Multiple sclerosis, protein, fats, and progesterone

From the original article in 2009. Author: Ray Peat.

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.

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 CO_2 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.

References

J Neurol Neurosurg Psychiatry 1988 Feb;51(2):260-5. Perivascular iron deposition and other vascular damage in multiple sclerosis. Adams CW. "The multiple sclerosis cases showed venous intramural fibrinoid deposition (7%), recent haemorrhages (17%), old haemorrhages revealed by haemosiderin deposition (30%), thrombosis (6%) and thickened veins (19%). In all, 41% of all multiple sclerosis cases showed some evidence of vein damage.""Haemosiderin deposition was common in the substantia nigra and other pigmented nuclei in all cases. It is concluded that the cerebral vein wall in multiple sclerosis is subject to chronic inflammatory damage, which promotes haemorrhage and

increased permeability, and constitutes a form of vasculitis."

Am J Pathol 1985 Dec;121(3):531-51. Sex hormones, immune responses, and autoimmune diseases. Mechanisms of sex hormone action. Ansar Ahmed S, Penhale WJ, Talal N. "Immune reactivity is greater in females than in males. In both experimental animals and in man there is a greater preponderance of autoimmune diseases in females, compared with males. Studies in many experimental models have established that the underlying basis for this sex-related susceptibility is the marked effects of sex hormones. Sex hormones influence the onset and severity of immune-mediated pathologic conditions by modulating lymphocytes at all stages of life, prenatal, prepubertal, and postpubertal."

J Appl Physiol 1996 Feb;80(2):464-71. Effects of changes in dietary fatty acids on isolated skeletal muscle functions in rats. Ayre KJ, Hulbert AJ The effects of manipulating dietary levels of essential polyunsaturated fatty acids on the function of isolated skeletal muscles in male Wistar rats were examined. Three isoenergetic diets were used: an essential fatty acid-deficient diet (EFAD), a diet high in essential (n-6) fatty acids [High (n-6)], and a diet enriched with essential (n-3) fatty acids [High (n-3)]. After 9 wk, groups of rats on each test diet were fed a stock diet of laboratory chow for a further 6 wk. Muscle function was examined by using a battery of five tests for soleus (slow twitch) and extensor digitorum longus (EDL; fast twitch). Tests included single muscle twitches, sustained tetanic contractions, posttetanic potentiation, sustained high-frequency stimulation, and intermittent low-frequency stimulation. Results for muscles from the High (n-6) and High (n-3) groups were very similar. However, the EFAD diet resulted in significantly lower muscular tensions and reduced response times compared with the High (n-6) and High (n-3) diets. Peak twitch tension in soleus muscles was 16-21% less in the EFAD group than in the High (n-6) and High (n-3) groups, respectively [analysis of variance (ANOVA), $P < 0.01$). During high-frequency stimulation, EDL muscles from the EFAD rats fatigued 32% more quickly (ANOVA, $P < 0.01$)]. Also, twitch contraction and half-relaxation times were significantly 5-7% reduced in the EFAD group (ANOVA, $P < 0.01$). During intermittent low-frequency stimulation, soleus muscles from the EFAD group generated 25-28% less tension than did the other groups (ANOVA, $P < 0.01$), but in EDL muscles from the EFAD group, endurance was 20% greater than in the High (n-6) group (ANOVA, $P < 0.05$). After 6 wk on the stock diet, there were no longer any differences between the dietary groups. Manipulation of dietary fatty acids results in significant, but reversible, effects in muscles of rats fed an EFAD diet.

Endocr Res 1999 May;25(2):207-14. Prolactin secretion is increased in patients with multiple sclerosis. Azar ST, Yamout B

Acta Neurol Scand 1999 Feb;99(2):91-4. Correlation between sex hormones and magnetic resonance imaging lesions in multiple sclerosis. Bansil S, Lee HJ, Jindal S, Holtz CR, Cook SD "Patients with high estradiol and low progesterone levels had a significantly greater number of Gd enhancing lesions than those with low levels of both these hormones. Patients with a high estrogen to progesterone ratio had a significantly greater number of active MRI lesions than those with a low ratio."

