Ray Peat's Newsletter

We are architects of violence against ourselves and our children, and we are the ones who must change the moral architecture of Western civilization. James W. Prescott

Serotonin, coherence and aging

45 years ago the "best" medical schools were still teaching that inflammation indicated the presence of an infection, and that it was the body's defensive reaction, an integral part of its immunity. Now, inflammation is seen to be intrinsic to the disease process itself, in an increasing number of the chronic and degenerative diseases—dementia, psychosis, atherosclerosis, osteoporosis, cancer, for example. One interpretation of the "autoimmune" diseases is that there is a specific occult infection, another interpretation puts the blame on a defective immune system which is attacking "self." An alternative view (Claudia Miller and Nicholas Ashford, 2012, for example) is that multiple chemical exposure has contributed to the problem of inflammatory sicknesses.

The change of official medical opinion on that issue is timely, since the prevalence of inflammatory disease is increasing very rapidly, among younger and younger people. Inflammatory bowel disease, kidney disease, certain cancers, SLE lupus, multiple sclerosis, rheumatoid arthritis, pulmonary arterial hypertension, and depression are conspicuous among these—pulmonary hypertension has been described as "an emerging epidemic" (Wijeratne, et al., 2018), and "major depressive disorder, a common and recurrent disorder, has been projected to become the second leading cause of disability worldwide by 2020" (Strekalova, et al., 2015). All of these diseases are more prevalent among women than men, and in some of them the difference is increasing along with the prevalence.

This changing pattern of disease is an opportunity to learn more about our nature, and about the factors involved in this association of femaleness and inflammatory-degenerative changes in the tissues. Changes in drug use seem to be responsible for some of these changes, and the pharmaceutical industry is already taking defensive measures.

The structural molecules of a cell, its metabolites and water are mutually dissolved, and their affinity for each other is affected by the cell's energetic relation to its environment. This mutual affinity is regulated by the balance of hormones and nutrients.

When pellagra, the niacin deficiency disease, was common, it was known that women were affected by it more seriously and much more often than men. The disease involved psychiatric problems, diarrhea, and skin photosensitivity, and I think it can give us an insight into the present preponderance of chronic disease in women.

Serotonin, tryptophan and melatonin all share a chemical structure known as an indole group. The indole structure is widely used by plants, animals and the simplest organisms in some of the most basic functions of life, including photosynthesis, movement, perception, structural maintenance, and regulation of water. The excitability of

its electron system makes it essential for the formation of the most highly interactive systems.

Dietary tryptophan is incorporated into all of our proteins except collagen, and it is also converted into a variety of small molecules, including niacinamide and serotonin. Estrogen strongly affects the metabolism of tryptophan, increasing its conversion to serotonin at the expense of niacinamide, which accounts for the symptoms of pellagra when the diet lacks tryptophan. When there's enough protein in the diet, promotion of serotonin synthesis won't result in a niacinamide deficiency, but conditions that increase the influence of estrogen will also increase the malfunctions involving serotonin.

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Estrogen increases the formation of serotonin, and both of these substances increase the formation of prolactin, and activate the renin-angiotensin system, and increase secretion of the antidiuretic hormone vasopressin, all of which synergize with estrogen in promoting water retention. Serotonin increases the formation of estrogen, so a vicious circle can easily develop when the organism is under stress.

The retention of water by the living substance is a topic that reductionist biology has been reluctant to discuss. There are no pumps for biological water, and it took a long time for a "water channel" protein to be proposed. The structural molecules of a cell, its metabolites and water are mutually dissolved, and their affinity for each other is affected by the cell's energetic relation to its environment. This mutual affinity is regulated by the balance of hormones and nutrients. ATP is a crucial factor in regulating the optimal state of water retention.

The outer region of cells near their surface is generally occupied by a layer of filamentous proteins, and this zone of the cell provides resistance and maintains the form of the cell. Every healthy cell has this distinct contrast between inside and outside, but this doesn't normally involve a mechanical stiffness, but the actin cytoskeleton becomes stiffer when the cell is under too much stress and unable to maintain its highest energy state. In this low energy distressed state, the barrier function begins to be lost.

Serotonin can activate the polymerization and stiffening of actin filaments, and increased polymerization can cause problems in breathing and blood circulation as well as increasing the leakiness of vascular walls (An, et al., 2002; Lai, et al., 2005; Shi, et al., 2016; Bloodworth, et al., 2018). Serotonin causes dissolved monomers of actin to polymerize, which can disrupt existing barriers as well as reducing the flexibility of cells (Gressner, et al., 2009).

