Multiple sclerosis and other hormone-related brain syndromes

Listed under Ray Peat. Theme

From the original article in 2013. Author: Ray Peat.

Since I am trying to discuss a complex matter in a single article, I have separately outlined the essential technical points of the argument in a section at the beginning, then I explain how my ideas on the subject developed, and finally there is a glossary. If you start with "Short-day brain stress," "Estrogen's effects," and "Symptoms and therapies," you will have the general picture, and can use the other sections to fill in the technical details.

The argument:

1) The hormones pregnenolone, thyroid, and estrogen are involved in several ways with the changes that occur in multiple sclerosis, but no one talks about them.

2) The process of myelination is known to depend on the thyroid hormone. The myelinating cells are the oligodendroglia (oligodendrocytes) which appear to stop functioning in MS (and sometimes to a milder degree in Alzheimer's disease, and other conditions). The cells' absorption of thyroid hormone is influenced by dietary factors.

3) The oligodendrocytes are steroid-producing cells (1), and steroidogenesis is dependent on thyroid hormone, and on thyroid-dependent respiratory enzymes and on the heme-enzyme P-450scc, which are all sensitive (2) to poisoning by carbon monoxide and cyanide. The steroid produced by the oligodendrocytes is pregnenolone, which is known to have a profound anti-stress action (3), and which appears to be the main brain-protective steroid.

4) Lesions resembling those of MS can be produced experimentally by carbon monoxide or cyanide poisoning.(4) The lesions tend to be associated with individual small blood vessels, which are likely to contain clots. (Since all animals have enzymes to detoxify cyanide, this poison is apparently a universal problem, and can originate in the bowel. "Detoxified" cyanide is still toxic to the thyroid.)

5) Pregnenolone and progesterone protect against nerve damage (5) by the excitotoxic amino acids (glutamic acid, aspartic acid, monosodium glutamate, aspartame, etc.), while estrogen (6) and cortisol (7) are nerve-destroying, acting through the excitotoxic amino acids. Excitotoxins destroy certain types of nerve, especially the dopaminergic and cholinergic types, leaving the noradrenergic types (8), paralleling the changes that occur in aging. The clustering of oligodendrocytes around deteriorating nerve cells could represent an adaptive attempt to provide pregnenolone to injured nerve cells.

6) The involvement of hormones and environmental factors probably accounts for the intermittent progress of multiple sclerosis. To the extent that the environmental factors can be corrected, the disease can probably be controlled.

Short-day brain stress

Shortly after I moved from Mexico to Montana, one of my students, a 32 year old woman, began having the same sensory symptoms her older sister had experienced at the same age, at the onset of multiple sclerosis. Vertigo and visual distortions of some sort made her consider withdrawing

from the university. I'm not sure why she tried eating a whole can of tuna for lunch a couple of days after the onset of symptoms, but it seemed to alleviate the symptoms, and she stayed on a high protein diet and never had a recurrence. She told me some of the lore of MS: That it mostly affects young adults between the ages of 20 and 40, that it is common in high latitudes and essentially unknown in the tropics, and that it is sometimes exacerbated by pregnancy and stress. (Later, I learned that systemic lupus erythematosis and other "auto-immune" diseases also tend to occur mainly during the reproductive years. I discussed some of the implications of this in "Bean Syndrome.")

Having enjoyed the mild climate of Mexico, I became very conscious of the harm done to us by northern winters, and began developing the idea of "winter sickness." In 1966-67, allergies, PMS, weight gain, colitis, and arthritis came to my attention as winter-related problems, and I assumed that the high-latitude incidence of MS related to what I was seeing and experiencing. Studies in Leningrad began revealing that mitochondria are injured during darkness, and repaired during daylight. I observed that hamsters' thymus glands shrank in the winter and regenerated in the summer; shrinkage of the thymus gland is a classical feature of stress, and usually reflects the dominance of cortisone, though estrogen and testosterone also cause it to shrink. Winter's darkness is stressful in a very fundamental way, and like any stress it tends to suppress thyroid function. In the hypothyroid state, any estrogen which is produced tends to accumulate in the body, because of liver sluggishness.

I began to see that PMS could be controlled by certain things--extra light, supplements of sodium and magnesium, high quality protein, and correction of deficiencies of thyroid and progesterone. In working on my dissertation, I saw that tissue hypoxia (lower than optimal concentrations of oxygen in the blood) may result from estrogen excess, vitamin E deficiency, or aging. There is a close biological parallel between estrogen-dominance and the other hypoxic states, such as stress/shock, and aging.

