Ray Peat's Newsletter

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Fibrosis is an outstanding feature of aging: Skin, joints, liver, kidneys, heart and blood vessels, even the brain, undergo fibrotic changes in association with disease, injury, and aging.

Excitotoxins are fibrogenic

Estrogen is excitotoxic and fibrogenic

Lactate is fibrogenic

Edema precedes fibrosis

Injury and inflammation are fibrogenic

Free radical peroxidation is a common pathway leading to fibrosis, as in cirrhosis of the liver in which unsaturated fats and free radicals have central roles.

Saturated fats, antihistamines, thyroid hormone, and other antiinflammatory agents prevent or reverse fibrosis.

The fibrous extracellular material regulates specialized cellular functioning, and is a protective buffer.

Fibrogenesis commonly precedes carcinogenesis.

Cancerization is a "field process," not primarily a unique "genetic event."

Proteolytic enzymes continuously dissolve and remodel the extracellular matrix.

Unsaturated fats inhibit proteolytic enzymes.

The resistance of the fibrin in blood clots to enzymic dissolution is increased by unsaturated fats.

Antifibromatogenic hormones oppose the development of the fibromas and cancers that are caused by estrogen.

The first principle in reversal is to stop the pathogenic process, and to stop the stress- induced cell death. Then restorative processes can come into balance with degenerative.

FIBROSIS: Estrogen, stiffness, excitotoxicity, aging--a problem more general than "collagen disease"

Thirty years ago, my professors said that any publication more than ten years old wasn't worth reading; that was apparently why I never saw the professors in the library. In a span of ten years, a change of 45 degrees in scientific orientation is thought to be progress. But in 40 years, those changes of orientation can produce a turn of 180 degrees, in which things that once seemed to be firmly established and full of potential have simply been removed from the academic canon. The biology of fibrosis is one of those important things that came to be neglected even while massive amounts of new evidence were confirming the old views.

At the beginning of the 20th century, Eli Metchnikov argued that changes in the connective tissues were the cause of aging. He also argued that intestinal toxins were important causes of the aging changes.

Early in the century, x-rays were found to produce tissue burns. The early effect of a radiation burn is inflammation and edema. The edema gradually gives way to fibrosis, and if the person lives long enough, the fibrotic tissue may calcify.

In the 1930s, Leo Loeb found that large doses of estrogen stimulated massive synthesis of collagen in the uterus.and vagina, and noticed that these effects resembled the increased accumulation of collagen that occurs with aging. In the 1940s, Alexander Lipshutz showed that very small, but continuous, doses of estrogen caused fibromas to develop in many tissues besides the uterus, and that these fibromas tended to develop

into cancers. Later, estrogen was found to accelerate the stiffening of the collagenous tissues that normally occurs with aging.

In the 1930s, the Shutes, father and sons, found that the clotting-associated diseases of pregnancy were prevented by vitamin E, and they proposed that vitamin E acts as an antiestrogen, protecting against the increased clotting problems caused by excessive estrogen. They showed that vitamin E activates the proteolytic, fibrinolytic, enzymes that remove blood clots.

Conventional beliefs identified vitamin E as an antioxidant that prevented oxidation of unsaturated fats, and this function of vitamin E appeared to make it inconceivable that vitamin E could also be of value in relation to the circulatory system. This attitude was still dominant in the 1970s among dietitians, physicians, and university professors. Besides ignoring or ridiculing the Shutes' work, mainstream journals would occasionally publish papers denying that vitamin E facilitates clot removal, or that estrogen promotes clotting, attempting to defend their 180 degree turn.

Just after the turn of the century, unsaturated fats were found to inhibit proteolytic enzymes. Repeatedly, the presence of unsaturated fatty acids has been shown to impair clot removal, either by its effect on proteolytic enzymes, or by being incorporated into the clot and making it resistant to dissolution.

Fibrin, the material that forms blood clots, is always in the process of formation and dissolution, in a kind of equilibrium. A thin layer of it coats the outside of blood cells, and the inside of blood vessels. When capillaries are leaky, some of the fibrin and its depolymerized subunits, leak out into the tissues. There is a complex interaction between fibrin and collagen, in which fibrin stimulates the formation of collagen (AJ Gray, et al., 1995) and collagen stimulates the fibrin clotting process.* Fibrin clots stimulate the growth of fibroblasts, and leaky blood vessels (Brown, et al., 1989) can lead to tissue fibrosis, though there are routes to fibrosis that don't involve fibrin.

