Estrogen and Osteoporosis

From the original article in 2006. Author: Ray Peat.

> *"How does estrogen enhance endotoxin toxicity? Let me count the ways."*
> J.J. Maher (Liver Center and Department of Medicine, University of California San Francisco) in Hepatology, 1998, 28(6):1720-1.

The government declared victory in the war on cancer, though the age-specific death rate from cancer keeps increasing. In the equally well publicized effort to prevent disability and death from osteoporosis, no one is declaring victory, because the only trend in its incidence that has been reported is an increase. The estrogen-promoting culture tells us that this is because of the aging of the population, but the age corrected numbers still show a great increase--for example, in Finland between 1970 and 1995, the number of women (for a given population of women older than 60) breaking their forearm because of osteoporosis more than doubled (Palvanen, et al., 1998). That this happened during a time when the use of estrogen had become much more common doesn't present a good argument for the protective effects of estrogen treatment. (And during this period there was a large increase in the consumption of estrogenic soy products.) Recently our local newspaper had a story at the bottom of the front page reporting that lean women who used estrogen and synthetic progestins had an 80% higher rate of breast cancer. Several days later, across the top of the front page, there was a rebuttal article, quoting some doctors including a "world class expert on hormone replacement therapy" and a woman who has taken Premarin for forty years and urges everyone to take it. The "protection against osteoporosis" and against heart disease, they said, must be weighed against a trifle such as the 80% increase in cancer. It appeared that the newspaper was apologizing for reporting a fact that could make millions of women nervous. (Jan 26, Register-Guard).

Medical magazines, like the mass media, don't like to miss any opportunity to inform the public about the importance of using estrogen to prevent osteoporosis. Their attention to the bone-protective effect of progesterone has been noticeably less than their mad campaign to sell estrogen, despite the evidence that progesterone can promote bone rebuilding, rather than just slowing its loss. Although I have spoken about progesterone and osteoporosis frequently in the last 25 years, I have only occasionally considered what estrogen does to bones; generally, I described estrogen as a stress-promoting and age-promoting hormone. In the 1970s, pointing out progesterone's protective antagonism to excessive amounts of other hormones, and that the catabolic glucocorticoids tend to increase with aging, I began referring to progesterone as the "anticatabolic" hormone that should be used to prevent stress-induced atrophy of skin, bones, brain, etc.

A former editor of Yearbook of Endocrinology had reviewed a series of studies showing that excess prolactin can cause osteoporosis. Then, he presented a group of studies showing how estrogen promotes the secretion of prolactin, and can cause hyperprolactinemia. In that review, he wryly wondered how something that increases something that causes osteoporosis could prevent osteoporosis.

Women have a higher incidence of osteoporosis than men do. Young women have thinner more delicate bones than young men. The women who break bones in old age are generally the women who had the thinnest bones in youth. Menstrual irregularities, and luteal defects, that involve relatively high estrogen and low progesterone, increase bone loss.

Fatter women are less likely to break bones than thinner women. Insulin, which causes the formation of fat, also stimulates bone growth. Estrogen however, increases the level of free fatty acids in the blood, indicating that it antagonizes insulin (insulin decreases the level of free fatty acids), and the fatty acids themselves strongly oppose the effects of insulin. Estrogen dominance is widely thought to predispose women to diabetes.

Between the ages of 20 and 40, there is a very considerable increase in the blood level of estrogen in women. However, bone loss begins around the age of 23, and progesses through the years when estrogen levels are rising. Osteoarthritis, which involves degeneration of the bones around joints, is strongly associated with high levels of estrogen, and can be produced in animals with estrogen treatment.

Thirty years ago, when people were already claiming that estrogen would prevent or cure osteoporosis, endocrinologists pointed out that there was no x-ray evidence to support the claim. Estrogen can cause a positive calcium balance, the retention of more calcium than is excreted, and the estrogen promoters argued that this showed it was being stored in the bones, but the endocrine physiologists showed that estrogen causes the retention of calcium by soft tissues. There are many reasons for not wanting calcium to accumulate in the soft tissues; this occurs normally in aging and stress.

Then, it was discovered that, although estrogen doesn't improve the activity of the cells that build bone, it can reduce the activity of the cells that remove bone, the osteoclasts. The osteoclast is a type of phagocytic cell, and is considered to be a macrophage, the type of cell that can be found in any organ, which can eat any sort of particle, and which secretes substances (cytokines, hormone-like proteins) that modify the functions of other cells. When estrogen was found to impair the activity of this kind of cell, there wasn't much known about macrophage cytokines.