J Neuroimmunol 1996 Mar;65(1):75-81. Circulating antibodies directed against conjugated fatty acids in sera of patients with multiple sclerosis. Boullerne A, Petry KG, Geffard M "These results suggest that in MS and RA, autoepitopes on cell membranes that are normally hidden from the immune system become immunogenic. This may arise because of previous membrane disruption by oxidative processes."

J Neurosci Res 2000 Nov 15;62(4):503-9. Dehydroepiandrosterone inhibits microglial nitric oxide production in a stimulus-specific manner. Barger SW, Chavis JA, Drew PD.

J Exp Med 1984 Nov 1;160(5):1532-43. Inhibition of autoimmune neuropathological process by treatment with an iron-chelating agent. Bowern N, Ramshaw IA, Clark IA, Doherty PC "Iron is believed to influence both the migration and function of immune effector cells. It can also act as a catalyst in the formation of free radicals, which are highly toxic agents causing tissue damage in sites of inflammation."

J Neurol Neurosurg Psychiatry 1981 Apr;44(4):340-3. Rheological and fibrinolytic findings in multiple sclerosis. Brunetti A, Ricchieri GL, Patrassi GM, Girolami A, Tavolato B. "The whole blood viscosity was found to be increased in multiple sclerosis."

J Neurochem 1988 Apr;50(4):1185-93. Induction of intracellular superoxide radical formation by arachidonic acid and by polyunsaturated fatty acids in primary astrocytic cultures. Chan PH, Chen SF, Yu AC "Other PUFAs, including linoleic acid, linolenic acid, and docosahexaenoic acid, were also effective in stimulating NBF formation in astrocytes, whereas saturated palmitic acid and monounsaturated oleic acid were ineffective. Similar effects of these PUFAs were observed in malondialdehyde formation in cells and lactic acid accumulation in incubation medium. These data indicate that both membrane integrity and cellular metabolism were perturbed by arachidonic acid and by other PUFAs."

Ann Neurol 1983 Jun;13(6):625-32. Induction of brain edema following intracerebral injection of arachidonic acid. Chan PH, Fishman RA, Caronna J, Schmidley JW, Prioleau G, Lee J "Intracerebral injection of polyunsaturated fatty acids (PUFAs), including linolenic acid (18:3) and arachidonic acid (20:4), caused significant increases in cerebral water and sodium content concomitant with decreases in potassium content and Na+- and K+- dependent adenosine triphosphatase activity. There was gross and microscopic evidence of edema. Saturated fatty acids and monounsaturated fatty acid were not effective in inducing brain edema. The [125I]-bovine serum albumin spaces increased twofold and threefold at 24 hours with 18:3 and 20:4, respectively, indicating vasogenic edema with increased permeability of brain endothelial cells" "These data indicate that arachidonic acid and other PUFAs have the ability to induce vasogenic and cellular brain edema and further support the hypothesis that the degradation of phospholipids and accumulation of PUFAs, particularly arachidonic acid, initiate the development of brain edema in various disease states."

Med Sci Sports Exerc 1997 Jan;29(1):58-62. Effects of acute physical exercise on central serotonergic systems. Chaouloff F "Works from the 1980's have established that acute running increases brain serotonin (5-hydroxytryptamine: 5-HT) synthesis in two ways. Lipolysis-elicited release of free fatty acids in the blood compartment displaces the binding of the essential amino acid tryptophan to albumin, thereby increasing the concentration of the so-called "free tryptophan" portion, and because exercise increases the ratio of circulating free tryptophan to the sum of the concentrations of the amino acids that compete with tryptophan for uptake at the blood-brain barrier level, tryptophan enters markedly in the brain compartment." "Indirect indices of 5-HT functions open the possibility that acute exercise-induced increases in 5-HT biosynthesis are associated with (or lead to) increases in 5-HT release."

Med Hypotheses 1995 Nov;45(5):455-8. Melanin, melatonin, melanocyte-stimulating hormone, and the susceptibility to autoimmune demyelination: a rationale for light therapy in multiple sclerosis. Constantinescu CS "The hypothesis formulated here is based on the observation that resistance to multiple sclerosis and experimental autoimmune encephalomyelitis is associated with dark skin pigmentation. While this may signify a protective role for melanin against environmental factors producing oxidative damage, the mechanism postulated here is that susceptibility to autoimmune demyelination is influenced by hormonal factors, i.e. the neurohormones melatonin and melanocyte stimulating hormone, which have opposing effects on immune functions and, the same time, are important determinants of the individual's production of melanin."