Estrogen's effects

As a portrait painter, I had been very conscious of the blue aspect that can often be seen in the skin of young women. In pale areas, the color may actually be blue, and in areas with a rich supply of blood, such as the lips, the color is lavender during times of high estrogen influence--around ovulation and puberty, for example. During these times of estrogen dominance, the blood is not only poorly oxygenated, but it has other special properties, such as an increased tendency to clot. The Shutes' work in the 1930s began with the use of vitamin E to antagonize estrogen's clot-promoting tendency, and led them to the discovery that vitamin E can be very therapeutic in heart disease. More recently, it has been found that men with heart disease have abnormally high estrogen (9), that women using oral contraceptives have higher mortality from heart attacks (10), and that estrogen tends to promote spasm of blood vessels (11). (These reactions are probably related to the physiology of menstruation, in which progesteronewithdrawal causes spasms in the spiral arteries of the uterus, producing endometrial anoxia and cell death.)

In toxemia of late pregnancy, or eclampsia, the exaggerated clotting tendency caused by excess estrogen (or by inadequately opposed estrogen, i.e., progesterone deficiency), can cause convulsions and strokes. Vascular spasms could be involved here, too. The stasis caused by the vasospasm would facilitate clotting. (Vascular spasm has been observed in epilepsy, too. Epilepsy can be brought on by the premenstrual excess of estrogen, and in that situation there is no evidence that clotting is involved. Leakage of hemoglobin out of red cells can cause vasospasm, so bleeding, clotting, strokes, and seizures can interact complexly.) The brains of women who have diedfollowing eclampsia show massive clotting in the blood vessels, and their livers are characteristically injured, with clots (12).

Tom Brewer and others have shown very clearly that malnutrition, especially protein deficiency, is the cause of toxemia of late pregnancy. (In Nutrition for Women, I discussed the importance of protein in allowing the liver to eliminate estrogen.)

Various researchers have demonstrated that the plaques of MS usually occur in the area served by a single blood vessel (13, 14), and some have suggested that clotting is the cause. MS patients

have been found to have an abnormal clotting time, and it has been suggested that an altered diet might be able to correct the clotting tendency.

Studies in animals have shown clearly that a protein deficiency increases the fibrinogen content of blood. (Field and Dam, 1946.) Other factors that increase blood clotting are elevated adrenalin and cortisone. Protein deficiency causes an adaptive decrease in thyroid function, which leads to a compensatory increase in adrenaline and cortisone. The combination of high estrogen with high adrenaline increases the tendency for both clots and spasms of the blood vessels (11).

In experimental poisoning of animals with carbon monoxide or cyanide, the brain lesions resembling MS include blood clots. The patchy distribution of these spots in the brain suggests that the clotting is secondary to metabolic damage in the brain. Presumably, the same would be true in ordinary MS, with clots and spasms being induced in certain areas by metabolic abnormalities in brain cells. The injured cells that are responsible for myelination of nerve fibers are steroid-forming cells. A failure to secrete their protective pregnenolone could cause a local spasm of a blood vessel. The circulatory problem would exacerbate the respiratory problem. Steroid production is dependent on NADH and NADPH, and so requires adequate energy supplies and energy metabolism. The phenomenon of blood-sludging, studied by M. Knisely at the University of Chicago in the l930s and l940s, is apparently a general result of decreased energy metabolism, and is likely to be a factor in energy-and-circulatory vicious circles.

Symptoms and therapies

Around 1976 I met a woman in her mid-thirties who heard about my work with progesterone in animals. She had been disabled by a brain disease that resembled MS or Devic's disease, inflammation of the optic nerves. It would sometimes cause blindness and paralysis that persisted for weeks at a time. During remissions, sometimes using a wheelchair, she would go to the medical school library to try to understand her condition. She came across Katherina Dalton's work with progesterone, and convinced a physician to give her a trial injection. Although she had trouble finding people who were willing to give her progesterone, her recovery was so complete that she was able to climb stairs and drive her car, and she came to my endocrinology class and gave a very good (and long) lecture on progesterone therapy. Although her sensory and motor functions became normal, she remained very fat, and chronically suffered from sore areas on her arms and legs that seemed to be abnormal blood vessels, possibly with phlebitis. She appeared to need thyroid hormone as well as larger amounts of progesterone, but never found a physician who would cooperate, as far as I know.

