Aging Ovaries: Not the Eggs

by Ray Peat, Ph.D.
Ray Peat's Newsletter

A few months ago public television ran a long program on the menopause, in which a rather glamorous woman physician said some shockingly ignorant things about the ovaries and menopause. I went to some book shops, to see what she might have been reading, or hearing in conversations.

One writer thought it would be nice to change the name of the menopause to "the pause." Another said it is too judgmental to say that the ovaries "fail" at menopause, and that they are really just maturing. Those concerns with terminological politeness remind me of Woody Allen's remark about death – that it is nature's way of telling us to slow down.

All of these current paperback books about menopause subscribe to the same doctrine about reproductive aging. Uniformity of opinion creates an environment in which publishers who want to sell a lot of books feel that they have to publish things that don't disturb the reading public. Books about menopause become books about an *attitude* toward menopause.

Even people who like to say that the ovaries "don't fail" at menopause describe a theory in which menopause and its consequences are the result of the disappearance of eggs from the ovary. That theory is so simple it can be described in three short sentences, none of which is true: (1) ovary runs out of eggs; (2) ovulation produces hormones, so you can tell when ovulation stops because the ovaries stop producing hormones; (3) menstruation stops because ovulation has stopped. Those principles are surrounded by various corollaries. "Estrogen is the female hormone." "Estrogen deficiency accelerates aging." "Treatment with estrogen makes you more feminine." "Progesterone deficiency is the result of anovulatory cycles."

Many experimenters have demonstrated that old animals that have become infertile keep producing eggs. Several experimenters (e.g., R. R. Maurer and R. H. Foote,[1] 1971, "Maternal ageing and embryonic mortality in the rabbit," *J. Reprod. Fert.* 25, 329-341) have removed eggs from the ovaries of old animals, and transplanted the fertilized eggs into young animals, where the embryos were able to implant and develop normally.

I found that old animals had too little oxygen in their uterus to keep the embryo alive at the time it would normally be ready to implant itself in the uterus. Giving estrogen to a young animal causes a similar lack of oxygen in the uterus, and prevents implantation of the embryo.

At the time old animals would normally have become infertile, they remain fertile if they are given a supplement of vitamin E and progesterone.

It is now established that aging animals, at the time they become infertile, are deficient in progesterone, but still produce estrogen. Even in young individuals, when stress occurs around the time of ovulation, interference with progesterone production will prevent implantation. If progesterone becomes deficient after the embryo has become implanted, miscarriage occurs.

Estrogen, acting alone or with insufficient progesterone, causes spasms in the spiral arteries that provide oxygen and nutrients to the endometrium. This seems to be the basis for menstruation, and is also believed to be a factor in miscarriage.

About 30 years ago, researchers began to understand that reproductive aging was not caused by the lack of eggs, and the aged uterus was able to support pregnancy if it had the right hormonal support. Interest turned to the brain cells in the hypothalamus which regulate the pituitary. G. H. Zeilmaker ("Effects of prolonged feeding of an ovulation inhibitor (Lyndiol) on aging of the hypothalamic-ovarian axis and pituitary gland tumorigenesis in rats," *J. Endocrin* 43, xxi, 1969)[2] was one of the first to suggest that ovarian hormones caused the brain to age. More recently, P.M. Wise[3,4] has clearly demonstrated that estrogen exhausts the cells which inhibit the pituitary gonadotropins, with the result that even abnormally high levels of estrogen are unable to turn off the pituitary secretion of the hormones that drive the ovary. Estrogen itself can impair the ovary's ability to produce progesterone, but the continuously high secretion of gonadotropins disturbs the ovary, the adrenals, and (according to recent observations) even the uterus.

Stress, especially when augmented by estrogen, leads to injury, exhaustion, and aging. The uterus and ovaries participate in the response to stress, but (as Zeilmaker and Wise have shown) the brain proves to be more directly involved in menopause than the ovaries or uterus. Coordination turns out to be crucial for complex processes such as ovulation, fertilization, and implantation. The destruction of the nerve cells that regulate the pituitary makes coordination impossible.