Neurosci Lett 1989 Nov 6;105(3):246-50. Presence of Schwann cells in neurodegenerative lesions of the central nervous system. Dusart I, Isacson O, Nothias F, Gumpel M, Peschanski M Ultrastructural analysis of neurodegenerative CNS lesions produced by an excitotoxic substance revealed that the majority of cells ensheathing axons were not oligodendrocytes. By their morphology and the presence of both a basal lamina and collagen fibers they were identified as Schwann cells. The presence of Schwann cells, whose growth-promoting role in the peripheral nervous system has been largely documented, may account for the development of regenerating growth cones which have been observed in the excitotoxically lesioned central nervous system. Further support for this hypothesis came from the analysis of fetal neural transplants implanted into the lesioned area. Schwann cells ensheathing axons were indeed numerous in the neuron-depleted area

surrounding the transplants, where neurite outgrowth of graft origin occurred.

J Neuroimmunol 2000 Nov 1;111(1-2):77-85. Female sex steroids: effects upon microglial cell activation. Drew PD, Chavis JA.

Neurology 1999 Nov 10;53(8):1876-9 Cerebrospinal fluid isoprostane shows oxidative stress in patients with multiple sclerosis. Greco A, Minghetti L, Sette G, Fieschi C, Levi G "The CSF level of the isoprostane 8-epi-prostaglandin (PG)-F2alpha (a reliable marker of oxidative stress in vivo) was three times higher in subjects with definite MS than in a benchmark group of subjects with other neurologic diseases."

J Intern Med 1989 Oct;226(4):241-4. Serum sex hormone and gonadotropin concentrations in premenopausal women with multiple sclerosis. Grinsted L, Heltberg A, Hagen C, Djursing H.

Am J Gastroenterol 1977 Dec;68(6):560-5. Multiple sclerosis and malabsorption. Gupta JK, Ingegno AP, Cook AW, Pertschuk LP.

Free Radic Res 1997 Apr;26(4):351-62. Toxicity of polyunsaturated fatty acid esters for human monocyte-macrophages: the anomalous behaviour of cholesteryl linolenate. Hardwick SJ, Carpenter KL, Law NS, Van Der Veen C, Marchant CE, Hird R, Mitchinson MJ. "The triglycerides showed a direct relationship between toxicity and increasing unsaturation, which in turn correlated with increasing susceptibility to oxidation.""Triarachidonin (20:4; omega-6), trieicosapentaenoin (20:5; omega-3) and tridocosahexaenoin (22:6; omega-3) were profoundly and rapidly toxic. There was a similar relationship between toxicity and increasing unsaturation for most of the cholesterol esters, but cholesteryl linolenate was apparently anomalous, being non-toxic in spite of possessing three double bonds and being extensively oxidised.""The toxicity of triglycerides suggests that polyunsaturated fatty acid peroxidation products are also toxic."

J Clin Invest 1990 Oct;86(4):1115-23. Essential fatty acid deficiency ameliorates acute renal dysfunction in the rat after the administration of the aminonucleoside of puromycin. Harris KP, Lefkowith JB, Klahr S, Schreiner GF.

Mikrobiyol Bul 1989 Oct;23(4):342-7. [Leukotrienes and neurological diseases]. [Article in Turkish] Irkec C, Ercan S, Irkec M "LTC4 levels were found to be elevated in MS and Behcet patient in comparison with controls. Augmentation of LTC4 levels underlines the fact that leukotrienes may be held responsible the pathogenesis of these disorders."

Lancet 1982 Feb 13;1(8268):380-6. Evidence for subacute fat embolism as the cause of multiple sclerosis. James PB "The neurological features of decompression sickness, which is thought to be due to gas embolism, are similar to those of multiple sclerosis (MS). This similarity suggested the re-examination of a concept, first proposed in 1882, that the demyelination in MS is due to venous thrombosis. Unfortunately, although the plaques of MS are often perivenular, thromboses are not always present. Nevertheless, vascular theories can explain the topography of the lesions in MS.""There is also evidence in man that fat may lodge in the microcirculation of the nervous system and cause distal perivenous oedema with the loss of myelin from axons."

