Menopause and its causes

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

When I was in graduate school at the University of Oregon, everyone in our lab was working on the problem of reproductive aging. Previously, people in the lab had established that the ovaries didn't "run out of eggs." There was never really any basis for that ridiculous belief. Many people just said it, the way they said "old eggs" (but never old sperms) were responsible for birth defects, or that "estrogen is the female hormone," a deficiency of which is the cause of menopausal infertility. (Old sperms have been implicated in some birth defects**.** People who are newly married, for example, were found to have children with fewer birth defects than people of the same age who had been married a long time, suggesting that more frequent intercourse involves fresher sperms.) When ovaries have been treated with x-rays to destroy their ability to ovulate, they have been found to produce more estrogen than before. Ovulation is one thing, and the production of hormones is another thing. You can't determine whether ovulation has occurred by measuring the hormones.

Knowing the large amount of work that has gone into our understanding of the age-related decline in fertility, it is disturbing to see people on television and in popular health books saying that menopause occurs when the "ovaries run out of eggs."

Around 1970, many people were saying that aging was caused by the loss of brain cells. There is a glimmer of truth in that silly idea, just as there would be in saying that "aging is caused by the death of skin cells," making the skin thinner and drier and less elastic. Both the brain and the skin are sources of steroid hormones, and it is possible that the death of skin cells and neurons is one factor in the age-related decline in the "sex steroids." An organism would be an easier thing to understand if cells just did their job for a certain period of time, and then died. A man named Hayflick has given people some publications to cite, when they want to simplify things by saying that aging occurs when cells have used up their quota of 50 divisions, but there are many more studies that clearly show that Hayflick's limit is nothing but a product of the cells' environment. The cell's environment, the signals and substances and energy it receives, is complex, but real progress is being made in understanding the things involved in the aging process. Luckily, the infinite complexity of the environment is channeled into an understandable array of processes by the cell's systematic ways of responding.

I knew, from talking with L. C. Strong,1 that early reproductive maturity was associated with early death; in his strains of cancer-prone mice, he showed that high estrogen was the cause of early puberty, a high cancer incidence, and a relatively short life. D. A. Snowdon, et al., showed that the occurrence of menopause at an early age in women is associated with a greater risk of death from all causes, including strokes and coronary heart disease.2 (They saw ovarian aging as an indicator of general aging.) P. W. F. Wilson, et al., reported that postmenopausal estrogen use was associated with an increased incidence of heart disease and stroke.3 P. M. Wise showed that estrogen accelerates aging of the central nervous system, destroying the nerves which regulate the pituitary gonadotropins, and causing ovarian failure and infertility.4 Many other studies of particular tissues show that estrogen accelerates the rate of aging.

In my work with hamsters, I found that the infertility that developed at middle age was caused by a high rate of oxygen consumption in the uterus, causing the oxygen needed by the developing embryo to be consumed by uterine tissues, and causing suffocation of the embryo. This is the central mechanism by which the estrogen-containing contraceptives work**:** at any stage of pregnancy, a sufficient dose of estrogen kills the embryo.

Polvani and Nencioni,5 among others, found that in women, the onset of menopause (the first missed period, suddenly increased bone loss, nervous symptoms such as depression, insomnia, and flushing) corresponds to the failure to produce progesterone, while estrogen is produced at normal levels. This results in a great functional excess of estrogen, because it is no longer opposed by progesterone. Typically, it takes about four years for the monthly estrogen excess to disappear. They suggested that the bone loss sets in immediately when progesterone fails because cortisol then is able to dominate, causing bone catabolism; progesterone normally protects against cortisol. Other researchers have pointed out that estrogen dominance promotes mitosis of the prolactin-secreting cells of the pituitary, and that prolactin causes osteoporosis; by age 50, most people have some degree of tumefaction of the prolactin-secreting part of the pituitary. But estrogen dominance (or progesterone deficiency) also clearly obstructs thyroid secretion, and thyroid governs the rate of bone metabolism and repair. Correcting the thyroid and progesterone should take care of the cortisol/prolactin/osteo- porosis problem.

P. M. Wise4 has demonstrated that the "menopausal" pituitary hormones, high levels of LH and FSH, are produced because the regulatory nerves in the hypothalamus have lost their sensitivity to estrogen, not because estrogen is deficient. In fact, he showed that the nerves are desensitized precisely by their cumulative exposure to estrogen. If an animal's ovaries are removed when it is young, the regulatory nerves do not atrophy, and if ovaries are transplanted into these animals at the normally infertile age, they are fertile. But if animals are given larger doses of estrogen during youth, those nerves atrophy prematurely, and they become prematurely infertile.

The mechanism by which estrogen desensitizes and kills brain cells is now recognized as the "excitotoxic" process, in which the excitatory transmitter glutamic acid is allowed to exhaust the nerve cells. (This explains the older observations that glutamic acid, or aspartic acid, or aspartame, can cause brain damage and reproductive failure.) Cortisol also activates the excitotoxic system, in other brain cells, causing stress-induced atrophy of those cells.6 Progesterone and pregnenolone are recognized as inhibitors of this excitotoxic process.

Besides estrogen's promotion of excitotoxic cell death, leading to the failure of the gonadotropin regulatory system, estrogen's stress-mimicking action probably tends to increase the secretion of LH, in ways that can be corrected by supplementing progesterone and thyroid. Since Selye's work, it has been known that estrogen creates the same conditions as occur in the shock phase of the stress reaction. (And shock, in a potential vicious circle, can increase the level of estrogen.7) It has recently been demonstrated that estrogen stimulates the adrenal glands, independently of the pituitary's ACTH. This can increase the production of adrenal androgens, leading to hirsutism, and other male traits, including anabolic effects.8

It was established in the 1950s that estrogen "erases" memories in well trained animals. I suppose that acute effect is related to the chronic toxicity that leads to cell death. (In the 1940s, DES was sold to prevent miscarriages, though it was already known that it caused them; then there was the argument that it slowed aging of the skin, despite the Revlon studies at the University of Pennsylvania showing that it accelerates all aspects of skin aging; lately there has been talk of promoting estrogen to improve memory.)

