

Ray Peat's Newsletter

Events are not the images of dead principles. Robert C. Creegan

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Demystifying dementia: Protective progesterone

There are effective treatments for degenerative nerve diseases, based on well understood biological mechanisms, but they are rarely used, because the relation of those mechanisms to the diseases isn't widely recognized. In recent years, there has been a significant amount of research on the use of progesterone for treating strokes and traumatic brain injury, which involve some of the same biological mechanisms as senile dementia and other brain "diseases." At the same time, though, there have been powerful commercial influences preventing progress in these therapeutic uses.

In the 1970s when I would describe progesterone's effectiveness in PMS, migraines, epilepsy, nephritis, depression, cancer, burns, arthritis, and dementia, it seemed impossible to physicians that a single substance could do those things; they had learned somewhere that "there are no panaceas." I explained some of the reasons for progesterone's "biological generality," but that information had little effect on a medical culture that is organized around the idea that each disease is a certain kind of thing, with its own unique cause or group of causes.

Therapeutic practices are limited by the lack of biological generality underlying the medical understanding of sickness. Hans Selye's concept of stress was part of his search for general biological principles relevant to medicine, but the "stress syndrome," if it has any importance for medicine, is likely to be treated as a thing in itself, rather than as an opportunity for enlarging the understanding of the various "diseases."

Historically, ideas of the causes of disease have changed as new information became available. Tuberculosis and pellagra, which had been thought of as hereditary diseases, came to be seen

as infectious and nutritional diseases, as experimental knowledge accumulated. At each stage of understanding, new factual knowledge was used to explain the nature of a disease.

But when the medical industry invested heavily in a certain way of treating a disease, the treatment became a component of how the disease was understood, and tended to freeze a certain way of defining the disease.

In 1847 Rudolph Virchow said "diseases are not isolated phenomena..., not beings that have penetrated into the body..., but they are a certain way in which living beings react to changed circumstances...." In the 20th century, most medical thinking about disease reverted to an earlier essentialist attitude, emphasizing single causes. Cancer was an extreme example of essentialist thinking--it was a "genetically" distinct sort of being, caused by mutant genes, implanted in the victim organism. The treatments all involved removing or killing tissue, and an industry based on those treatments couldn't consider other definitions of the disease.

The same cultural factors are involved in the understanding of functional conditions, including the degenerative brain diseases. When L-DOPA was found to alleviate some of the symptoms of Parkinson's disease, the disease came to be seen as a dopamine deficiency, to the neglect of nearly everything else involved (such as excessive serotonergic activity--Kaya, et al., 2008) in the degenerative processes. For about 20 years after the drug industry invested in the "cholinergic hypothesis" of Alzheimer's disease, a deficiency of acetylcholine was thought to be an essential feature of the condition, despite a considerable amount of evidence that the theory was unfounded.

Although a disproportionate amount of research was directed by these narrow

pharmaceutical ideas, some basic research continued to be done in universities, but even that was strongly influenced by the cultural and economic situation, the availability of funding and the possibility of publishing. For example, the brain toxic effects of estrogen were usually neglected, and the much higher incidence of Alzheimer's disease in women was usually interpreted as evidence that the disease is caused by a *deficiency* of estrogen. The neurotoxic effects of lipid peroxides and prostaglandins were often ignored, while fish oil was advocated to prevent and treat dementia. The toxic effects of serotonin and nitric oxide were seldom considered, while drugs to increase those were advocated to treat Alzheimer's disease.

These distortions, caused by the economic pressure to make the disease conform to the existing drug business, have prevented the generalization of the understanding and treatment of disease, in line with Virchow's (and Selye's) thinking. If we understand the basic life processes, and the ways in which organisms "react to changed circumstances," then we can look for ways to support more appropriate reactions and to improve the circumstances.

At an early stage of the disease, the brain's glucose consumption rate decreases, and later the blood flow through the brain and the consumption of oxygen decrease. This means that at the beginning of the disease there is a shift from glucose to fatty acids for energy production. This kind of change of fuel occurs during fasting, stress, diabetes, and estrogenic stimulation.