In the late 1970s I was seeing a lot of people who had puzzling health problems. In a period of two or three years, there were five people who had been diagnosed by neurologists as having multiple sclerosis. In talking to them, it seemed clear that they had multiple symptoms of hypothyroidism. They weren't severely disabled. Since they weren't fat or lethargic, their physicians hadn't thought they could be hypothyroid. When they tried taking a thyroid supplement, all of their symptoms disappeared, including those that had led to their MS diagnosis. One of the women went to her doctor to tell him that she felt perfectly healthy since taking thyroid, and he told her to stop taking it, because people who have MS need a lot of rest, and she wouldn't get enough rest if she was living in a normally active way. The assumption seemed to be that the diagnosis was more important than the person. (When I refer to a "thyroid supplement" I mean one that contains some T3. Many people experience "neurological symptoms" when they take thyroxine by itself. Experimentally, it has been found to suppress brain respiration, probably by diluting the T3 that was already present in the brain tissue.)

Metabolism of the oligodendrocytes

The rate-regulating step in steroid synthesis involves the entry of cholesterol into the mitochondria, where the heme-enzyme P-450scc then removes the side-chain of cholesterol (by introducing oxygen atoms), to produce pregnenolone. This enzyme can be poisoned by carbon monoxide or cyanide, and light can eliminate the poison (15); this could be one aspect of the winter-sickness problem.

Peripheral nerves are myelinated by essentially the same sort of cell that is called an oligodendrocyte in the brain, but outside the brain it is called a Schwann cell. It is easier to study the myelin sheath in peripheral nerves, and the electrical activity of a nerve is the most easily studied aspect of its physiology. Certain experiments seemed to indicate a "jumping" (saltatory) kind of conduction along the nerve between Schwann cells, and it was argued that the insulating function of the myelin sheath made this kind of conduction possible. This idea has become a standard item in physiology textbooks, and its familiarity leads many people to assume that the presence of myelin sheaths in the brain serves the same "insulating" function.

For a long time it has been known that heat production during nerve conduction reveals a more continuous mode of conduction, that doesn't conform to the idea of an electrical current jumping around an insulator. Even if the myelin functioned primarily to produce "saltatory conduction" in peripheral nerves, it isn't clear how this process could function in the brain. I think of the issue of "saltatory conduction at the nodes of Ranvier" as another of the fetish ideas that have served to obstruct progress in biology in the United States. A more realistic approach to nerve function can be found in Gilbert Ling's work. Ling has demonstrated in many ways that the ruling dogma of "cell membrane" function isn't coherently based on fact. He found that hormones such as progesterone regulate the energetic and structural stability of cells. Many people, unaware of his work, have felt that it was necessary to argue against the idea that there are anesthetic steroids with generalized protective functions, because of their commitment to a textbook dogma of "cell membrane" physiology.

I think the myelinating cells do have relevance to nerve conduction, but I don't think they serve primarily as electrical insulators. If the adrenal cortex were inside the heart, it would be obvious to ask whether its hormones aren't important for the heart's function. Since the oligodendrocytes are steroid-synthesizers, it seems obvious to ask whether their production of pregnenolone in response to stress or fatigue isn't relevant to the conduction processes of the nerves they surround.

Old age

A biologist friend of mine who was about 85 became very senile. His wife started giving him thyroid, progesterone, DHEA and pregnenolone, and within a few days his mental clarity had returned. He continued to be mentally active until he was 89, when his wife interfered with his access to the hormones.

In old age the brain steroids fall to about 5% of their level in youth. Pregnenolone and DHEA improve memory in old rats, and improve mood stability and mental clarity of old people. Pregnenolone's action in improving the sense of being able to cope with challenges probably reflects a quieting and coordinating of the "sequencing" apparatus of the forebrain, which is the area most sensitive to energy deprivation. This is the area that malfunctions in hyperactive and "dyslexic" children. Weakening of the sequencing and sorting processes probably explains the common old-age inability to extract important sounds from environmental noise, creating a kind of "confusion deafness." Insomnia, worry and "restless legs" at bedtime are problems for many old people, and I think they are variations of the basic energy-depletion problem.

The oligodendrocytes were reported (Hiroisi and Lee, 1936) to be the source of the senile plaques or amyloid deposits of Alzheimer's disease.(16) Hiroisi and Lee showed the cells in different stages of degeneration, ending with translucent "mucoid" spots that stained the same as amyloid, the material in the senile plaques. This type of cell also appears to form a halo or crown around degenerating nerve cells--possibly in a protective reaction to provide the nerve cell with any pregnenolone the oligodendrocytes are able to make. The oligodendrocytes, the source of the brain steroids (that people previously believed came from the adrenals and gonads, and were just stored in the brain), myelinate nerve fibers under the influence of thyroid hormone (17). Thyroid is responsible for both myelination and hormone formation. In old age, glial cells become more numerous, and nerve cells become structurally and functionally abnormal, but usually there is no problem with the formation of myelin. In MS, the problem is just with myelination, and there are no senile plaques or defects in the nerve cells themselves.