J Clin Pathol 1979 Oct;32(10):1025-9. Antithrombin activities in childhood malnutrition. Jimenez RA, Jimenez E, Ingram GI, Mora LA, Atmetlla F, Carrillo JM, Vargas W.

Arch Latinoam Nutr 1980 Dec;30(4):580-9. [Prethrombosis in child malnutrition]. Jimenez R, Jimenez E, Mora LA, Vargas W, Atmetlla F, Carrillo JM

Stroke 1991 Nov;22(11):1448-51. Platelet secretory products may contribute to neuronal injury. Joseph R, Tsering C, Grunfeld S, Welch KM "The view that certain endogenous substances, such as glutamate, may also contribute to neuronal injury is now reasonably well established. Blood platelets are known to contain and secrete a number of substances that have been associated with neuronal dysfunction. Therefore, we hypothesize that a high concentration (approximately several thousand-fold higher than in plasma, in our estimation) of locally released platelet secretory products derived from the causative thrombus may contribute to neuronal injury and promote reactive gliosis.""We further observed that serotonin, a major platelet product, has neurotoxic properties."

Zh Nevropatol Psikhiatr Im S S Korsakova 1985;85(2):198-206. [Role of disorders of the hemostatic system in the pathogenesis of multiple sclerosis and ways of correcting them]. [Article in Russian] Karlov VA, Makarov VA, Savina EB, Seleznev AN, Savin AA The changes in the hemostatic system were studied in 77 patients with different patterns of disseminated sclerosis (DS). The studies demonstrated activation of both vasculothrombocytic and coagulation components of hemostasis as well as of fibrinolytic blood properties. The latent course of the disseminated intravascular coagulation was revealed in 20.7% of cases. The role of hemostatic disorders in the pathogenetic mechanisms of DS is discussed. The patients with DS received pathogenetic treatment including drugs eliminating hemostatic disorders, which was beneficial for most patients.

Zh Nevropatol Psikhiatr Im S S Korsakova 1990;90(11):47-50. [Changes in rheological properties of blood in multiple sclerosis and their correction]. [Article in Russian] Karlov VA, Savin AA, Smertina LP, Redchits EG, Seleznev AN, Svetailo LI, Margosiuk NV, Stulin ID As many as 45 patients with multiple sclerosis were examined for rheological blood properties. As compared to controls, the group under examination manifested the rise of plasma viscosity, acceleration of red blood cell aggregation. 26.2% of patients demonstrated an appreciable increase of blood viscosity. It is assumed that these changes contribute to the deterioration of microcirculation and aggravate the demyelinating process. Correction of the rheological properties of the blood by plasmapheresis coupled with other methods of pathogenetic therapy turned out effective.

Brain Res 1997 Jun 20;760(1-2):298-303 Iron deposits in multiple sclerosis and Alzheimer's disease brains. LeVine SM "In summary, the localization of iron deposition in MS and AD brains indicates potential sites where iron could promote oxidative damage in these disease states."

Circ Shock 1990 Jun;31(2):159-70. Resistance of essential fatty acid-deficient rats to endotoxin-induced increases in vascular permeability. Li EJ, Cook JA, Spicer KM, Wise WC, Rokach J, Halushka PV.

FEBS Lett 1978 Nov 1;95(1):181-4. Selective inactivation of the NADH-ubiquinone segment of the respiratory chain of submitochondrial particles by endogenous free fatty acids during hyperthermia. Ludwig P, Bartels M, Schewe T, Rapoport S.

J Pain Symptom Manage 2000 Nov;20(5):388-91. Ondansetron in multiple sclerosis. Macleod AD. "Two young women with chronic nausea and vertigo caused by multiple sclerosis responded to the introduction and maintenance of the 5HT3 receptor antagonist, ondansetron."

Am J Phys Med Rehabil 1994 Jul-Aug;73(4):283-5. Intracranial venous thrombosis in a patient with multiple sclerosis. A case report and review of contraceptive alternatives in patients with disabilities. Malanga GA, Gangemi E.