Metabolic energy is fundamental to the development and maintenance of the body, and to the "ways in which living beings react to changed circumstances." It's an obvious first thing to consider when thinking about any "disease," whether it's cancer, radiation sickness, dementia, depression, or traumatic injury.

The well known anatomical features of Alzheimer's disease (neurofibrillary tangles and amyloid plaques) appear as a result of the energy failure, with stress increasing free fatty acids, which inhibit glucose oxidation and promote inflammation and lipid peroxidation, and cause the accumulation of amyloid, which seems to be responsible for the development of the tangles.

The mitochondria are responsible for the efficient production of energy needed for the functioning of complex organisms, and especially for nerves. The enzyme in the mitochondria that reacts directly with oxygen, and that is often rate limiting, is cytochrome c oxidase.

This enzyme is dependent on the thyroid hormone and is inhibited by nitric oxide, carbon monoxide, estrogen, polyunsaturated fatty acids, serotonin, excess or free iron, ionizing radiation, and many toxins, including bacterial endotoxin. Red light, which passes easily through the tissues, reactivates the enzyme, which slowly loses its function during darkness.

Estrogen impairs the mitochondria in multiple ways, including blocking the function of cytochrome oxidase, decreasing the activity of ATP synthase, increasing heme oxygenase which produces carbon monoxide and free iron, damaging mitochondrial DNA, and shifting metabolism from glucose oxidation to fat oxidation, especially by inhibiting the mitochondrial pyruvate dehydrogenase complex. These changes, including the loss of cytochrome oxidase, are seen in the Alzheimer's brain. The fact that this kind of energy impairment can be produced by estrogen doesn't imply that estrogen is the cause, since many other things can cause similar effects--radiation, aluminum, and endotoxin, for example.

But it happens that in the Alzheimer's brain there is an increase of the enzyme aromatase, which synthesizes estrogen. Mice can be genetically modified to lack the aromatase gene, and this kind of mouse was crossed with a mouse that develops a condition similar to Alzheimer's disease. These mice didn't deteriorate mentally as they aged, as related mice with the aromatase gene did, and tests found that no estrogen could be detected in their serum or brain (McAllister, et al., 2010). While the "Alzheimer's" mice with the ability to produce estrogen had 50% less testosterone than normal, the mutant mice unable to produce estrogen had more testosterone in their brains and serum than either the normal mice or the Alzheimer's mice.

Testosterone has intrinsic cell-protective effects, including opposition to estrogen and cortisol, but in the presence of aromatase, it can be

converted to estrogen. Progesterone has the same basic cell-protective effects, but its metabolites in the brain, the neurosteroids, are specific neuroprotectors. DHEA also has brain-protective effects.

All of these cell-protective steroids have a negative feedback relation to the luteinizing hormone, LH, that is, as they are increased by its action, they inhibit the secretion of LH. Estrogen has a positive feedback relation to the gonadotropins, meaning that a little estrogen can stimulate an increase of LH and FSH, leading to greater production of estrogen. This means that a deficiency of progesterone, relative to estrogen, will tend to cause increased LH, unless other factors change. Both FSH and LH are generally increased at menopause and in Alzheimer's disease. LH increases about 3 to 4-fold in both men and women with aging (Casadesus, et al., 2006), but it increases more (in both the brain and serum) in Alzheimer's disease.

The increased LH in Alzheimer's disease (rather than the low ratio of progesterone to estrogen) is being discussed as a basic cause of Alzheimer's disease. A drug that lowers LH (leuprolide) decreases the formation of amyloid and improves cognitive functions in mice, and it has been suggested that the use of leuprolide in prostate cancer patients might account for their lower incidence of degenerative nervous diseases. LH is present in increased amounts in both the serum and nerves of Alzheimer's patients, and in vitro, it increases the formation of amyloid (Meethal, et al., 2005). Transgenic mice that produce increased amounts of LH perform poorly in maze tests, but similar mice that lack the LH receptor perform normally (Casadesus, et al., 2007).