These differences suggest the possibility that Alzheimer's disease involves a specific premature

loss of brain pregnen- olone production, but not of thyroid. Recent work suggests a central role for pregnenolone and progesterone in the regulation of consciousness (18), and possibly in the brain's detoxifying system. Elsewhere, I have suggested that vitamin A deficiency might cause the excessive production of the "amyloid" protein. A vitamin A deficiency severely inhibits steroid synthesis. (It is used so massively in steroid synthesis that a progesterone supplement can prevent the symptoms of vitamin A deficiency.) I suspect that vitamin A is necessary for the side-chain cleavage that converts cholesterol to pregnenolone. Iron-stimulated lipid peroxidation is known to block steroid formation, and vitamin A is very susceptible to destruction by iron and oxidation. Iron tends to accumulated in tissues with aging. Gajdusek has demonstrated that brain deterioration is associated with the retention of whatever metal happens to be abundant in the person's environment, not just with aluminum. (One type of glial cell is known for its metal-binding function, causing them to be called "metallophils."). According to Gajdusek, "calcium and other di- and trivalent elements" are "deposited as hydroxyapatites in brain cells" in brain degeneration of the Alzheimer's type.(19)

Even early forms of Alzheimer's disease begin at an age when the youth-associated steroids have begun to decline. If MS involves a deficiency of thyroid (or of T3 within the oligodendrocytes, where T3 normally can be made from thyroxine; many things, including protein deficiency, can block the conversion of T4 to T3), those cells would necessarily be deficient in their ability to produce pregenolone, but in young people the brain would still be receiving a little pregnenolone, progesterone, and DHEA from the adrenals and gonads. This relatively abundant youthful supply of hormones would keep most of the body's organs in good condition, and could keep the bodies of the major brain cells from deteriorating. But if proper functioning of the nerve fibers requires that they be fed a relatively high concentration of pregnenolone from their immediately adjacent neighbors (with the amount increasing during stress and fatigue), then their function would be impaired when they had to depend on the hormones that arrived from the blood stream.

For many years it has been recognized that the brain atrophy of "Alzheimer's disease" resembles the changes seen in the brain in many other situations: The traumatic dementia of boxers; toxic dementia; the slow-virus diseases; exposure of the brain to x-rays(20); ordinary old age; and in people with Down's syndrome who die around the age of thirty.

In menopause, certain nerve cells have lost their ability to regulate the ovaries, because of prolonged exposure to estrogen (6). The cells that fail as a result of prolonged estrogen exposure aren't the same cells that fail from prolonged exposure to the glucocorticoids (7), but they have in common the factor of excitatory injury.

Since people who experience premature menopause are known to be more likely than average to die prematurely, it is reasonable to view menopause as a model of the aging process. It is now well established that progesterone fails to be produced at the onset of menopause (the first missed period, increased loss of calcium, symptoms such as hot flashes, etc.), and that estrogen continues to be produced at monthly intervals for about four years. The essential question for aging, in the present context, is why the anesthetic steroids are no longer produced at a rate that allows them to protect tissues, including brain cells, from the excitotoxins. Using menopause as a model for aging, we can make the question more answerable by asking why progesterone stops being produced.

During stress, we are designed not to get pregnant, and the simplest aspect of this is that ACTH, besides stimulating the adrenals to produce stress-related hormones, inhibits the production of progesterone by the ovary. Other stress-induced factors, such as increased prolactin and decreased thyroid, also inhibit progesterone production. Stress eventually makes us more susceptible to stress. Menopause and other landmarks of aging simply represent upward inflections in the rate-of-aging curve. Individual variations in type of stress, hormonal response and diet, etc., probably govern the nature of the aging process in an individual.

The amphetamine-like action of estrogen, which undoubtedly contributes to the general level of stress and excitotoxic abuse of nerve cells, is probably the only "useful" facet of estrogen treatment, but a little cocaine might achieve the same effect with no more harm, possibly less. The toxicity of catecholamines has been known for over thirty years, and estrogen's stimulating effects

are partly the result of its conversion to catechol-estrogens which increase the activity of brain catecholamines. Estrogen's powerful ability to nullify learning seems never to be mentioned by the people who promote its use. The importance of a good balance of brain steroids for mood, attention, memory, and reasoning is starting to be recognized, but powerful economic forces militate against its general acceptance.