Folia Biol (Praha) 1999;45(4):133-41. Essential fatty acids and related molecular and cellular mechanisms in multiple sclerosis: new looks at old concepts. Mayer M.

J Clin Endocrinol Metab 1994 Sep;79(3):848-53. Multiple sclerosis is associated with alterations in hypothalamic-pituitary-adrenal axis function. Michelson D, Stone L, Galliven E, Magiakou MA, Chrousos GP, Sternberg EM, Gold PW "Compared to matched controls, patients with

MS had significantly higher plasma cortisol levels at baseline. Despite this hypercortisolism and in contrast to patients with depression who had similar elevations in plasma cortisol levels, patients with MS showed normal, rather than blunted, plasma ACTH responses to ovine CRH, suggesting that the pathophysiology of hypercortisolism in MS is different from that in depression." "Taken together, these findings are compatible with data from studies of experimental animals exposed to chronic inflammatory stress, which showed mild increased activation of the HPA axis with increased relative activity of AVP in the regulation of the pituitary-adrenal axis."

Exp Neurol 1977 Oct;57(1):142-57. Tryptophan availability: relation to elevated brain serotonin in developmentally protein-malnourished rats. Miller M, Leahy JP, Stern WC, Morgane PJ, Resnick O.

Am J Physiol 1989 Oct;257(4 Pt 2):H1192-9. Lung injury caused by cobra venom factor is reduced in rats raised on an essential fatty acid-deficient diet. Morganroth ML, Schoeneich SO, Till GO, Pickett W, Ward PA.

Eur J Haematol 2000 Jul;65(1):82-3. More on the relationship between cystic fibrosis and venous thrombosis. Mori PG, Acquila M, Bicocchi MP, Bottini F, Romano L. Letter

Acta Neurol Scand 1982 Oct;66(4):497-504, Platelet aggregation and multiple sclerosis. Neu IS, Prosiegel M, Pfaffenrath V Measurements of blood platelet aggregation were carried out in 30 patients suffering from multiple sclerosis (MS) and in 15 healthy individuals. Compared with the control group, the MS patients showed an increase in both spontaneous and induced (ADP and serotonin) platelet aggregation. The possible pathogenetic significance of these results is discussed.

Neurology 1975 Aug;25(8):713-6. Schwann cells and regenerated peripheral myelin in multiple sclerosis: an ultrastructural study. Ogata J, Feigin I Tissue of a multiple sclerosis plaque in the brachium conjunctivum of the pons known to contain peripheral myelin by light microscopic studies were removed from the paraffin block and processed for electron microscopic studies. The cells related to the peripheral myelin possessed the ultrastructural characteristics of Schwann cells, with basement membranes and associated collagen fibers. No continuity was seen with the peripheral within the central nervous tissues by selective maturation of multipotential primitive reticular cells, a phenomenon consistent with the view that Schwann cells are mesenchymal in character.

Tohoku J Exp Med 1999 Dec;189(4):259-65. Elevated plasma level of plasminogen activator inhibitor-1 (PAI-1) in patients with relapsing-remitting multiple sclerosis. Onodera H, Nakashima I, Fujihara K, Nagata T, Itoyama Y "Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system and one of the earliest changes in inflammatory focus involves the activation of vascular endothelial cells." "The level of plasma PAI-1 was significantly higher in active MS cases when compared to stable MS and controls." "These results suggested that PAI-1 plasma levels are associated with MS disease activity and is a good marker for MS relapse."

J Mol Med 1997 Mar;75(3):174-86. The role of nitric oxide in multiple sclerosis. Parkinson JF, Mitrovic B, Merrill JE "Elevated nitric oxide bio-synthesis has been associated with nonspecific immune-mediated cellular cytotoxicity and the pathogenesis of chronic, inflammatory autoimmune diseases including rheumatoid arthritis, insulin-dependent diabetes, inflammatory bowel disease, and multiple sclerosis."