Blood vessels leak under the influence of estrogen, irradiation, oxygen deprivation, vitamin E deficiency, free fatty acids, lactic acid, and various stress mediators, such as histamine and serotonin; particles as large as red blood cells can pass right through the endothelial cells. The loss of the blood vessels' ability to serve as a barrier corresponds to a disturbance in the structure of the cells, and this structural permeability is apparently the result of an imbalance in the state of the electrons in the proteins, the redox (reduction and oxidation) state, regulated by glutathione and other antioxidants and energy regulators.

The internal state of any cell, not just in the blood vessels, is governed in similar ways by cellular energy and the redox state of proteins, and in the oxidatively disturbed state, cells take up water, as well as being abnormally "permeable" in both directions. For example, when a cell is deficient in vitamin E it loses molecules such as ATP and proteins, that diffuse out into the extracellular spaces. When cells are in an energy deficient state, as in hypothyroidism, they are in this leaky, edematous state.

This state of near exhaustion is similar to the "excitotoxic" state that's caused by an imbalance between stimulation and energy production. In the brain, excitotoxins have been found to produce a kind of fibrosis, in which the cells that normally produce the myelin sheath surrounding nerve axons begin producing collagen, and appear to change into a type of cell (Schwann cell) that is not normally found in the brain. **The production of collagen seems to be a very basic kind of defensive reaction to excessive stimulation or oxygen deprivation.** This makes it possible to see "excitotoxicity" as a general process, that includes the kind of fibrosis and calcification of skin that Hans Selye produced (by combining vitamin E deficiency with heavy metal toxicity and local

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**In the 1920s, W. F. Koch was proposing that oxidative free-radical processes governed the clotting of blood, the healing of wounds, and possibly the calcification of devitalized tissues. At that time, free radicals were an esoteric matter of interest mainly to a few polymer chemists, and it was considered absurd to suggest that cellular respiration could relate to extracellular fibrous matter.*

irritation), as well as the aging of brain cells produced by prolonged estrogenic stimulation. Scleroderma, like the other "collagen diseaes," affects women (during their reproductive years) much more often than men. Retroperitoneal fibrosis, which can seriously damage the kidneys and other abdominal organs, has been compared to uterine fibroid tumors, and it is commonly treated successfully with the antiestrogenic drug, tamoxifen. Tamoxifen has also been used to treat keloids and to prevent abnormal scars in plastic surgery. (I have seen keloids regress quickly following the application of vitamin E with antiestrogenic hormones.) The fibrotic response to the excitotoxic imbalance can be seen in practically all chronic and degenerative diseases.

Fibrosis is an abnormal progression of the normal formation of fibrous material between cells, and it usually involves an increase in the volume of the extracellular material, and an increase in the percentage of collagen in that matrix, and an increased rigidity of the collagen that results from chemical cross-links, that are analogous to the polymerization of a plastic, or the vulcanizing of rubber. Arteriosclerosis is probably the best known medical example of tissue fibrosis, but it's the same phenomenon that makes the meat from an old animal tough and rubbery.

Although "stiffness" is a familiar term in engineering and biology, it has some different meanings in different situations. When a tissue swells up with water until it's tight, it is stiffer than in its natural condition. The material of tendons and ligaments gets stiffer by increasing its density and toughness. When a bone gets old, it gets brittle and weak, and in one sense it is stiffer than a child's bone, since a child's bone can be deformed without breaking. While the engineering definitions can't be applied to all tissues in a simple way, biologically it's useful to think of stiffness as something that progresses along with fibrosis, as the function of a tissue decreases. In the first stage of tissue injury, swelling stiffens a tissue; after prolonged edema, there may be an increased volume and concentration of collagen around cells; finally, the density of the collagen can increase, and can calcifiy, as in the sclera of the eye, the arteries, heart valves, pericardium, and even the heart muscle itself.

In diseases of stress and aging, there is a general inflammatory state, that can end in multiple organ failure. Congestive heart failure illustrates some of the effects of this energy-poor, inflamed and edematous state: The heart's function is reduced because of stiffness caused by increased water and calcium in the cells; at the same time, arteries are stiff and resistant, impairing the flow of blood and making regulation of blood pressure difficult. In chronic hypothyroidism, the heart gradually becomes fibrotic, and this provides an opportunity for calcification to occur.

If a callus is a metaphor for the normal, protective function of connective tissue, then a corn is a metaphor for the harmful overdevelopment of the protective reaction. The ordinary minor mechanical tensions and pressures that occur in any living animal, as well as the biochemical gradients produced by metabolizing cells, shape the connective tissues that keep cells in their particular place in the organism. When gelatin, made by boiling connective tissues in water, is injected into a growing organism, the randomly arranged molecules of the melted collagen can be seen to organize themselves back into the coherently aligned cable-like structures of normal connective tissue.