With the clear evidence that estrogen inhibits the osteoclasts without activating the bone-building osteoblasts, estrogen was said to "prevent bone loss," and from that point on we never heard again about estrogen promoting a positive calcium balance. Calcium retention by soft tissues has come to be an accepted marker of tissue aging, tissue damage, excitotoxicity, and degeneration. Positive calcium balance had been the essence of the argument for using estrogen to prevent osteoporosis: "Women are like chickens, estrogen makes them store calcium in their bones." But if everyone now recognizes that calcium isn't being stored in bones, it's better for the estrogen industry if we forget about the clearly established positive calcium balance produced by estrogen.

The toxic effects of excessive intracellular calcium (decreased respiration and increased excitation) are opposed by magnesium. Both thyroid and progesterone improve magnesium retention. Estrogen dominance is often associated with

magnesium deficiency, which can be an important factor in osteoporosis (Abraham and Grewal, 1990; Muneyyirci-Delale, et al., 1999). As part of the campaign to get women to use estrogen, an x-ray (bone density) test was devised which can supposedly measure changes in the mineral content of bone. However, it happens that fat and water interfere with the measurements. Estrogen changes the fat and water content of tissues. By chance, the distortions produced by fat and water happen to be such that estrogen could appear to be increasing the density of a bone, when it is really just altering the soft tissues. Ultrasound measurements can provide very accurate measurements of bone density, without the fat and water artifacts that can produce misleading results in the x-ray procedure, and don't expose the patient to radiation, but the ultrasound method is seldom used.

In recent years, there has been quite a lot of research into the effects of the macrophage cytokines. Immune therapy for cancer was considered quackery when Lawrence Burton identified some substances in blood serum that could cause massive tumors in rodents to disappear in just a few hours. One of the serum factors was called Tumor Necrosis Factor, TNF. An official committee was formed to evaluate his work, but it reported that there was nothing to it. A member of the committee later became known as "the authority" on tumor necrosis factor, which was thought to have great potential as an anticancer drug. However, used by itself, TNF killed only a few cancers, but it damaged every organ of the body, usually causing the tissues to waste away. Other names, lymphotoxin and cachectin, reflected its toxic actions on healthy tissues.

Aging involves many changes that tend to increase the inflammatory reaction, and generally the level of TNF increases with aging. Although cancer, heart failure, AIDS, and extreme hormone deficiency (from loss of the pituitary or thyroid gland, for example) can cause cachexia of an extreme and rapid sort, ordinary aging is itself a type of cachexia. Progeria, or premature aging, is a kind of wasting disease that causes a child's tissues (including bones) to atrophy, and to change in many of the ways that would normally occur in extreme old age.

Recent studies have found that both men and women lose minerals from their bones at the rate of about 1% per year. Although men have lower estrogen in youth than women do, their bones are much heavier. During aging, as their bones get thinner, men's estrogen levels keep rising.

Besides having weaker bones, old people have weaker muscles, and are more likely to injure themselves in a fall because their muscles don't react as well. Muscle loss occurs at about the rate of 1% per year.

Women's muscles, like their bones, are normally smaller than men's, and estrogen contributes significantly to these differences.

TNF can produce very rapid loss of tissue including bone, and in general, it rises with aging. Some of the people who like to say that "osteoporosis is caused by estrogen deficiency" know about the destructive actions of TNF, and argue that it rises at menopause "because of estrogen deficiency." There are very good reasons for rejecting that argument; the experiments sometimes seem to have been designed purely for propaganda purposes, using toxic levels of estrogen for a specific result.

One researcher noted that the effects of estrogen on cells in vitro are biphasic: Low doses increased TNF, high doses decreased TNF. Everyone knows that unphysiologically high doses (50 or 100 or more times above the physiological level of around 0.25 micrograms per liter) of estrogen are toxic to cells, producing functional and structural changes, and even rapid death. So, when a researcher who wants to show estrogen's "bone protective" effect of lowering TNF adds a lethal dose of estrogen to his cell culture, he can conclude that "estrogen inhibits TNF production." But the result is no more interesting than the observation that a large dose of cyanide inhibits breathing.