The issue of "running out of eggs" can be settled simply by demonstrating the presence of viable eggs at the time reproductive ability has ended. In the 1940s, menopause was "explained" in terms of an estrogen deficiency, without a basis in fact, and now an "egg deficiency" is combined with the "estrogen deficiency," compounding the confusion. Facts aren't everything in science;* it is necessary to look at the context from which these ideas develop.

Two of America's most productive researchers in reproductive physiology, Edgar Allen and Herbert M. Evans, made observations that they believed showed that the germinal epithelium of the ovary goes through a cycle of cell proliferation that produces a new generation of oocytes during each menstrual cycle. It is recognized that new egg cells appear in the ovaries of adult prosimian primates, and at puberty in cats and pigs. Observations of newly developed egg cells have been reported in some other species. But the dominant view prefers to see the number of egg cells declining from birth, or earlier, with absolutely no new egg cells being formed later.

During gestation and infancy, the gonadotropins are very high. These hormones decline during childhood, during the time that the number of egg cells is so visibly declining. The high level of the gonadotropins during infancy hasn't been explained, but it is reasonable to suppose that it has something to do with the development of the ovaries, since a "developmental"

function can be demonstrated for the gonadotropins in the ovaries and testes of older animals.

The number of brain cells peaks a few months before birth, just as the number of egg cells does. Many people have argued that this somehow means that brain cells are incapable of dividing after infancy, though there is no factual basis for making that argument, and in fact adult brain cells are now known to be able to divide. (That is true of heart cells, too.)

In a variety of tissues, it can be shown that the presence of mature cells inhibits the division of other cells. If part of the liver is removed, the remaining cells divide to replace the lost tissue. If the skin is cut, cells divide to help fill in the defect. If there is an adequate number of egg cells, this principle suggests that there is no need to produce more. There is a treatment for polycystic ovaries called "wedge resection." This can reduce the production of masculinizing hormones. By analogy with other tissues, it seems likely that the removal of a mass of malfunctioning tissue leads to the growth and development of new cells which function the way a new ovary would. Regeneration seems to be a capacity of every tissue, given the right environment. If the ovary were studied after such treatment, I suspect that "new eggs" would be found. (But even in the seemingly simple process of healing a wound in the skin, there is still disagreement as to the relative contribution made by local cell division, and the invasion of the region by structural cells from elsewhere in the body. The appearance of a cell can be misleading; histology is often a matter of making educated guesses. For example, white blood cells can look like epithelial cells.)

Although the question of whether all the woman's eggs are in existence at or before birth doesn't logically have anything to do with the other question, whether there are still eggs in the ovary at menopause, there is a reason that people connect them. This has to do with the idea of a "germ line" as distinct from the "somatic cells." The eggs are "from the germ line," all the rest of the body (and much of the ovary) is a different sort of stuff. The "germ line" has the special property of immortality and it is "isolated" and independent. The body is susceptible to being modified by the environment, and is mortal. These are the traditional formulations of the idea, and the people who learn their orientation from textbooks are not necessarily conscious of how the ideas fit together. For biologists of my professors' generation, these ideas seemed to be a sacred core of biology, but with their death, maybe biology can be liberated.

August Weismann, working at the end of the last century and the beginning of the 20th century, created the basic ideology of genetics, to combat the idea of the inheritance of acquired characteristics, which had been supported by Darwin and others. He argued that the hereditary substance, or germ plasm, was derived only from preexisting germ plasm, and couldn't be formed anew, or modified by the environment. It created every part of the perishable body, by a process in which traits were segregated, so that the germ plasm contained the full complement of hereditary material, and each part of the body contained only the limited fraction needed for its characteristics. Thus, the body was inferior created material, while the germ line was the immortal creative stuff. Since the body adapts in response to the environment, it had seemed that these changes would be passed on to descendants, until Weismann's argument showed that it was only the perishable, dead-end body lacking the hereditary principle which was adapting. The germ line was somehow isolated from the body and from the environment.

