Letters to the Editor

Diagnosing Porphyria for Labor and Industries Claims

Editor:

Polycythemia, scleroderma, and porphyria have several elements in common, but I have never seen a discussion of this. Although I have written about them before, my articles on these subjects haven't been widely published. When I saw all of these topics mentioned on the same page of the *Townsend Letter* (February/March 1996, page 98), it seemed that I should point out some of the features that make these a sort of family of disorders.

These are disorders of tissue respiration and energy production. Oxygen, estrogen, and iron have important roles in all of them. Men are more likely to have polycythemia, women are more likely to have scleroderma and some types of porphyria.

The Washington State Department of Labor and Industries' review of porphyria is representative of a bureaucratic approach to a disease in its exclusion of all of the publications that offer an opportunity to understand its mechanism in a general way; I think it is setting the stage for a pro-industry/anti-worker policy, in drawing its distinction between problems "triggered by" exogenous chemicals, and those "potentially *caused* by an exogenous chemical exposure." Scientifically, this sort of categorization is meaningless. I think it is reasonable to interpret any increase in porphyrin metabolism as possible evidence of work-related damage, which compromises the worker's adaptive capacity in many ways.

The document at one point approaches a recognition of the silliness of their approach: "It can be argued semantically that this was not a true 'porphyria,' because of the absence of hereditary enzyme deficiency; however, there is little question that this acquired 'porphyria-like' condition was highly morbid and also clinically indistinguishable from the inherited form of porphyria cutanea tarda."

Until the doctrine of significant genetic causation is subjected to the requirement of being obtained in *"a rigorously designed, blinded and appropriately controlled manner,"* it would have to be considered *"speculative and unestablished,"* if this document were coherent. (It appears that its authors drew their gun intending to cripple a branch of alternative medicine, and shot their argument in the head.) The document's emphasis on defining the disease in terms of genetic deficiency gives the enterprise an overwhelmingly anecdotal quality, at best. Let us see the rigorous evidence on which the categorization is based.

The document bases its whole presentation on the presumed reality of "hereditary *deficiency*" of enzymes, and – probably for a reason – ignores the evidence for an enzyme *excess*, which can be so easily induced chemically or hormonally. Early steps in the prophyrin synthetic pathway are influenced by the availability of precursor substances and by the concentration of heme, and are extremely susceptible to environmental influences. The issue of the role of genes in the balance and organization of a complex enzyme system is so tenuous that the citizens of Washington should look into the state's manner of choosing its experts.

There is a long history of investigating the interactions of porphyria metabolism with estrogen (L.C. Strong, Sex differences in pigment content of Harderian glands of mice, *Proc. Soc. Exp. Biol. Med.* 60, 1223-125, 1942), with cancer (e.g. F.H.J. Figge, et al., *Cancer Res.* 2, 335-342, 1942), with diet, and with excess iron. Estrogens are known to cause porphyria (R.D. Levere, *Blood* 28, 569-572, 1966), and to exacerbate the symptoms and biochemical disturbances in people with subclinical porphyria. Sometimes symptoms occur premenstrually, during the time of increased estrogen production – the term "ovulocyclic porphyria" has been in use for a long time. Puberty therefore increases the susceptibility to symptomatic episodes.

Porphyria synthesis begins at an important cross-over point of protein and carbohydrate metabolism. Succinyl CoA and amino levulinic acid can enter the Krebs cycle or the porphyria pathway. Protein catabolism feeds into these pathways. Increased protein catabolism or blockage of oxidative consumption of Krebs cycle fuel – for example by poisoning – makes these precursors available to enter the prophyrin pathway. Stress-induced oxidation of heme can eliminate feedback control, but the specific outcome can be modified in many ways.

