A R T I C L E

Multiple sclerosis, protein, fats, and progesterone

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We are always subjected to antigenic burdens. The important question has to do with our ability to limit the inflammatory response to these burdens.

In MS, it is clear that the inflammatory process itself is destructive, and that estrogen is a major predisposing factor. Unsaturated fatty acids, and dietary imbalance of amino acids interact closely with hyperestrogenism and hypothyroidism to produce the autoimmune degenerative diseases.

Reduction of the mediators of inflammation is better than augmenting a single antiinflammatory agent such as cortisol. Although immunosuppressive drugs, including the "essential fatty acids," do alleviate inflammatory symptoms temporarily, they probably contribute to the underlying pathology.

People with MS have chronically increased production of cortisol. This creates a distortion of protein assimilation, resembling a nutritional protein deficiency. Excessive serotonin and estrogen cause a relatively uncontrolled production of cortisol. A vicious circle of inflammatory mediators and amino acid imbalance can result.

Depression, lupus, migraine, menopause, diabetes, and aging have several important metabolic features in common with MS.

Popular therapies are illogical, and are likely to cause disease progression.

High quality protein, thyroid, pregnenolone and progesterone tend to correct the underlying pathology. These are antiinflammatory, but they are not immunosuppressive or catabolic.

High altitude and sunny climate are associated with a low incidence of MS.

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Multiple sclerosis (MS), like other autoimmune diseases, affects women more often than men (about 2 to 1), has its onset during the reproductive years (especially after the age of 30, when estrogen is very high), is often exacerbated premenstrually, and is sometimes alleviated by pregnancy (Drew and Chavez, 2000), when progesterone is very high. Women with a high ratio of estrogen to progesterone have been found to have the most active brain lesions (Bansil, et al., 1999). Most of the mediators of inflammation that are involved in MS--mast cells, nitric oxide (NO), serotonin, prolactin, lipid peroxidation, free fatty acids, prostaglandins and isoprostanes, and the various cytokines (IL, TNF)--are closely associated with estrogen's actions, and in animals, autoimmune diseases can be brought on by treatment with estrogen (Ahmed and Talal).

The strong association of MS with estrogen has led to an illogical, but popular and well-publicized medical conclusion that estrogen is protective against MS, and some have claimed that estrogen has beneficial therapeutic effects. This strange way of thinking has its equivalent in the idea that, since women are much more likely than men to develop Alzheimer's disease, estrogen is protective against it; or that, since women have more fragile bones than men do, and their progressive bone loss occurs during the times of their greatest exposure to estrogen, estrogen prevents osteoporosis.

In this medical environment, close associations between estrogen and degenerative diseases are acknowledged, but they are given a meaning contrary to common sense by saying that the association occurs because there isn't enough estrogen. The stove burns you because it isn't hot enough.

As Dave Barry would say, I'm not making this up. Recently well publicized articles have suggested that estrogen protects the brain (even against stroke!) because it increases serotonin and NO. There is something almost esthetically pleasing when so many major errors are concentrated into a single article. Nitric oxide and serotonin are both neurotoxic (Joseph, et al., 1991; Skaper, et al., 1996; Parkinson, et al., 1997; Santiago, et al., 1998; Barger, et al., 2000), as a result of suppressing mitochondrial respiration. NO plays a major role in lipid peroxidation and demyelination. It's interesting to see serotonin and NO openly associated with estrogen, whose mitochondrial toxicity has been carefully hidden from public view.

There are several theories about the cause of MS, old theories about genes and viruses, and newer theories about bacteria, vitamin deficiencies, oil deficiencies, poisons, and reactions to vaccinations (especially for hepatitis B and influenza). The only theory that has been abandoned is the 19th century psychiatric theory about "hysterical paralysis," though occasionally someone does still talk about emotional causes of multiple sclerosis; the term "female hysteria" has evolved into "conversion disorder."