When metabolic energy is failing, as in hypothyroidism, muscles become easily fatigued, and take up excess water, and the barrier structure is loosened, allowing macromolecules and ATP and other metabolites to leak out, while extraneous substances enter. Typical muscle enzymes such as lactate dehydrogenase and creatine kinase appear in the bloodstream in typical hypothyroid myopathy, and heart proteins, including a particular form of lactic dehydrogenase and a muscle protein, troponin, appear in the blood after a heart stress or fatigue combined with hypothyroidism or systemic inflammation. In the case of the liver, its specific enzymes appear in the blood when the cells' barrier function is weakened by stress. The "immune system" regularly deals with substances that are released by stressed cells.

Hyperventilation tends to increase under various stresses, and the resulting loss of carbon dioxide increases the alkalinity of the blood, which causes the platelets to release serotonin. Estrogenic stimulation and hypothyroidism are common causes of chronic hyperventilation, with its effect on platelets, releasing serotonin, with all its harmful consequences. A great source of error in serotonin research is to think of the binding of serotonin to its "transporter" protein as something intrinsic and genetically determined, when it is actually susceptible to momentary changes in energy and pH. When serotonin is tightly held by

the platelets, there is very little of it free in the plasma, and so it has little effect on the rest of the organism. However, if something suddenly reduces the amount of CO2 in the blood, the amount of serotonin in the plasma can increase greatly, making the blood vessels more permeable, and potentially interfering with the functioning of the organs, with leaked proteins creating edema, decreasing oxygen delivery, causing inflammation. Administering oxygen to sick people, or mechanically hyperventilating them, displaces CO2 and by causing the platelets to release serotonin can increase their sickness and likelihood of dying. This is a common practice, despite the evidence of increased mortality with even moderate hyperoxia (Rodríguez-González, et al., 2014; Page, et al., 2018; Kim, et al, 2018).

Any disruption of normal cell or tissue structure is recognized by the organism as a problem to be corrected; the appearance of ATP outside cells is a basic sign of damage and danger. Special enzymes degrade extracellular ATP into ADP, AMP, adenosine, and other purines, and these contribute to the alarm-stress signals. Increased synthesis of serotonin is one of the most important responses to leaked ATP and adenosine, but serotonin can increase the disorder of the actin system, increasing leakiness, in a vicious circle; both serotonin and ATP increase estrogen secretion (Rossato, et al., 2001; Klempan, et al., 2011). Extracellular ATP reaches a high level in tumors and becomes part of a self-stimulating growth promoting system. Fragments of actin in the bloodstream are a common consequence of stress-induced leakiness that must be controlled to preserve health; it happens that the vitamin D binding protein is a scavenger for this potential cause of "autoimmune disease," and this might relate to the fact that these diseases generally involve vitamin D deficiency.

The SSRI antidepressants are frequently used to treat people with traumatic brain injury, but it has been found that the synthesis of serotonin in the brain is increased by trauma and contributes to the injury (Pappius, et al., 1988), and that decreasing serotonin by a variety of means (Sharma, et al., 2000; 2019) improves recovery from brain injuries.

The Blood Brain Barrier, BBB, has sometimes been treated as something unique, but it's just a special case of the cellular resistance that exists everywhere. For example, after intense exercise that produces fatigue and damage to muscles, a unique brain protein, S100B, that is considered a crucial part of the BBB, can be found in the blood stream. The exchange of substances, even proteins and nucleic acids, between cells and their environment, increases during stress. The detection of substances such as S100B in the blood is now recognized as evidence of depression and brain damage (Arora, et al., 2019; Park, et al., 2019). It has been known for a long time that serotonin is able to increase the permeability of blood vessels, including the BBB, but there hasn't been much publicity of the fact that SSRIs can increase the leaking of S100B into the blood (Akhisaroglu, et al., 2003; Dai, et al., 2018; Pawluski, et al., 2019).

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The great majority of the body's serotonin is produced in the intestine, where the tissue is constantly exposed to foreign material such as endotoxin, but all cells in the body can produce serotonin and histamine during stress, and the blood platelets are one of the body's defenses against serotonin; they can sequester it and carry it to the lungs for destruction. The lungs have a great capacity to oxidize it.

Severe stresses in one part of the body spread their influence through the body, in the process now called the bystander or "off-target" effect. Serotonin, nitric oxide, and ATP are among the substances that are known to spread damage

signals through the body, for example from ionizing radiation, localized infection, or surgery.

The capillaries in the brain resemble those of the lung in their ability to take up and destroy serotonin; they treat it as a toxin to eliminate. (Hardebo and Owman, 1980 a,b; Hardebo, et al., 1979.) If something (such as estrogen excess) reduces the cells' ability to oxidize and inactivate the serotonin, its action on the actin cytoskeleton will allow harmful amounts of serotonin and other materials to enter the brain.