LH, like other pituitary hormones, has a variety of pro-inflammatory effects, for example in rheumatoid arthritis and lung inflammation. DHEA and testosterone can reduce inflammation and lower LH, but both of those can be converted to estrogen by aromatase. Progesterone, however, has a very broad spectrum of antiinflammatory actions, including the inhibition of LH, and its metabolites (the "neurosteroids") also have various protective effects in the brain. One of the metabolites is able to inactivate the aromatase enzyme

(Pasqualini and Chetrite, 2008). Although they are called neurosteroids, they are also protective against cancer and are an important part of the progestational system in pregnancy.

Progesterone's antiinflammatory effects include the inhibition of the enzymes that form prostaglandins, overlapping with aspirin in that function. However, unlike aspirin, progesterone also activates an enzyme that degrades prostaglandins. Besides being important amplifiers of inflammatory reactions, the prostaglandins inhibit mitochondrial energy production (Cherkasskaia, et al., 1982) and activate aromatase and estrogen synthesis. Estrogen activates the formation of prostaglandins (Toda, et al., 2012) and inhibits the enzyme that degrades them (Chang and Tai, 1985). Progesterone also inhibits the synthesis of nitric oxide (Wang, et al., 2012); its inhibition of nitric oxide protects mitochondrial respiration (Deniselle, et al., 2012). Since estrogen increases the production of prostaglandins and nitric oxide, and decreases the degradation of prostaglandins, progesterone's various estrogen-inhibiting actions are a very important part of its protective effects.

More than 40 years ago D.G. Stein started studying brain injury in animals and the possibility of preventing or reducing its long range effects. For more than 20 years he didn't find anything that helped, but in 1992 a student, Robin Roof, did experiments showing that progesterone injections reduced or prevented brain edema after a brain contusion. Pseudopregnancy, in which there is a high ratio of progesterone to estrogen, also prevented brain edema. An oxidative breakdown product of arachidonic acid, isoprostane, associated with dementia was reduced by 2/3 in the animals treated with progesterone (Roof, et al., 1997). In 2000 and 2001, both Roof and Stein published some articles suggesting that estrogen might also be beneficial, but after the 2002 WHI announcement that estrogen increased dementia, I haven't seen any more estrogen publications from either of them. Referring later to the early studies, Roof said she "didn't look at estrogen during that time because it did not seem to be neuroprotective in that model (at least in terms of edema)."

Brain edema, which is an early response to any brain injury, is seldom discussed as a feature

of Alzheimer's dementia, but MRI studies clearly show that brain water is disproportionately intracellular, meaning that the cells are swollen. A protein called "aquaporin-4" is associated with brain injury and edema, and it is increased by estrogen, and decreased by progesterone.

Progesterone's very large effect on oxidative damage in the animal studies was very important, because the isoprostanes and prostaglandins are now known to be closely associated with Alzheimer's disease and other age related neurodegenerative diseases. The spontaneously formed isoprostanes were discovered in 1992, and it was several years before their role in degenerative diseases began to be studied.

Other new knowledge of the ways in which polyunsaturated fats break down has become available in this same period. For example, acrolein, which is elevated in Alzheimer's disease, is from 10 to 100 times more reactive than some of the better known oxidative fragments, and it is formed mainly from omega-3 polyunsaturated fatty acids, especially DHA and EPA. It inhibits respiration in brain mitochondria, damages proteins, forming "advanced glycation end-products" (Pietkiewicz, et al., 2011), and is toxic to brain cells. It inhibits the uptake of glutamate (Lovell, et al., 2000) which would contribute to excitotoxicity to nerve cells. (Polyunsaturated fatty acids and estrogen tend to promote excitotoxicity in other ways, too.)

Acrolein's self-stimulating production from DHA is another factor that could account for the predominance of Alzheimer's disease in women, since, under the influence of estrogen, women accumulate significantly more DHA than men (Giltay, et al., 2004), and similar effects can be seen in animal studies (McNamara, et al., 2008).

This is probably related to the increased vitamin E requirement caused by estrogen (Briggs, 1975), and to the ability of estrogen to increase the age pigment, lipofuscin (Harris, 1966; Graham, 1968; MÅntzing and Nilsson, 1972; Karkare, et al., 1995). The shorter chain fatty acids of coconut oil are more easily oxidized for energy than long chain fatty acids, and their saturation makes them resistant to the random oxidation produced by inflammation, so they don't support

the production of acrolein or age pigment; along with their reported antiinflammatory effects, these properties might be responsible for their beneficial effects that have been seen in Alzheimer's disease.