Since the brain is the organ that can allow us to adapt without undergoing stress in the hormonal sense, it is very important to protect its flexibility and to keep its energy level high, so it can work in a relaxed way. It is the low energy cellular state that leads to the retention of calcium and iron, and to the production of age pigment, and other changes that constitute the vicious circle of aging. And mental activity that challenges obsession and rigidity might be the most important brain energizer. Pseudo-optimism, humor-as-therapy, has a certain value, but a deeper optimism involves a willingness to assimilate new information and to change plans accordingly.

Supplements

Nutritional supplements that might help to prevent or correct these brain syndromes include: Vitamin E and coconut oil; vitamin A; magnesium, sodium; thyroid which includes T3; large amounts of animal protein, especially eggs; sulfur, such as magnesium sulfate or flowers of sulfur, but not to take continuously, because of sulfur's interference with copper absorption; pregnenolone; progesterone if needed. Bright light, weak in the blue end of the spectrum and with protection against ultraviolet, activates respiratory metabolism and quenches free radicals. Raw carrot fiber and/or laxatives if needed; charcoal occasionally for gas or bowel irritation. Coconut oil serves several purposes. Its butyric acid is known to increase T3 uptake by glial cells. It has a general pro-thyroid action, for example by diluting and displacing antithyroid unsaturated oils, its short- and medium-chain fatty acids sustain blood sugar and have antiallergic actions, and it protects mitochondria against stressinjury.

P.S.: In 1979, a woman whose husband was suffering from advanced Amyotrophic Lateral Sclerosis (ALS) asked me if I had any ideas for slowing his decline. I described my suspicion that ALS involved defective metabolism or regulation of testosterone. In some tissues, testosterone is selectively concentrated to prevent atrophy, and ALS is a disease of middle-age, when hormone regulation often becomes a special problem. In the late 1970s, there was discussion of a higher incidence of ALS in males, and especially in athletes. I told her about progesterone's general protective effects, its antagonism to testosterone, and its prevention of atrophy in various tissues. She decided to ask her doctor to try progesterone for her husband. Later, I learned that her husband had gone into a very rapid decline immediately after the injection, and died within a week; the physician had given him testosterone, since, he said, "testosterone and progesterone are both male hormones." Besides making me more aware of the problems patients have in communicating with physicians, this tended to reinforce my feeling that a hormone imbalance is involved in ALS. Although I haven't written much about testosterone's toxicity, Marian Diamond's work showed that prenatal testosterone is similar to prenatal estrogen, in causing decreased thickness of the cortex of the brain; both of those hormones oppose progesterone's brain-protecting and brain-promoting actions.

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GLOSSARY

1. Amyloid is the old term for the "starchy" appearing (including the way it stains) proteins seen in various diseases, and in the brain in Alzheimer's disease.

2. Cytochrome P450scc. The cytochromes are "pigments," in the same sense that they contain the colored "heme" group that gives hemoglobin its color. P450 means "protein that absorbs light at a wavelength of 450. The scc means "side-chain cleaving," which refers to the removal of the 6 carbon atoms that distinguish cholesterol from pregnenolone. Other Cyt P450 enzymes are important for their detoxifying oxidizing action, and some of these are involved in brain metabolism.

3. Glial means "glue-like," and glial cells are mostly spidery-shaped cells that used to be thought of as just connective, supportive cells in the brain.

4. Mitochondria (the "thread-like bodies") are the structures in cells which produce most of our metabolic energy by respiration, in response to the thyroid hormones.

5. Mucoid--refers to a mucoprotein, a protein which contains some carbohydrate. A glycoprotein; usually not intended as a precise term.

6. Myelination. Myelin is a multilayered enclosure of the axons (the long processes) of nerve cells, composed of proteins and complex lipids, including cholesterol. The layered material is a flat, thin extension of the cytoplasm of the oligodendroglial cells.

7. Oligodendrocytes are one of the kinds of glial (or neuroglial) cells, and structurally they are unusual in having sheet-like, rather than just thread-like processes; they have a sensitivity ("receptors") to stress and valium, and produce pregnenolone when activated. Under the influence of thyroid hormone, they wrap themselves in thin layers around the conductive parts of nerve cells, leaving a multilayered "myelin" coating. Their absorption of thyroid hormone is promoted by butyrate, an anti-stress substance found in butter and coconut oil.

8. Steroidogenesis is the creation of steroids, usually referring to the conversion of cholesterol to hormones.