Cells decide what they will be and do according to their surroundings. Normally, cells live in contact with a layer of non-cellular material containing fibrous and elastic and gelatinous material, that functions as a medium of communication with other cells. Irritation, stress, and shock commonly produce a series of tissue reactions, including edema, fibrosis, calcification, and death, but with certain possible alternatives, such as a return to the normal state, or early cell death, or lipodystrophy (fatty degeneration), or tumefaction (development into a tumor).

Although there are specialized cells, fibroblasts, that form large amounts of connective tissue, they are very closely related to muscle cells, fat cells, and glial cells, and the functions of one can sometimes change into those of another type. One of the main problems of biology in the

last century has been to understand the factors that cause one kind of cell to change into another. One of the functions of the collagen layer secreted around cells appears to be to provide a degree of insulation from the numerous "inductive" factors, so that a cell can remain what it is.

Conditions in the whole organism affect the way an individual cell will relate to its immediate environment. Nutritional deficiencies or imbalances will make special demands on certain types of tissue. Increased collagen production can provide some protection against toxins, but the protective layer also limits the cells' access to the blood supply.

Cells in their excited and exhausted state are increasingly open to penetration of the toxins, because of their own increased permeability, and because of the increased leakiness of the blood vessels. Certain environmental toxins accumulate more rapidly as the cells lose their ability to destroy them. Several kinds of toxin, including the unsaturated fats, inhibit the proteolytic enzymes that remodel tissue, and reduce the ability to dismantle and rebuild the extracellular matrix.

Collagen is a very unusual protein, since it lacks tryptophan and cysteine, and contains a very high percentage of glycine. Glycine is the simplest amino acid, and serves as an inhibitory transmitter. It has some remarkable protective activities against toxins, but even the process of forming it has some uniquely protective consequences: It is made from sugar, with the addition of ammonia removed from glutamic acid, leaving ketoglutaric acid as the product; ketoglutarate is a component of the Krebs cycle. In effect, the formation of glycine helps to eliminate an excitotoxin while replenishing the pathway of oxidative metabolism. When collagen is dissolved, a large amount of the antitoxic glycine is released, but not a bit of the excitotoxic antithyroid amino acids cysteine and tryptophan.

The increased energy deficiency produced by accumulated toxins and fibrosis can stimulate the production of porphyrins for the heme enzymes that control respiration and detoxification, and this can lead to the production of carbon monoxide and other anti-respiratory factors. Increasing amounts of ammonia and lactic acid circulate through the tissues. As excitatory states replace the capacity for resting inhibition, increased amounts of many hormones and other signal substances circulate, and many of them are produced in unusual sites, often in the same tissues that respond to them, as when a breast cancer produces estrogen. In the absence of communication between the tissue and its environment, these locally produced factors probably serve to maintain local homeostasis, but at the expense of the functions of the whole organism.

In every different part of the body, the extracellular matrix reflects the individuality of its cell types and their particular function. But as the body's exposure to toxic imbalances progresses, the general properties of deterioration start to become more important than the specialized functions.

To reverse this process, it's necessary to avoid doing the things that caused the problem to develop. The accumulation of heavy metals and of the unstable unsaturated fats (linoleic, linolenic, and arachidonic acids) can be slowed or reversed by careful dietary choices. The calorie-restricted diets that slow the aging process reduce the accumulation of the unstable fats and the heavy metals. Vitamin E reduces the vascular leakiness and the free radical peroxidation that are so closely involved in fibrosis. Since serotonin and nitric oxide are involved in these processes, they should be minimized by keeping carbon dioxide production high (by optimizing thyroid function), and by eating proteins that have a safe balance of the amino acids. Too much arginine increases nitric oxide formation, and too much tryptophan increases serotonin production. Too much glutamic acid aspartic acid, and cysteine can be directly excitotoxic, and the metabolites of cysteine include proinflammatory homocysteine, which can disrupt collagen structure.

Since estrogen is often a promoter of fibrosis, acting in a variety of ways, it should be kept under control by eating enough protein, keeping thyroid function relatively high, and if necessary by using progesterone and other antiestrogenic hormones. A protein deficiency is thrombogenic (clot forming), and probably excitotoxic.

Magnesium, taurine, and niacinamide have many protective functions, and can help to reduce or reverse inflammatory and fibrogenic processes.

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