Each of the main theories has a few facts that seem to support it, but neglects to account for many other facts. Everyone agrees that the immune system is involved in MS in some way, but that's really where the problem starts, because of the idea that inflammation is an intrinsic part of immunity. If "inflammation is necessary and good," then it becomes a problem to define exactly where the boundary is between an appropriate reaction and a degenerative process. Edema, reduced cellular respiration, loss of normal functions, fibrosis in its various degrees, each component of inflammation can be seen in a good light, as part of a "defensive immune reaction." When tissue injury leads to repair, it "must" be seen as beneficial, even if it leads to the formation of a scar in place of functional tissue, because the comparison is between an imagined worst possible outcome, and an imperfect recovery, rather than comparing the inflammatory process with the possibility that a potentially noxious agent might have done no harm at all.

The simplest illustration of how inflammation relates to the organism's resources was an experiment in which blood glucose was varied, while an animal was exposed to chemicals that varied from mildly irritating to potentially deadly. When the animal had very low blood sugar, the mildest irritant could be deadly, but when its blood glucose was kept very high, even the deadly antigens were only mildly irritating. Varying the blood sodium concentration had similar, but weaker, effects.

There is a tendency to see inflammation not only as a normal part of immunity, but to see it as being proportional to the nature of the antigen, except when the immune system has been primed for it by previous contact, in which case the organism will either not react at all (because it has become immune), or it will react much more violently than it did on the first exposure, because it has become allergic. But, in reality, the mere concentration of glucose and sodium in the blood (and of thyroid, and many other substances that aren't considered to be part of the immune system) can make a tremendous difference in the degree of "immunological" reaction.

In the excessively sensitive condition produced by hypoglycemia, several things happen that contribute to the maladaptive exaggerated inflammatory response.

Adrenaline increases in hypoglycemia, and, if the adrenaline fails to convert glycogen into glucose, it will provide an alternative fuel by liberating free fatty acids from fat cells.

If the liberated fatty acids are unsaturated, they will cause serotonin to be secreted, and both serotonin and the unsaturated fatty acids will suppress mitochondrial respiration, exacerbating the hypoglycemia. They will stimulate the release of cytokines, activating a variety of immunological and inflammatory processes, and they will cause blood vessels to become leaky, creating edema and starting the first stages of fibrosis. Both adrenaline and serotonin will stimulate the release of cortisol, which mobilizes amino acids from tissues such as the large skeletal muscles. Those muscles contain a large amount of cysteine and tryptophan, which, among other effects, suppress the thyroid. The increased tryptophan, especially in the presence of free fatty acids, is likely to be converted into additional serotonin, since fatty acids release tryptophan from albumin, increasing its entry into the brain. Free fatty acids and increased serotonin reduce metabolic efficiency (leading to insulin resistance, for example) and promote an inflammatory state.

Fats in the blood-stream have easy access to the brain, and the unsaturated free fatty acids produce brain edema (Chan, et al., 1983, 1988). When brain edema is caused by vascular leakage, proteins that are normally excluded can enter. The stimulated, excited and fatigued brain exchanges glutamine for tryptophan, accelerating its uptake from the blood.

When a tissue is injured or stressed, antibodies are formed in response to the altered components of that tissue. Therefore, we could call a bruise or a sprain an autoimmune condition, but there are no commercial tests for bruised-shin antibodies. The availability of tests for specific antibodies seems to be the essential factor in classifying a condition as autoimmune, as in "autoimmune thyroiditis." Unfortunately, this way of using language is nested in a culture that is full of unrealistic ideas of causality, and thousands of people build their careers on the search for the "mutated genes that are responsible for the disease," and for the drugs that will correct the defect.

Early in the study of immunology, the focus was on antibodies. Even earlier, inflammation had been conceptualized in terms of the "humors," and other prescientific ideas. As soon as multiple sclerosis/hysterical paralysis was classified as an autoimmune disease, primitive ideas about the nature of the immune system, interacting with primitive ideas about the nature of the brain and the structure of cells, blended into the various theories of what the disease is.

Rather than seeing immunological nerve damage as the cause of all the other features of multiple sclerosis, I think it's important to look at some of the general features of the condition, as contexts in which to interpret the events in the nerves.

It has been known for a long time that the incidence of MS tends to increase with distance from the equator. Incidence is low in sunny dry climates, and at high altitudes. Two clear dietary influences have been found: eating pork, and horsemeat.

