can probably protect against stress in any tissue.

In the premenstrual syndrome, as in pregnancy, a progesterone deficiency can cause generalized edema. Tom Brewer, who founded the Society for the Protection of the Unborn through Nutrition, and S. Shanklin and J. Hodin, in *Maternal Nutrition and Child Health,* argued that salt restriction, expecially when combined with diuretics and a diet without adequate protein, caused exaggerated edema in pregnancy, producing a great risk of hypertension by reducing the blood volume needed for adequate perfusion of the kidneys, and damaged the development of the fetus, because of inadequate blood perfusion of the uterus and placenta.

After I was convinced of the manner in which salt restriction could cause edema, and knowing that women are told to restrict salt to prevent premenstrual edema, I began suggesting that women salt their food to taste, increasing their salt consumption premenstrually if they craved it. I had never known of salt restriction to prevent premenstrual edema, but I immediately began hearing that the women who ate all the salt they wanted no longer experienced premenstrual edema.

After a couple of years, I was satisfied that adequate protein and salt consistently prevented premenstrual edema. I read an article by some people who noticed that their patients who were on low sodium diets "for high blood pressure" very often developed insomnia. They knew that sodium restriction raised adrenalin levels, so they took their patients off the low sodium diet, and cured their insomnia.

Since I had become a sound sleeper as soon as I began taking thyroid, and had seen that thyroid alone would cure most people's insomnia (sometimes, as one doctor described his experience, "better than morphine") I began to understand that the adrenalin which disturbed sleep was an indicator of defective energy production, and that the things which restored sleep—thyroid, salt, sugar, protein, and progesterone, for example—were acting directly on the cells' energy production.

Since elevated adrenalin tends to raise blood pressure, I began explaining the effects of salt and thyroid to friends who were over 80. They found that they slept better, had more regular heartbeats, and didn't suffer from swollen feet when they ate a normal amount of salt. It didn't cause their blood pressure to rise.

Sodium bicarbonate and sodium chloride are known to have diuretic action; sodium

bicarbonate is often used to treat poisoning, to accelerate elimination of the toxin, for example.

Although there are complex theories about their effects, I suspect that two main processes are involved. By increasing the osmolarity of the blood, the blood volume is expanded by the entry of water from the tissues, and this increased perfusion of the kidneys would increase the formaton of urine, and, secondly, their increased concentration might simply increase the energy production of the kidneys. **The kidneys normally have a high oxygen consumption and an unusually high carbon dioxide concentration, which participates in the formation of urine. Acetazolamide, an inhibitor of the enzyme carbonic anydrase, is known to increase the body's retention of carbon dioxide,** and is sometimes used to increase the formation of urine, though its more important uses are in the prevention of edema of the lungs and brain in "mountain sickness" (a result of hyperventilation), and to reduce swelling of the eyes in glaucoma. It is also used to prevent sleep apnea, by correcting the alkalosis that causes it. The inhibition of carbonic anhydrase causes carbon dioxide retention, and this can produce acidosis. Intracellular acidosis has many important cell-protecting effects. By reducing the ionization of the cell's macromolecules, the cell's affinity for water is decreased.

Sodium bicarbonate is a more active diuretic than sodium chloride. I think this has to do with carbon dioxide's special properties, including its relative lipophilicity (preferential solubility in oils or cells), and its chemical combination with water.

Since salt restriction is the commonest way to try to correct edema, it's important to think about the physiological reasoning and evidence that support that common practice. In physiology lab classes, professors sometimes have one group of students drink a quart of ordinary water at the beginning of the class, while another group drinks a quart of isotonic saline (containing roughly a rounded teaspoonful of salt). Everyone measures their urine output over the next few hours, and by the end of the class, it turns out that those who drank the plain water produced about a quart more urine than those who drank the slightly salty water. The conclusion is obvious: For every 9 grams of salt, we retain a quart of water. That's an unfortunate experiment, though, because it creates such a clear impression of salt's immediate effect, but provides no information at all about its longer-range effects. Recently, a British physician, from Mongolia or northern China, studied the incidence of hypertension in her native region, where people consume at least 30 grams of salt per day. She found no hypertension at all, even among the oldest people. In my experiments, it has taken the body only two or three days to adjust completely to a massive change in salt consumption. Many hormones adjust quickly to retain or release sodium, according to the amount consumed, if the person is otherwise well nourished. Hypothyroid people, however, are unable to maintain a normal sodium concentration in their body fluids even when they increase their salt consumption.

Thyroid, protein, sodium, and magnesium will correct most edemas. Progesterone, acting on mitochondria to increase respiratory efficiency, and on structural proteins to change their ionic affinities, synergizes with the other natural factors to correct permeability and water regulation. One of the first people I saw use progesterone was a woman who (after being studied at the Mayo Clinic and many other places) believed she had Bright's disease, and habitually produced an extremely small quantity of urine. A few hours after taking just a few milligrams of progesterone, she telephoned to report that she "had to stop at every gas station on the way home," because she was forming urine at such a great rate. Increased perfusion of the kidneys is one of progesterone's normal functions, that accounts for its ability to prevent or cure "toxemia" of pregnancy. Besides its ability to increase blood perfusion of the kidneys (and other organs), progesterone has an important role in mineral regulation, since it acts as a "weak aldosterone," protecting against both a deficiency and an excess of that adrenal hormone. (The kallikrein enzymes which produce kinins and related hormones are probably involved in the effects of progesterone, estrogen, fatty acids, etc., on the permeability of blood vessels, blood

pressure, swelling, etc., but researchers have surprisingly little interest in that system..)

Brain edema causes seizures, lung edema causes "respiratory distress syndrome," and is a factor in pulmonary hypertension. In the heart and blood vessels, it increases rigidity and decreases the efficiency of blood circulatoin. Degenerative nerve and muscle diseases often begin with edema; degenerative spinal disks, and lens cataracts, are produced by an excess of water.

Although estrogen increases during acute sickness in both men and women, women have a higher incidence of estrogen-related diseases than men do. In spite of a large number of degenerative diseases caused by estrogen, women live significantly longer than men do, and both animal and human studies have shown that it is probably progesterone which gives women this advantage.

It is this female longevity that has allowed the drug companies to suggest that estrogen can prevent degenerative diseases. Estrogen's known promotion of clotting diseases, edema, diabetes, liver disease and blood pressure abnormalities, are ignored while cholesterol is emphasized as a "risk factor" that is favorably influenced by estrogen. Estrogen's elevation of free fatty acids, and the edema produced by these, are ignored as if they had no significance in the degenerative diseases.

I have already written about estrogen's contributions to brain aging and blood clotting diseases, but I plan to write soon about progesterone and thyroid as the important "heart protective" hormones.

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