Ray Peat's Newsletter

"At the core of all well-founded belief lies belief that is unfounded." Ludwig Wittgenstein

Gender, Aging & Disease Susceptibility

In the last two years, the corona virus disease has renewed medical interest in the role of gender in resistance to disease, especially the reason that men are 50% more likely than women to die from covid. (Young women are generally more resistant to infections than men, but to a less extreme degree.) Understanding this big difference in covid mortality could have great implications for the prevention and treatment of other diseases. The inflammatory and degenerative diseases increase greatly during the menopause; covid causes its damage mainly by increasing inflammation.

Confronting an unfamiliar disease, people rely on their existing knowledge of biology, immunity, and medicine, and some of their assumptions turn out to be very wrong. For example, knowing that the corona virus attaches to an enzyme, ACE2, on the surface of cells, there were many official warnings to stop using drugs that are known to increase ACE2. Drugs that increase ACE2 are being developed, because of clear evidence that this enzyme protects against covid by shifting the pro-inflammatory actions of the angiotensin system to anti-inflammatory actions. Unfortunately, the mistaken idea that increasing ACE2 would make the disease worse, predominated in the most prestigious journals. In the virologists' perspective on infection, ACE2 was essential because the virus enters there, but to people who understood the universal role of the angiotensin system in inflammation, disease, and resistance to disease, ACE2 was a central protective factor.

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Everything that seems very clear in medical knowledge is primarily a matter of opinion, which is usually very firmly held, because it harmonizes with hundreds of other long-held opinions in the culture. We know that immunity and general health deteriorate with age, but opinions on the reasons for that vary. We know that certain kinds of disease become more frequent or intense after menopause, but little progress has been made in treating or preventing them. I think a major reason for this is that both the medical culture and the general culture promote archaic and mistaken ideas about the nature of the menopause.

I occasionally hear doctors say that menopause occurs when the ovaries run out of eggs, or that the depletion of primary oocytes causes menopause, or that aging ovaries cause

menopause. This is usually followed by claims that, in the absence of eggs that develop into follicles, there is a failure to produce estrogen, and that the lack of estrogen leads to disease. Mainstream medicine and biology have accepted two dogmatic ideas held by August Weisman in the late 19th and early 20th century — the wear and tear theory of aging, and the Weissman Barrier, an absolute separation of the "germ line" from the body cells. When any part of the system "wears out," it can't be replaced, and results in aging. There is no valid evidence for any of these ideas, but they have been taught in universities for several generations, and shaped the preferred explanations for the occurrence of menopause.

In recent decades, very clear evidence has shown that something other than intrinsic aging of the ovaries is responsible for their changed function in midlife, that is, that something in the ovaries' environment is responsible for the changes of menopause.

The repeating cycles of ovulation expose the brain, especially the hypothalamus and the pituitary gland to estrogen, and cumulative estrogen exposure (especially when it isn't offset regularly by adequate progesterone secretion) causes tissue changes, "aging" the tissues. **The hypothalamus and pituitary functions are "aged" in proportion to their exposure to estrogen, disrupting the normal cycles of gonadotropin excretion** (Rodriquez, et al., 1993; Desjardins, et al., 1992; Brawer, et al., 1992; Rossmanith, 1995). Intermittent exposure to progesterone protects against the estrogen neurotoxicity (Schipper, et al., 1990).

If young ovaries are transplanted into estrogen-exposed old mice, they fail to function. If an animal's ovaries are removed in youth, those changes in the brain and pituitary don't occur, and if ovaries are transplanted into these "estrogen deprived" old animals they function normally.

Despite evidence of this sort, the great majority of physicians continue to believe that menopause is a state of estrogen deficiency, resulting from intrinsic ovarian failure. The persistence of this unfounded belief is encouraged by the estrogen industry, which has promoted it since the early 1940s, to increase their sales. Men are more likely than women to die from heart disease, and the estrogen industry has said that this is because men have less estrogen; a study in which men were given supplemental estrogen found that it increased their incidence of heart attacks. In fact, men with heart disease have very high estrogen, and old men in general have serum estrogen levels higher than those of women of the same age (Vermeulen, et al., 2002). Beginning at menopause, the prevalence of heart disease in women rises toward the male prevalence.