Fed Proc 1987 Jan;46(1):91-6. Role of the clotting system in the pathogenesis of neuroimmunologic disease. Paterson PY, Koh CS, Kwaan HC "Our studies of the clotting system and ensuing fibrinolysis implicate coagulation and cleavage of fibrin within or on the luminal surface of the cerebrovasculature as events initiating the inflammation characterizing EAE." "We postulate that the critical event precipitating EAE is binding of circulating MBP-reactive immune effector cells to MBP immunodeterminants on the surface of cerebrovascular endothelial cells. Coagulation and ensuing fibrinolysis occur at sites of binding of effector cells to cerebrovascular endothelium. Release of biologically active peptides cleaved from fibrin open the BBB, thereby setting the stage for the cascade of inflammatory events culminating in clinical manifestations of EAE."

Neurotoxicology 1998 Aug-Oct;19 (4-5):599-603. In vitro effect of the cysteine metabolites homocysteic acid, homocysteine and cysteic acid upon human neuronal cell lines. Parsons RB, Waring RH, Ramsden DB, Williams AC "Cysteine (CYS) is a non-essential amino acid which elicits excitotoxic properties via the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor.. CYS levels are known to be elevated in association with neurological disease such as Alzheimers Disease (AD) and Parkinsons Disease (PD)." "These results show that toxic responses are cell-type specific for CYS and its metabolites and this may be reflected in the patterns of neurodegeneration observed in such diseases as AD and PD."

WMJ 1983 Mar-Apr;55(2):146-50. [Effect of tryptophan excess in a diet on amino acid composition of skin collagen and on an initial stage of protein biosynthesis in rat liver]. Pechenova TN, Sushkova VV, Solodova EV, Gulyi MF Protein deficiency and tryptophane load against its background lead to the acid-soluble collagen synthesis in the rat skin. The amino acid composition of the collagen differs from the norm. This is accompanied by changes in the free amino acid pool of blood serum and liver, under tryptophane load the free amino acids pool of the liver increasing twice as high. At the same time protein deficiency increases and tryptophane load decreases the level of tRNA amino acylation with tryptophane in the animal liver. Thus, protein deficiency and tryptophane load against its background cause deep changes in the protein biosynthesis.

Fed Proc 1987 Jan;46(1):91-6. Role of the clotting system in the pathogenesis of neuroimmunologic disease. Paterson PY, Koh CS, Kwaan HC "Our studies of the clotting system and ensuing fibrinolysis implicate coagulation and cleavage of fibrin within or on the luminal surface of the cerebrovasculature as events initiating the inflammation characterizing EAE." "We postulate that the critical event precipitating EAE is binding of circulating MBP-reactive immune effector cells to MBP immunodeterminants on the surface of cerebrovascular endothelial cells. Coagulation and ensuing fibrinolysis occur at sites of binding of effector cells to cerebrovascular endothelium. Release of biologically active peptides cleaved from fibrin open the BBB, thereby setting the stage for the cascade of inflammatory events culminating in clinical manifestations of EAE."

Rev Esp Fisiol 1983 Mar;39(1):39-44. Intralipid and free plasmatic tryptophan in vitro. Pena JM, Aulesa C, Vinas O, Bosch J, Farriol M, Schwartz S "In an attempt to investigate the role of the lipidic emulsion Intralipid in the development of metabolic encephalopathy in a patient showing high free tryptophan levels, the relationship between lipidic emulsion and free tryptophan was examined in in vitro experiments. The addition of intralipid to normal serum produces an immediate increase in non-esterified fatty acids and a parallel rise in free tryptophan. Moreover, when serum with intralipid is incubated at 37 degrees C, the lipases release new non-esterified fatty acids and the free tryptophan increases proportionally." "It is concluded that intralipid causes an increase in free tryptophan levels. It is known that in vivo free tryptophan modulates 5-hydroxytryptamine synthesis and thus may be considered a possible causal agent for encephalopathy."