People with MS don't regulate their body temperature very well. Their nerve conduction is slow, and in normal people, conduction is faster at higher temperatures, but in people with MS the conduction is slower at the normal temperature of 98.6O F than at lower temperatures. A subnormal temperature is also associated with old age, and with the hot flashes of menopause.

Brain metabolism of glucose is very low in multiple sclerosis, and in my own observations, the general metabolic rate is subnormal. However, some people reason that the hypometabolism is caused by the lesions, rather than vice versa.

Animals that lack the unsaturated fatty acids have a higher metabolic rate and ability to use glucose, converting it to CO2 more readily, have a greater resistance to toxins (Harris, et al., 1990; even cobra venom: Morganroth, et al., 1989), including endotoxin (Li, et al., 1990)--preventing excessive vascular leakage--and to immunological damage (Takahashi, et al., 1992), and to trauma, and their neuromuscular response is accelerated while fast twitch muscles are less easily fatigued (Ayre and Hulber, 1996).

In people with MS, the blood is more viscous, and the platelets tend to clump together more easily. Their cortisol level is higher than normal, and their pituitary adrenal-cortex-stimulating hormone is harder to suppress. This is a condition that is also seen in depression and old age. Despite the chronically elevated cortisol, people with MS typically have hypoglycemia. They are occasionally found to have low blood sodium, hyponatremia, but this is hard to determine when the blood's water content is variable. Their prolactin is likely to be high, and this can result from high estrogen, high serotonin, low sodium, or low thyroid. Drinking too much water can increase prolactin, and can damage the nerves' myelin enclosures; too much serotonin tends to cause excessive drinking. Disturbances of blood glucose, sodium, and water content can disrupt the brain's myelin structure. High estrogen disturbs the blood osmotically, making it retain too much water in relation to the solutes, and this relates to many of estrogen's effects; since simple osmotic variations can damage the myelin structures, it seems that this mechanism should be investigated thoroughly before it is assumed that the immunological events are primary.

Mast cells, which promote inflammation by releasing substances such as histamine and serotonin (and make blood vessels leaky), are more numerous in the brain in multiple sclerosis than in normal brains. Since platelet clumping releases serotonin, and also because serotonin excess is suggested by so many other features of MS, serotonin antagonists (ondansetron and ketanserin, for example) have been used therapeutically with success.

Estrogen causes mast cells to release their inflammatory mediators, and it causes platelets to aggregate, releasing their serotonin. Since estrogen dominance is closely associated with the presence of active brain lesions,

antiestrogen therapy would seem obvious in MS. Progesterone counteracts estrogen's effects on both mast cells and platelets.

Aspirin protects against a variety of inflammatory processes, but it's most famous for the inhibition of prostaglandins. While aspirin is often used to relieve pain in MS, and another inhibitor of prostaglandin synthesis, indomethacin, has been used therapeutically in MS, it would seem appropriate to investigate more carefully aspirin's possible role in preventing or relieving MS.

A simple protein deficiency has many surprising effects. It lowers body temperature, and suppresses the thyroid, but it increases inflammation and the tendency of blood to clot. Since the brain and heart and lungs require a continuous supply of essential amino acids if they are to continue functioning, in the absence of dietary protein, cortisol must be produced continuously to mobilize amino acids from the expendable tissues, which are mainly the skeletal muscles. These muscles have a high concentration of tryptophan and cysteine, which suppress the thyroid. Cysteine is excitoxic, and tryptophan is the precursor for serotonin. Presumably, their presence in, and stress-induced release from, the muscles is one of the mechanisms that reduce metabolic activity during certain types of stress.

When pregnant animals are deprived of protein, the newborn animals have abnormally high levels of serotonin, and the enzymes responsible for that excess tend to maintain the serotonin excess even when they are grown and have adequate protein. This is analogous to the effect of excess estrogen early in life, which creates a tendency to develop breast or prostate cancer in adulthood. It would be interesting to study the gestational experience, e.g., length of gestation and birth weight, of the people who later develop MS.

Although people in the northern countries aren't normally protein-starved, they do tend to get a large part of their protein from the muscle meats. In traditional cultures, all parts of the food animals were eaten--chicken feet, heads, and necks, animals' ears and eyeballs, etc.--and so the amino acid balance was favorable for maintaining a high metabolic rate and preventing stress.