The causes of menopause and the associated diseases of inflammation and aging are apparent as soon as you realize that the ideas of "running out of eggs," "ovarian failure," and "estrogen deficiency" don't correspond to the facts.

The actual causes of menopause and the associated diseases of inflammation and aging are the cumulative stress effects of prolonged excitatory estrogen exposure (Desjardins, 1995**).** Estrogen damages the control of pituitary gonadotropin, for example leading to a failure of luteinizing hormone, with a resulting failure of progesterone synthesis. Blocking progesterone synthesis contributes to increased levels of its precursor, cholesterol. Unopposed estrogen, and reduced progesterone, cause increased permeability of blood vessels with reduced barrier function of the intestine, leading to chronic absorption of bacterial endotoxin into the blood stream; endotoxin also increases vascular permeability. Endotoxemia results in chronic inflammation, and can promote asthma, atherosclerosis, osteoporosis, inflammatory bowel disease, diabetes, obesity, periodontal disease and the "autoimmune" diseases.

Endotoxin (acting on Toll-like receptors) produces inflammation in many ways, increasing nitric oxide, serotonin, histamine, and pro-inflammatory cytokines including TNF-alpha, IL-6, and IL-1.

Evidence from animal experimentation shows that excessive estrogen can create autoimmune diseases. Injected endotoxin has similar effects; estrogen and endotoxin tend to increase each other's concentration, in a vicious circle. Most, if not all the menopause-related diseases have an autoimmune component. I think the best explanation for the tendency of multiple autoimmune diseases to occur at the same time is that their basic cause doesn't origination in changes in the immune system, **but rather in the alterations of antigens caused by the toxic effects** of estrogen and endotoxins, and by the cascade of cytokines, nitric oxide, prostaglandins, etc., brought on by the injurious conditions produced by the failure to keep producing progesterone and the energy needed to correct them.

Histamine (in menopause, aging, autoimmunity, and covid) is one of the mediators of damage and inflammation and immune activity, including the stimulation of B-cell antibody production (Akdis and Blaser, 2003), involved in autoimmunity. There are several ways to reduce histamine production, including an increased amount of carbohydrate in the diet (Clementsen, et al., 1990a, 1990b; Norn, et al., 1990), and supplementation of progesterone.

Antihistamines are increasingly recognized to have value in treating a broad range of inflammatory and degenerative diseases, including inflammatory bowel disease, inflammatory brain disease, even atherosclerosis (Rosenberg, et al., 2010) and osteoporosis (Kinjo, et al., 2008). Aspirin has some similar effects that are helpful in menopause and aging, including correcting osteoporosis, and treating rheumatoid arthritis (Csuka and McCarty, 1989) and calcification of arteries (Shen, et al., 2022), and reducing the inflammation leading to sarcopenia in aging (Ratchford, et sl., 2017).

Another very basic approach to reducing systemic inflammation is to block the effects of the pro-inflammatory angiotensin system, with angiotensin receptor blockers such as losartan. Losartan inhibits the sarcopenia of aging, protects bones against osteoporosis, and is protective against the covid infection. Since angiotensin stops the formation of progesterone (Stirling, et al., 1990), its blockers, such as losartan, are helping to restore the body's main protective system.

The flavonoids that occur in many fruits, vegetables, milk, and coffee, have anti-inflammatory effects at many levels, that are protective against various features of menopause and autoimmune diseases, and against the sarcopenia and bone loss of aging. Calcium and vitamin D are protective against infectious diseases as well as the inflammatory, autoimmune, and degenerative diseases.

One of the indirect effects of the mistaken understanding of menopause as "running out of eggs" is that it reinforces a reductionist mechanistic view of the organism, and discourages interest in the possibility of delaying or reversing, not only the menopause, but the many degenerative processes associated with it. It indirectly affects the expectations regarding the effects of estrogen and progesterone in general health and immunity.

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