TNF is produced by endotoxin, and estrogen increases the amount of endotoxin in the blood. Even without endotoxin, though, estrogen can stimulate the production of TNF. Lactic acid and unsaturated fats and hypoxia can stimulate increased formation of TNF. Estrogen increases production of nitric oxide systemically, and nitric oxide can stimulate TNF formation. How does TNF work, to produce tissue damage and wasting? It causes cells to take up too much calcium, which makes them hypermetabolic before it kills them. It increases formation of nitric oxide and carbon monoxide, blocking respiration. TNF can cause a 19.5 fold increased in the enzyme which produces carbon monoxide (Rizzardini, et al., 1993), which blocks respiration.

All of the normal conditions associated with high estrogen also are found to involve increased production of TNF, and treatment of animals with estrogen clearly increases their TNF. Premature ovarian failure (with low estrogen levels) leads to reduced TNF, as does treatment with antiestrogens. If bone resorption is significantly regulated by TNF, then it should be concluded that increased estrogenic influence will tend to produce osteoporosis.

Tamoxifen, which has some estrogenic effects, including the inhibition of osteoclasts, can kill osteoclasts when the dose is high enough. The inhibition of osteoclast activity by either estrogen or tamoxifen is probably a toxic action, that has been characterized as "beneficial" by the estrogen industry simply because they didn't have any better argument for getting women to use their products.

Some types of dementia, such as Alzheimer's disease, involve a life-long process of degeneration of the brain, with an inflammatory component, that probably makes them comparable to osteoporosis and muscle-wasting. (In the brain, the microglia, which are similar to macrophages, and the astrocytes, can produce TNF.) The importance of the inflammatory process in Alzheimer's disease was appreciated when it was noticed that people who used aspirin regularly had a low incidence of that dementia. Aspirin inhibits the formation of TNF, and aspirin has been found to retard bone loss. In the case of osteoporosis (A. Murrillo-Uribe, 1999), as in Alzheimer's disease, the incidence is two or three times as high in women as in men. In both Alzheimer's disease and osteoporosis, the estrogen industry is arguing that the problems are caused by a suddenly developing estrogen deficiency, rather than by prolonged exposure to estrogen.

Similar arguments were made fifty years ago regarding the nature of the menopause itself--that it was caused by a sudden decrease in estrogen production. The evidence that has accumulated in the last forty years has decisively settled that argument: Menopause is the result of prolonged exposure to estrogen. (Even one large dose destroys certain areas in the

brain, and chronic, natural levels damage the nerves that regulate the pituitary. Overactivity of the pituitary leads to many other features of aging.)

The links between estrogen and TNF appear to be essential factors in aging and its diseases. Each of these substances has its constructive, but limited, place in normal physiology, but as excitatory factors, they must operate within the appropriate constraints. The basic constraint is that resources, including energy and oxygen, must be available to terminate their excitatory actions. Adequate oxygen, a generous supply of carbon dioxide, saturated fats, thyroid, and progesterone restrain TNF, while optimizing other cytokines and immune functions, including thymic protection. In the development of the organism and its adaptive functions, there are patterned processes, functional systems, that can clarify the interactions of growth and atrophy. The respiratory production of energy and carbon dioxide, and the respiratory defect in which lactic acid is produced, correspond to successful adaptation, and to stressful/excitotoxic maladaptation, respectively. Excitotoxicity, and Meerson's work on the protective functions of the antistress hormones, have to be understood in this framework. This framework integrates the understanding of cancer metabolism with the other stress metabolisms, and with the metabolism of normal growth.

Unsaturated fats, iron, and lactic acid are closely related to the actions and regulation of TNF, and therefore they strongly influence the nature of stress and the rate of aging.

The fact that cancer depends on the presence of polyunsaturated fats probably relates to the constructive and destructive actions of TNF: The destructive effects such as multiple organ failure/congestive heart failure/shock-lung, etc., apparently involve arachidonic acid and its metabolites, which are based on the so-called essential fatty acids. When oxygen and the correct nutrients are available, the hypermetabolism produced by TNF could be reparative (K. Fukushima, et al., 1999), rather than destructive. Stimulation in the presence of oxygen produces carbon dioxide, allowing cells to excrete calcium and to deposit it in bones, but stimulation in the absence of oxygen produces lactic acid and causes cellular calcium uptake.

It is in this context that the therapeutic effects of saturated fats, carbon dioxide, progesterone, and thyroid can be understood. They restore stability to a system that has been stimulated beyond its capacity to adapt without injury.

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