The observation that multiple sclerosis is associated with the consumption of pork and horsemeat, but not beef, lamb, or goat, is very interesting, since the fat of those animals is essentially like the fats of the plant materials that they eat, meaning that it is extremely high in linoleic and linolenic acids. The rumen of cows, sheep, and goats contains bacteria that convert the polyunsaturated fats into more saturated fats. Unsaturated fats inhibit the enzymes that digest protein, and MS patients have been reported to have poor digestion of meat (Gupta, et al., 1977).

The polyunsaturated fats are in themselves toxic to mitochondria, and suppress glucose oxidation, and inhibit the thyroid function, with the same suppressive effect on the ability to oxidize glucose, but they are also turned, enzymically, into the prostaglandins, and non-enzymically, by spontaneous lipid peroxidation, into the toxic isoprostanes. The isoprostanes, and some of the prostaglandins, are elevated in the brain and other tissues of people with MS.

Lipid peroxidation is very high in multiple sclerosis. Nitric oxide (whose synthesis is promoted by estrogen in most parts of the brain) is a free radical that activates peroxidation.

Lipid peroxidation selectively destroys, naturally, the unstable

polyunsaturated fats. In atherosclerosis, the blood vessel plaques contain very little unsaturated fat. This is because they are peroxidized so rapidly, but their high ratio of saturated to unsaturated fats has been used to argue that the polyunsaturated oils are "heart protective." Similar arguments are often made in MS, though some studies don't support the idea that there is a lack of any of the unsaturated fats. Since lipid peroxidation is very high, it would be reasonable to assume that there was an abundance of polyunsaturated fats being peroxidized through reactions with catalysts such as iron (S.M. LeVine, 1997) and nitric oxide and peroxynitrile.

I believe that an important aspect of the intolerance for heat so often reported in people with MS could be the tendency of relative hyperthermia to release increased amounts of free fatty acids into the blood stream. Women, because of estrogen's effects, usually have much higher levels of free fatty acids in the blood than men do. Estrogen increases the release of free fatty acids from stored fat, and the unsaturated fats synergize with both estrogen and prolactin, increasing their effects.

Temperature regulation apparently involves some nerve cells that sense temperature very accurately, and change their activity accordingly. Water has a remarkably high heat capacity, meaning that it takes a relatively large amount of heat to change its temperature. The "disappearing heat" is being consumed by structural changes in the water. Proteins have the same sort of structural complexity as water, and together they can make effective temperature transducers, "thermometers." (Other substances tend to undergo major structural changes only as they melt or vaporize. The famous "liquid crystals" have a few distinct structural phases, but cytoplasm is like a very subtle liquid crystal.) The "thermostat cells" are actually responding to a degree of internal structure, not to the temperature in the abstract. So things that change their internal structure will modify their temperature "set-point."

Increased estrogen causes an animal to lower its temperature, and it probably does this by increasing the "structural temperature" of the thermostat cells, "melting" their internal structure. Progesterone causes the animal to increase its temperature, and it apparently does this by increasing the structure/decreasing the structural temperature of the thermostat cells. If you put ice in the thermostat, the room gets hot.

A cell's internal structure is equivalent to its readiness to work. Fatigue represents a slightly "melted" state of the cell, in which structure appears to have been consumed along with the chemical energy reserves. Experiments that demonstrated this effect were very clear, but they were ignored because they didn't fit people's stereotyped idea of the cell. With a very sensitive thermometer, it's possible to measure the heat produced by a nerve when it is stimulated. That's not surprising. But it's surprising that, when the nerve is recovering from the stimulation, it absorbs heat from its environment, lowering the temperature locally. That even violated some people's conception of "entropy," but it can easily be demonstrated that changing the form of some materials changes their heat capacity, as when a rubber band is stretched (it gets hot), or contracts (it gets cooler).

The excitants, estrogen and cortisol, slow the conduction of nerves, because they cause its internal structure to be dissipated. They create a "pre-fatigued" state in the cell.

In experiments with rabbit hearts, Szent-Gyorgyi showed that estrogen decreased the heart's readiness to work, and that progesterone

increased its readiness to work, and he said it did this by "building structure." He pointed out that, for a given drug or other stimulus, cells have a characteristic response, becoming either more activated or more inhibited, but he showed that, outside the normal concentration or intensity range of the stimulus, a cell's response is often reversed.