Weismann's theoretical germ line became identified with the chromosomes and the genes. His theory was shown to be simply wrong, in that each type of cell in the body contains a full complement of chromosomes and genetic information. Although his facts were wrong, his ideology became deeply embedded in the culture of genetics. To keep the idea that the "germ line" is somehow something distinct from the body required a special effort, once the chromosomes were seen to be identical in every part of the body. Weismann's whole point in his "germ line" idea was to show an absolute distinction between the body and the hereditary substance. If his ideology that had been built to deny the inheritance of acquired characteristics were to be saved, the *isolated* germ line would have to be found elsewhere than in the chromosomes.

The idea of "germ line (or *Keimbahn*) determinants" now took over, and was believed to be something in a certain spot in the egg. As the egg divided, into cells that look very much like each other, the cells which came from *that* part of the egg represented the germ line. As the embryo developed, the region that seemed to be traceable back to that part of the egg, represented the germ line. As the gonad began to grow, cells from the region representing the germ line were thought to travel over and invade the gonad, where they multiplied into vast numbers, but always remained the same isolated strain of germ cells with their "separate" history that could be traced back to the determinants in the special place in the egg. During the early days of embryonic development, these immigrant cells looked exactly like their neighbors which were somatic cell sprouts from the embryonic kidney region.

If it weren't for the ideology of absolute isolation of the hereditary substance, an embryologist might have suggested that cells or material of one part of the embryo *induced* a specialized, differentiated state in some cells that happened to be suitably located. If the cells derived from that certain part of the egg didn't carry unique genetic material – and they didn't – then what they carried with them was an incipient state of differentiation. Why the big deal about that particular history of differentiation? It was because the ideology that motivated Weismann was still active, and its purpose was to argue that only the "gene" was the creative productive source, and that the body – the "somatic cells" – was the passive product, whose adaptations meant nothing in the long run. This has been called the "central dogma" of genetics, that information flows only from the gene to the cell, and not back from the cell to the gene. That ideology forced geneticists to deny the existence of RNA viruses (including retroviruses such as the HIV-"AIDS" virus), and is still active in blocking research on the prion or scrapie virus, which is a protein. To say it bluntly, many highly respected biologists acted stupidly because they

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blindly believed in a false ideology.

Incidentally, this ideology was always impossible for horticulturists to accept, since they were in the habit of grafting (cloning) vegetative (somatic) parts of plants, which would then produce flowers and fruits. For them, the "germ" was often a product of the "body." Luther Burbank's work was consistently ridiculed by the academic biologists, who believed his achievements were impossible, that is, fraudulent. Many of Burbank's perceptions have been supported by recent evidence, but they couldn't be accepted by people whose ideology of the germ line/somatic distinction seemed to be contradicted by his work.

Another problem with the doctrine of the germ line was revealed when embryologists separated the embryo at a very early stage into two groups of cells, and found that each was able to grow into a complete animal. The idea of the germ line predicts that one member of the pair of twins could get the ability to reproduce while the other would be sterile. Some important ideas can survive their disproof.

It is exactly the same academic ideology of the priority of the germ line which blames the whole complex process of reproductive aging on the mechanical process of an "ovary running out of eggs." The ovary doesn't run out of eggs, and running out of eggs would have no great consequences if it did happen, because the main events in ovulation are produced by cells other than the eggs. But the ideology says that the "germ line" controls everything, and the eggs are the germ line. In other words, genes control the organism, and eggs control the woman.

I think it will be instructive to consider the three steroid secreting glands – ovaries, testes, and adrenals – together, to see what they might have in common. In the testes, it is generally believed that pituitary gonadotropins regulate steroid synthesis and gametogenesis. In the ovaries, the gonadotropins also regulate the production of steroids, and – to some extent – the production of eggs, if not the whole gametogenic process. In the adrenal, ACTH governs the production of cortisol and sex steroids, and the transformation of the glomerulosa cell type into the other types, which secrete those hormones.