Many serious long-range consequence of excess heme/porphyrin production and metabolism are currently being investigated, suggesting that a criterion of "twice the upper limit of normal" excretion, for recognizing that a problem exists, could allow far more serious problems to develop over time, that on the surface might seem unrelated to porphyria. In some cases of porphyria cutanea tarda, scleroderma-like hardening of skin occurs, but the ramifications of disturbed heme metabolism, resulting from exogenous factors, are far-reaching. For example, G.Y. Kennedy, at the Cancer Research Laboratory, University of Sheffield, observed that a porphyrin shortened the time required to induce tumors, and porphyrin derivatives have been proposed to be "cancer hormones." The carbon monoxide produced in the breakdown of heme inhibits many enzymes.

The synthesis of heme/porphyrin, and the production of red blood cells, are stimulated by a lack of oxygen, or by toxins such as arsenic and iron, which cause oxidative stress. Emphysema, high elevation, sluggish circulation, and nocturnal breathing problems can cause enough oxygen deficiency to stimulate the formation of new red blood cells. Newborn babies often have polycythemia, as a result of limited prenatal oxygen supply. At a certain point, the continued production of red blood cells can make the blood so viscous that this viscosity impairs circulation through capillaries, and creates a vicious circle, stimulating the formation of more red blood cells. Men are more likely than women to have polycythemia rubra vera, possibly because testosterone is anabolic to the bone marrow, and estrogen tends to slow blood cell formation (females of all species are relatively "anemic," compared to males, partly because their blood is more dilute), but I think the greater ability of men's marrow to respond proliferatively to hypoxia is influenced by many factors, including different nutritional requirements. (Estrogen tends to cause certain vitamin deficiencies and fluid retention.) Estrogen also significantly lowers body temperature, while testosterone tends to raise it, and the temperature of the bones is a powerful factor in forming new blood cells. But this isn't to suggest that the patient could benefit from increased estrogen, because

estrogen consistently lowers the availability of oxygen.

Excess estrogen reduces the blood's oxygenation, for example by producing a barrier to oxygen diffusion in the lung. Hypothyroidism (which is causally related to an excess of estrogen) is known to predispose to emphysema, and treatment with thyroid hormone has often cured polycythemia vera, presumably by improving respiratory efficiency. Progesterone, which is known to stimulate the brain's respiratory control system, has also been used successfully to treat polycythemia, and in animal studies it corrects experimentally induced emphysema. These treatments for polycythemia vera were mentioned about 30 years ago (in *JAMA*, I think, though I don't mention that to give the observations credibility, just to show how generally distributed the information has been). In Colorado, where the incidence of polycythemia is high, it was found that teaching men to get in the habit of breathing more deeply could solve the problem.

Although there has been a medical faction that liked to compare polycythemia with leukemia, to justify treatment with radiation or cytotoxic/carcinogenic chemotherapy (and following the treatment, the patients did get leukemia, confirming the doctors' belief in the connection between the two diseases), simply removing some blood and replacing it with fluid to bring the volume of red cells down to 45 to 50% improves exercise performance in polycythemia patients with chronic bronchitis, emphysema, overinflated lungs and hypoxia (B.D.W. Harrison, et al., *Clin. Sci.* 45, 833-847, 1973). H.P. Ward, et al. (*Am. J. Med.* 45, 880-888, 1968) found that in some patients, lying down or sleeping could cause enough oxygen deficiency to increase red blood cell formation. Increased viscosity of blood, and increased levels of adrenalin produced in response to hypoxia, cause increased risk of excessive blood clotting and thrombosis.

In my experience, clinical emphysema responds very well to pregnenolone, and for men, this has advantages over both progesterone and thyroid.

Impaired lung function is very common in scleroderma, even when there seems to be no evidence of lung involvement (C.T. Huang and H.A. Lyons, *Am. Rev. Resp. Dis.* 93, 865-875, 1966).