Estrogen's nerve-exciting action is known to lower seizure thresholds; premenstrual epilepsy is probably another acute sign of the neurotoxicity of estrogen.

When fatigue and lethargy are associated with aging, the brain stimulating action of estrogen can make a woman feel that she has more energy. (Large doses given to rats will make them run compulsively; running wheels with odometers have shown that they will run over 30 miles a day from the influence of estrogen.) Estrogen inhibits one of the enzymic routes for inactivating brain amines, and so it has more general effects on the brain than just the glutamate system. This generalized effect on brain amines is more like the effects of cocaine or amphetamine. If that is a woman's basis for wanting to use estrogen, a monoamine oxidase inhibitor would be safer.

The reason for the menopausal progesterone deficiency is a complex of stress-related causes. Free-radicals (for example, from iron in the corpus luteum) interfere with progesterone synthesis, as do prolactin, ACTH, estrogen, cortisol, carotene, and an imbalance of gonadotropins. A deficiency of thyroid, vitamin A, and LDL-cholesterol can also prevent the synthesis of progesterone. Several of the things which cause early puberty and high estrogen, also tend to work against progesterone synthesis. The effect of an intra-uterine irritant is to signal the ovary to suppress progesterone production, to prevent pregnancy while there is a problem in the uterus. The logic by which ACTH suppresses progesterone synthesis is similar, to prevent pregnancy during stress. Since progesterone and pregnenolone protect brain cells against the excitotoxins, anything that chronically lowers the body's progesterone level tends to accelerate the estrogen-induced excitotoxic death of brain cells.

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Chronic constipation, and anxiety which decreases blood circulation in the intestine, can increase the liver's exposure to endotoxin. Endotoxin (like intense physical activity) causes the estrogen concentration of the blood to rise. Diets that speed intestinal peristalsis might be expected to postpone menopause. Penicillin treatment, probably by lowering endotoxin production, is known to decrease estrogen and cortisone, while increasing progesterone. The same effect can be achieved by eating raw carrots (especially with coconut oil/olive oil dressing) every day, to reduce the amount of bacterial toxins absorbed, and to help in the excretion of estrogen. Finally, long hours of daylight are known to increase progesterone production, and long hours of darkness are stressful. Annually, our total hours of day and night are the same regardless of latitude, but different ways of living, levels of artificial illumination, etc., have a strong influence on our hormones. In some animal experiments, prolonged exposure to light has delayed some aspects of aging.

General aging contributes to the specific changes that lead to menopause, but the animal experiments show that fertility can be prolonged to a much greater age by preventing excitotoxic exhaustion of the hypothalamic nerves. The question that still needs to be more clearly answered is, to what extent can general aging be prevented or delayed by protecting against the excitotoxins? Minimizing estrogen (and cortisone) with optimal thyroid activity, and maximizing pregnenolone and progesterone to prevent excitotoxic cell fatigue, can be done easily. A diet low in iron and unsaturated fats protects the respiratory apparatus from the damaging effects of excessive excitation, and--since pregnenolone is formed in the mitochondrion--also helps to prevent the loss of these hormones.

References

1. L. C. Strong, Biological Aspects of Cancer and Aging, Pergamon Press, 1968.

2. D. A. Snowdon, et al., "Is early natural menopause a biologic marker of health and aging? Am. J. Public Health 79, 709-714, 1989.

3. P. W. F. Wilson, et al. [The Framingham Study], N. E. J. M. 313(17), 1038-1043, 1985

4. P. M. Wise, "Influence of estrogen on aging of the central nervous system: Its role in declining female reproductive function," in Menopause: Evaluation, Treatment, and Health Concerns, pages 53-70, 1989.

5. Nencioni, T., and F. Polvani, Calcitonin, p. 297-305, A. Pecile, editor, Elsevier, N.Y., 1985.

6. T. I. Belova, "Structural damage to the mesencephalic reticular formation induced by immobilization stress," Bull. Exp. Biol. & Med. 108(7), 126030, 1989.

7. F. Fourrier, et al., "Sex steroid hormones in circulatory shock, sepsis syndrome, and septic shock," Circ. Shock 43(4), 171-178, 1994.

8. E. C. Ditkoff, et al., "The impact of estrogen on adrenal androgen sensitivity and secretion in polycystic ovary syndrome," J. Clin. Endocrinol. Metab. 80(2), 603-607, 1995.

9. C. Bain, et al., "Use of postmenopausal hormones and risk of myocardial infarction," Circulation 64, 42-46, 1981.

10. T. L. Bush, et al., "Estrogen use and all-cause mortality: Preliminary results from the Lipid Research Clinics Program follow-up study," JAMA 249, 903-906, 1983.

11. M. S. Hunter and K. L. M. Liao, "Intentions to use hormone replacement therapy in a community sample of 45-year-old women," Maturitas 20(1), 13-23, 1994. (Women who expressed an intention to use hormone replacement therapy at menopause reported significantly lower self-esteem, more depressed mood, anxiety, and negative attitudes toward menopause. The also expressed stronger beliefs in their doctors' ability--as opposed to their own--to control their menopause experience.)

12. L. Dennerstein, et al., "Psychological well-being, mid-life and the menopause," Maturitas 20(1), 1-11, 1994.