If this is the situation in the nerves in MS, it explains the strange behavior, in which warming the nerve reduces its function. The implication is that internal structure (and energy) must be restored to the nerves. In experiments that I have described in previous newsletters, increasing sodium, ATP, carbon dioxide, and progesterone, and increasing the ratio of magnesium to calcium, have been found to increase cellular energy and structure. The thyroid hormone is ultimately responsible for maintaining cells' energy and structure, and responsiveness, but if it is increased suddenly without allowing all the other factors to adjust, it will raise the temperature too suddenly. It needn't take a long time, but all the factors have to be present at the same time.

Serotonin, melatonin, estrogen, and polyunsaturated fats all tend to lower body temperature. Since estrogen and the unsaturated fats are cellular excitants, the actual decrease in body temperature helps to offset their excitatory effects.

Both bright light and high altitude tend to reduce serotonin's effects. The tissue carbon dioxide retained at high altitude reduces the incidence of many diseases, and multiple sclerosis might be affected as heart disease and cancer are. It is known that carbon dioxide is involved in myelin's regulation of its own water content. Hyperventilation, by causing a loss of carbon dioxide, releases both histamine and serotonin, making blood more viscous, while making blood vessels more permeable, and causing them to constrict.

If people with MS have developed it through the interactions of excessive estrogen, serotonin, unsaturated fats, iron, and water, and deficient thyroid, and deficient pregnenolone produced in the myelin-forming cells (oligodendrocytes), there are many things that can be done to stop its progress, and possibly to reverse it.

Since a sudden increase in temperature will release increased amounts of the pro-inflammatory fats, things should be changed gradually. Increased salt is thermogenic, but increased magnesium is protective against hyperthermia, so increased magnesium (epsom salts baths, for example, coffee, fruits, some vegetables and meats) would be helpful. Magnesium is rapidly lost from cells in hypothyroidism. Sugar, when accompanied by fats and minerals, as in milk, is needed to lower cortisol, and to maintain thyroid activity. Balanced proteins, such as cheese, potatoes, eggs, and beef- or lamb-broth (for the gelatin and mineral content in particular) will prevent the tryptophan excess that suppresses the thyroid and is potentially a nerve toxin. Saturated fats, used regularly, reduce the immediate toxic antimetabolic effects of the stored unsaturated fats, but it takes a long time to change the balance of stored fats.

Since aspirin lowers temperature, is antiinflammatory, in some situations antiestrogenic, and is a powerful antioxidant, it is likely that it would alleviate symptoms and prevent progression of MS, as it does in other degenerative diseases. Since platelet aggregation is likely to be involved in the focuses of inflammation, aspirin might help to prevent the formation of new areas of damage.

While the glucocorticoids are useful for their antiinflammatory actions, cortisol is known to promote the killing of brain cells by excitotoxicity. Since estrogen decreases GABA, and both estrogen and serotonin activate the excitatory amino acid transmitters, the addition of synthetic glucocorticoids to the pre-existing cortisol excess is likely to damage parts of the brain in addition to the inflamed areas.

The excess cortisol of depression, old age, and hyperestrogenism often comes down with use of a thyroid supplement, but pregnenolone has a very direct action (in opposition to serotonin) that can quiet the pituitary, reducing ACTH and cortisol. Progesterone has some similar effects, and is protective against excess cortisol, and is a major factor in nerve and brain restoration. Thyroid, progesterone, and pregnenolone are all involved in the formation of new myelin, and in the prevention of the edema that damages it.

Since thyroid and progesterone decrease the formation of estrogen in inflamed tissue, while cortisol stimulates its formation, it would seem wise to use thyroid and progesterone for their immediate antiinflammatory effects, which include the inhibition of NO formation (Drew and Chavez, 2000), and their lack of the excitotoxic, estrogen-stimulating effects of the glucocorticoids. While the glucocorticoids are catabolic and liberate cysteine and tryptophan from muscles, thyroid and progesterone are not catabolic, and protect against the toxic consequences of those amino acids.

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