Med Hypotheses 1980 May;6(5):545-557. Fatty acids, fibrinogen and blood flow: a general mechanism for hyperfibrinogenemia and its pathologic consequences. Pickart LR, Thaler MM Plasma fibrinogen is elevated in various stressful states and conditions in which active mobilization of free fatty acids (FFA) occurs. Reduction of plasma FFA by an assortment of hypolipidemic drugs is consistently followed by a decrease in the accompanying hyperfibrinogenemia. A direct link between FFA and fibrinogen has been demonstrated in animals, and in experiments employing incubated liver slices. Based on these clinical and experimental observations, we postulate that hepatic fibrinogen synthesis is stimulated by FFA. Since fibrinogen is a major determinant of whole blood viscosity, erythrocyte aggregation, and sludging of red cells in terminal and pre-terminal blood vessels, we propose that microcirculatory blood flow may be impaired in the presence of chronically elevated plasma FFA levls. Consequently, hypolipidemic drugs may be effective in prevention of circulatory complications associated with

FFA-induced hyperfibrinogenemia.

Neurologia 1996 Aug-Sep;11(7):272. [Exacerbation of spasticity induced by serotonin reuptake inhibitors. Letter]. del Real MA, Hernandez A, Vaamonde J, Gudin M

J Neurol Neurosurg Psychiatry 1997 Mar;62(3):282-4. Ondansetron, a 5-HT3 antagonist, improves cerebellar tremor. Rice GP, Lesaux J, Vandervoort P, Macewan L, Ebers GC. "It has been previously shown that ondansetron, a 5-HT3 antagonist, can ameliorate vertigo in patients with acute brainstem disorders. A coincidental benefit was the improvement of cerebellar tremor in some patients with both vertigo and tremor. To further evaluate this effect, a placebo controlled, double blind, crossover study was conducted of a single dose of intravenous ondansetron in 20 patients with cerebellar tremor caused by multiple sclerosis, cerebellar degeneration, or drug toxicity.""Thirteen of 19 patients were deemed to have improved spiral copying after treatment with ondansetron when compared with baseline performance."

Neurologia 1993 Oct;8(8):252-5. [Retinal periphlebitis in multiple sclerosis. A prospective study]. Rio J, Colin A, Salvador F, Tintore M, Viguera ML, Montalban J, Codina A "In three cases (12.5%) retinal periphlebitis was observed.""Given the absence of myelin in the retina, the presence of retinal periphlebitis suggests the existence of a vascular mechanism in the pathogenesis of multiple sclerosis."

Int J Neurosci 1995 Dec;83(3-4):187-98. Premenstrual exacerbation of symptoms in multiple sclerosis is attenuated by treatment with weak electromagnetic fields. Sandyk R. "The present report concerns two women with chronic progressive stage MS who experienced, coincident with increasing functional disability, regular worsening of their symptoms beginning about a week before menstruation and abating with the onset of menstruation. These symptoms resolved two months after the initiation of treatment with EMFs."

J Physiol Biochem 1998 Dec;54(4):229-37. The role of nitric oxide in the pathogenesis of multiple sclerosis. Santiago E, Perez-Mediavilla LA, Lopez-Moratalla N "The inducible NOS (iNOS) is associated with the development of a number of autoimmune diseases.""Induction of the enzyme is effected by proinflammatory cytokines, immunomodulating peptides, and even beta-endorphin through a mechanism involving an increase in cAMP. An excessive production of NO has been implicated in the severe lesions observed in multiple sclerosis (MS)."

J Neurol 1980 Jan;222(3):177-82. Cerebrospinal fluid lipids in demyelinating disease. II. Linoleic acid as an index of impaired blood-CSF barrier. Seidel D, Heipertz R, Weisner B "The linoleic acid content of control CSF (1.6 +/- 0.8 nMol/ml) is considerably lower than the corresponding serum value (2.5--4.1 muMol/ml). Although CSF from MS patients contains a significantly higher linoleic acid concentration than controls the close correlation between CSF linoleic acid and CSF albumin is maintained. The high CSF concentration of cholesterol esters rich in linoleic acid, which are abundant in serum but represent only traces in CNS lipids, points towards an impaired BBB function as the cause of CSF linoleic increase. We are able to show that both albumin and linoleic acid are suitable as "serum markers...."