The myelin content is decreased in Alzheimer's disease, and progesterone is known to stimulate its resynthesis by the oligodendrocytes; the neurosteroids are known to be involved in the regeneration, survival, and function of brain cells (Schumacher, et al., 1996). Cholesterol, which is the precursor for pregnenolone, progesterone, and DHEA, is lost from the white matter in Alzheimer's disease (Roher, et al., 2002), and replacing cholesterol in the brain can have protective effects against the deposition of amyloid (Sponne, et al., 2004). Thyroid hormone is involved in the synthesis of the neurosteroids, the repair of myelin, and all the essential brain functions, as well as systemic regulation of hormones.

Although the growth hormone is one of the hormones increased by stress and estrogens which produce free fatty acids by lipolysis, it's generally assumed that it decreases in Alzheimer's disease, as it does in normal aging. However, it's known that somatostatin, the inhibitor of growth hormone secretion, is decreased (by about 50%) in Alzheimer's disease. Normal people have very low serum growth hormone in the morning, but Alzheimer patients' growth hormone is high in the morning. Somatostatin is inhibited by estrogen and serotonin, which are both increased in Alzheimer's disease, and hypothyroidism could also contribute to the lack of somatostatin (Baldini, et al., 1992). The deficiency of somatostatin probably contributes to the increased TSH as well as growth hormone found in Alzheimer's disease (Christie, et al., 1987). Decreased T3, the active thyroid hormone, in the Alzheimer's brain is another factor in the elevated TSH.

Other lipolytic hormones that are increased in Alzheimer's disease and other neurodegenerative diseases include ACTH, cortisol, and adrenalin. Growth hormone stimulates the release of serotonin (and reduces dopamine), and serotonin in turn stimulates growth hormone release.

The maladaptive sequence, starting from stress or hypothyroidism, would typically involve increased absorption of endotoxin, leading to interference with mitochondrial respiration, a shift to fat oxidation, inflammation, and the increase of a wide range of stress hormones. Each of these steps happens to interfere with the production of progesterone, leading to increased LH.

Even a seemingly minor brain trauma can start a process that leads to permanent and progressive impairment. A brain injury increases the likelihood of later developing Alzheimer's disease or Parkinson's disease. A mild concussion, or exposure to ionizing radiation, or even chronic exposure to "weak" electromagnetic fields, can activate these same mechanisms of inflammation and deterioration. These after-effects involve the same mechanisms as the radiation bystander effects—a spreading of inflammatory processes and edema. Strokes, tumors, and infections also typically activate the same processes of inflammation and swelling.

Although just supplementing with progesterone and/or thyroid can sometimes produce rapid improvement in brain function, it would be reasonable to correct as many of the metabolic defects as possible, starting with the elimination of polyunsaturated fats from the diet, and eating an antiinflammatory diet, low in iron, phosphate, antithyroid or estrogenic substances, and starches, with fruits and saturated fats as the main calorie sources. Aspirin, vitamin K (essential for brain lipid synthesis and growth regulation), magnesium, niacinamide, caffeine, antihistamines and antiserotonin drugs (such as cyproheptadine), antibiotics (especially antiinflammatory antibiotics such as minocycline) and diuretics such as acetazolamide are supplements that are likely to be beneficial. Vitamin D should be measured, because a deficiency can impair brain functions. (The correct blood test for vitamin D status is 25(OH)vitamin D, not 1,25 dihydroxyvitamin D.) Small amounts of baking soda, or rebreathing in a bag to increase carbon dioxide, can increase blood circulation to the brain.

Getting a generous amount of light on the head has beneficial effects on mental functions, by increasing the activity of cytochrome oxidase (Rojas, et al., 2012) and reducing inflammation. Cytochrome oxidase in the brain can also be

increased by mental stimulation, learning, and moderate exercise, but excessive exercise or the wrong kind of exercise ("eccentric") can lower it (Aguiar, et al., 2007, 2008), probably by increasing the stress hormones and free fatty acids. Sedentary living at high altitude has beneficial effects on mitochondria similar to moderate exercise at sea level (He, et al., 2012).

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