Metal poisoning is often mentioned as a cause of both porphyria and scleroderma. It was probably this medical association that caused Hans Selye to create the animal model, in which the injection of iron contributed to the development of scleroderma. (H. Selye, *J. Invest. Derm.* 39, 259, 1962; Selye and B. Tuchweber, *Quart. J. Exper. Physiol.* 50, 196, 1965.) Injected iron damages the liver (J.A. Nissim. The entry of iron into liver parenchyma cells following injection of different iron preparations, and the different lesions produced with toxic doses, *J. of Physiology* 117, 66-67, 1952), and practically any kind of liver damage leads to estrogen excess and a chronic stress-like adaptive response.

Scleroderma used to be described as one of the "collagen diseases," because similar changes in blood vessels and connective tissues were seen in systemic lupus erythematosus, rheumatoid arthritis, polyarteritis, drug hypersensitivity, etc. (G.P. Rodnan; Progressive systemic sclerosis (scleroderma), in J.I. Hollander and D.J. McCarty, Jr., editors, *Arthritis and Allied Conditions*, Lea & Febiger, 1972). Scleroderma (similar to several other "autoimmune" diseases) is much more common in women than in men, and animal models for several autoimmune diseases can be produced with estrogen treatment. Scleroderma often begins with edema of the extremities, Raynaud's phenomenon, and muscle weakness or "polymyositis," which are commonly seen in hypothyroidism/hyperestrogenism.

It is generally agreed that collagen is overproduced in scleroderma, and there is evidence of increased mucopolysaccharides in the skin (O. Braun-Falco, *Derm. Wschr.* 136, 1085, 1957). This is reminiscent of hypothyroid myxedema; it has been suggested that mucopolysaccharides can act as a matrix for calcification (W.C. Johnson, et al., *J. Invest. Derm.* 43, 453, 1964). Estrogen stimulates the formation of collagen, and increases its age-like properties, and progesterone opposes some of these pro-aging effects on connective tissues. Mere lack of oxygen stimulates collagen formation, and the opposing effects of estrogen and progesterone on tissue oxygenation can account for many of the tissue changes they produce.

Oxygen deprivation causes tissues to retain calcium (and iron), as does estrogen in many cases, being similar to aging in promoting cellular uptake of calcium. Since the porphyrins strongly bind metals, it has been suggested that they may have a role in mediating the deposition of metals in stressed tissues. Paroxysmal vasospasm occurs in about 90% of scleroderma patients, and estrogen and adrenalin are known to synergize in producing vascular spasm; hypothyroidism normally involves elevations of both estrogen and adrenalin.

More Letters

I have known women who developed scleroderma after beginning the use of estrogen, and who are reluctant to stop, because they had been told that estrogen would protect them from osteoporosis and heart disease. Men who have had a diagnosis of scleroderma have told me that with the use of thyroid and magnesium supplements, Epsom salts baths, and topical progesterone and vitamin E, their symptoms regressed.

Polymyositis sometimes leads to calcification, and this would be expected if the problem is related to mitochondrial respiration, as is now generally thought to be the case; thyroid and magnesium are often the factors needed to normalize mitochondria and prevent calcification.

Tumoral calcinosis is sometimes treated as a variant of scleroderma, but it is very different, and tends to be localized, without internal complications. I think many people get minor bony excrescences (bone spurs, osteophytes, exostoses, hyperostoses) during puberty, or at other times of hormone imbalance, which often disappear spontaneously, but this probably represents the same basic process, and would have very little to do with the severe oxygen deficiency states in which collagen synthesis is overstimulated. Growth hormone and prolactin imbalances have been suspected to have a role in some of these growths. (Both of these pituitary hormones are elevated by estrogen, and hypothyroidism is often the cause.) Progesterone, thyroid, bromocriptine, and other things are available to normalize the pituitary, when that is responsible.

A weakened ability to oxidatively produce energy can lead to the maladaptive over-production of collagen, porphyrins, and red blood cells. Considered together, I think the mechanisms involved in these diseases argue for the importance of the nutritional-environmental approach to health care. The medical/bureaucratic preference for a "genetic" rationale for disease has overtones of "eugenics." When the state gets involved in genetics, eugenics, or medicine, they had better keep their own scientific standards at least as high as those they demand of the people they disagree with.

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