J Neurol Sci 1987 Feb;77(2-3):147-52. Chronic periphlebitis retinae in multiple sclerosis. A histopathological study. Shaw PJ, Smith NM, Ince PG, Bates D Retinal periphlebitis in multiple sclerosis is of particular interest in relation to our understanding of the pathogenesis of the demyelinating central nervous system plaques. Previous studies have largely been clinical, and there is little detailed histopathological information relating to this condition. We present the first detailed report in the neurological literature on the histological findings in chronic periphlebitis retinae associated with multiple sclerosis. The most significant abnormalities of the affected retinal veins were the presence of thick laminated collagen in the wall, associated with a scanty infiltration of plasma cells.

Am Heart J 2000 Aug;140(2):212-8. Low intracellular magnesium levels promote platelet-dependent thrombosis in patients with coronary artery disease. Shechter M, Merz CN, Rude RK, Paul Labrador MJ, Meisel SR, Shah PK, Kaul S.

J Neurochem 1996 Mar;66(3):1157-66. Mast cell activation causes delayed neurodegeneration in mixed hippocampal cultures via the nitric oxide pathway. Skaper SD, Facci L, Romanello S, Leon A. "Neurotoxicity required a prolonged period (12 h) of mast cell incubation, and appeared to depend largely on elaboration of the free radical nitric oxide by astrocytes.""Myelin basic protein and 17 beta-estradiol had a synergistic action on the induction of mast cell-associated neuronal injury.""Further, palmitoylethanolamide, which has been reported to reduce mast cell activation by a local autacoid mechanism, decreased neuron loss resulting from mast cell stimulation in the mixed cultures but not that caused by direct cytokine induction of astrocytic nitric oxide synthase.""These results support the notion that brain mast cells could participate in the pathophysiology of chronic neurodegenerative and inflammatory diseases of the nervous system, and suggest that down-modulation of mast cell activation in such conditions could be of therapeutic benefit."

International Journal of Microcirculation--Clinical and Experimental, 1996, Vol 16, Iss 5, pp 266-270. Hyperventilation enhances transcapillary diffusion of sodium fluorescein. J Steurer, D Schiesser, C Stey, W Vetter, MV Elzi, JP Barras, UK Franzeck. "Voluntary hyperventilation (HV) provokes hemoconcentration due to a loss of fluid from the intravascular space.""The exact, mechanism of enhanced transcapillary diffusion of Na fluorescein is not known, The distinct increase in FLI without a significant change in microvascular skin flux suggests an HV-induced increase in capillary pressure or an enhancement in capillary permeability for water and small solutes."

Kidney Int 1992 May;41(5):1245-53. Essential fatty acid deficiency normalizes function and histology in rat nephrotoxic nephritis. Takahashi K, Kato T, Schreiner GF, Ebert J, Badr KF.

Arthritis Rheum 1981 Aug;24 (8):1054-6. Sex steroid hormones and systemic lupus erythematosus. Talal N.

Clin Rheum Dis 1982 Apr;8(1):23-8. Sex hormones and modulation of immune response in SLE. Talal N.

Ann N Y Acad Sci 1986;475:320-8. Hormonal approaches to immunotherapy of autoimmune disease. Talal N, Ahmed SA, Dauphinee M.

Ann Nucl Med 1998 Apr;12(2):89-94. Clinical significance of reduced cerebral metabolism in multiple sclerosis: a combined PET and MRI study. Sun X, Tanaka M, Kondo S, Okamoto K, Hirai S "The severity of cerebral hypometabolism was also related to the number of relapses." "Our results suggest that measurement of cerebral metabolism in MS has the potential to be an objective marker for monitoring disease activity and to provide prognostic information."

Fed Proc 1987 Jan;46(1):118-26. Pathway to carrageenan-induced inflammation in the hind limb of the rat. Vinegar R, Truax JF, Selph JL, Johnston PR, Venable AL, McKenzie KK "Antiserotonin agents inhibited the hypoalgesia and part of the edema. These findings and histological observations suggested that dermal mast cells were injured by C. The hyperalgesia and part of the edema were sensitive to arachidonate cyclooxygenase inhibitors (AACOIs). It is speculated that injured mast cells metabolize arachidonic acid and reactive intermediates, not prostaglandins, mediate the NPIR hyperalgesia and part of the edema.""Arachidonic acid metabolism by neutrophils is speculated to produce the mediators of phagocytic inflammatory (PI) edema and hyperalgesia."