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The large controlled studies of SSRI antidepressants found a significant, but very small difference in effect between the drugs and a placebo. Their antidepressant effects have often been found to depend on effects other than the availability of serotonin in the brain. For example, a large proportion of depressed people are constipated, and SSRIs have a prokinetic, accelerating effect in the intestine, functioning as a laxative (Gorard, et al., 1994). Relieving constipation has a powerful effect on mood and sense of well-being. For example, naloxone or naltrexone, by correcting an excessive endorphin balance, has a laxative action, which undoubtedly contributes to its significant antidepressive effect. Large doses of vitamin C, functioning as a cathartic, have many therapeutic effects, and it is gaining recognition as an antidepressant.

Because it hasn't been possible to provide evidence to support the idea that serotonin is a mood elevator "happy hormone," the industry has looked for some way to explain the therapeutic benefit that they claim. They have generally settled on the idea that the SSRIs, after several weeks of use, increase the synthesis of the progesterone metabolite allopregnanolone, in the brain.

That does happen, but the synthesis of those defensive steroids is also increased by any injury to the brain (di Michele, et al., 2000). Electroshock convulsive therapy, which is commonly used when severe depression isn't relieved after more than a year of drug treatment, also increases the production of those neurosteroids, but at the cost of brain cell death.

The public is slowly becoming aware of the association of the SSRIs with obesity, sexual malfunction, hair loss, and osteoporosis, but that information is always put into the context of their supposed therapeutic value. If the drugs' only real value is their laxative effect, and the adaptive neurosteroid synthesis that occurs after any brain damage, then it's clear that the safer antidepressants that are known should be used.

Although it's not reflected in the mass media or the practice of medicine, many studies show that increased serotonin and tryptophan are associated with depression and suicidality, anxiety, aggression, and violence (de Boer and Koolhaas, 2005; van der Vegt, et al., 2003).

The actual properties of the drugs and the serotonin system that they distort should be considered in relation to each of the epidemic conditions, for example their effect of lengthening the heart's repolarization (QT) interval, which is known to sometimes cause cardiac arrest, in relation to the hundreds of thousands of sudden cardiac deaths that are occurring annually in the US, including tens of thousands of apparently healthy young people. How many of those were using the drugs?

Serotonin slows oxidative metabolism (in many animals it's involved in preparation for hibernation), and reduces the circulation of blood in the brain (Szabo and Hofmann, 1989; Aleksandrin, et al., 2005). The reduced use of glucose and oxygen by brain tissue characterizes depression, hypothyroidism, aging, and dementia, as well as the effects of serotonin produced by stress or trauma. The lower energy production makes the organism more susceptible to stress.

Aerobic glycolysis, the metabolism characteristic of cancer, in which lactic acid is produced from glucose despite the presence of oxygen, is promoted by serotonin (Balitskii and Vinnitskii, 1972; Koren-Schwartzer, et al., 1994; Rudzit, et al., 1968; Kornberg, et al., 2018), and can be found in the autoimmune diseases.

50 to 60 years ago Hans Selye and his associates were showing that increased serotonin made specific organs and tissues more susceptible to

stress and degenerative diseases, such as ulceration and sclerosis. Considering their work in relation to the current epidemic of female-related diseases, we should consider the possibility that the SSRIs are among the causes of this epidemic.

A recent article on autoimmunity suggests that prolactin can be considered as a cytokine affecting inflammation in the "autoimmune diseases" such as multiple sclerosis and SLE, as well as a hormone (Borba, et al., 2019). Since prolactin depends on estrogen, the estrogen industry has discouraged this line of thinking. Whether the issue has been inflammatory bowel disease, autism, Alzheimer's disease, breast cancer, or rheumatoid arthritis, money for research, advertising, and lobbying has always been able to turn attention away from estrogen as the cause.

Serotonin, along with estrogen, is the major promoter of prolactin secretion, and it also promotes TSH, ACTH, FSH, LH, GH, MSH, POMC, vasopressin, and oxytocin--all the pituitary hormones.

Stresses of different sorts increase the formation of serotonin and the various pituitary hormones, leading to adaptive changes in the organism, but at the cost of causing inflammation and degeneration. Studies of several of the pituitary hormones have shown age-accelerating effects, leading to edema, inflammation, fibrosis, and decreased longevity. W.D. Denckla's experiments showing the great life extending effect of removing the pituitary gland, while supplementing thyroid and glucocorticoid hormones, suggest the possibilities inherent in finding ways to prevent the over-production of serotonin and its associated hormones and cytokines.

As it becomes generally known that serotonin promotes, and that anti-serotonin measures can prevent, alleviate, and sometimes cure most of the problems caused by stress and serotonin dominance--cancer, dementia, arthritis, and dozens of other disabling and killing conditions--the drug industry's social and political power will be threatened. Their historical behavior suggests that their response will be to interfere with the use of the safe inexpensive generic substances that solve those problems.

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