The outer layer of cells in the adrenals can form the other two cell types, and since stress ACTH converts them to the other types, new ones must be formed. If the inner layers are removed, the whole adrenal cortex can regenerate from the outer layer Obviously, if stress causes cells to multiply and differentiate, cells are disappearing from the inner layers.

When I was in graduate school, immunologists were aware that new cells were continually appearing in the thymus gland, but the gland didn't get bigger, and there was no visible trace of dying cells. At that time, it was considered a major puzzle, but gradually it came to be understood that a special kind of cell dissolution (called apoptosis) was occurring that accounted for the missing cells.

In the testes, apoptosis or cell-dissolution is always occurring, even though sperm cells are being produced and leaving the organ.

In the ovary, "waves" of egg cell degeneration are constantly taking place in young women. Radioactive labelling that has been used to argue that egg cells aren't being replaced seem to show that there is continual cell division in all the other ovarian cells. Interestingly, those researchers didn't seem to be interested in this apparent regeneration of the other parts of the ovary.

Apoptosis always seems to be part of a shaping process of the organ in which it occurs. Regeneration provides new cells, apoptosis recycles the substance of a certain fraction of the tissue's cells. We are just starting to notice that various hormones inhibit or promote apoptosis, and so participate in the "shaping" of the organism. In many systems, it seems that the need for a cell type or function calls it into existence, while idleness makes a cell susceptible to dissolution.

I have been referring to the "pituitary gonadotropins," and deliberately avoided referring to them as LH – luteinizing hormone – and FSH – follicle stimulating hormone – because their names reflect a theory of what they do. In some textbook descriptions of testicular function, for example, it has been said that LH produces testosterone, and that negative feedback from testosterone suppresses LH, while FSH governs the formation of sperms. That description is completely worthless, and probably was largely built up by analogy with their supposedly neatly divided functions in the ovary, reflected in their names. These gonadotropins participate in the development, maintenance, and functioning of the ovaries, and their effects depend on their timing, their balance with each other and with the steroids produced by the ovaries in response to their stimulation, and their actions are modified by many other factors, ovarian, nervous, pituitary, uterine, and immunological. During youth, the system functions in a coordinated way, with ovulation as a consequence. During aging, the crucial changes appear to be a decreased ability of the ovary and the brain to produce progesterone. Thyroid hormone, cholesterol, vitamin A and efficient cellular respiration are essential factors for synthesizing progesterone. Accumulated iron, unopposed estrogen, and impaired use of cholesterol and oxygen are factors known to contribute to the widespread and variable damage to the system of coordination.

Two things can cause the pituitary to secrete excessive amounts of the gonadotropins: A deficiency of the steroids, and damage to the steroid sensing nerves that regulate the pituitary. When an ovary is moved (transplanted into the spleen) so that its hormones are destroyed before getting to the brain, there is hypersecretion of gonadotropic hormone,[5,6,7] and tumors develop in the ovary. The interpretation, that hypersecretion causes the tumors, is supported by other observations, e.g., that removal of one ovary increases the chance of developing a cancer in the other ovary and that prolonged use of estrogen (known to create the conditions for later hypersecretion of gonadotropin)[3,4] increases the risk of ovarian cancer after menopause.[9]

Psychologists have noticed that naming an object according to a certain function often limits the way people will be able to use it. This happens in science. If we know one function of a substance, and name it for that function, we will find it harder to think of its other possible roles. Hans Selye argued that

steroids, for example, should be named according to their place of origin, rather than by a single aspect of their function. I think this applies even to the phrases "male hormone" and "female hormone": it's better to think of them in terms of their origin, and not to count on them to promote femininity or masculinity.

A note about "the female hormone." In the absence of the testicular or "male" hormones, animals differentiate as females.

Progesterone is an anti-androgen, and blocks testosterone's effects. When testosterone is given to newborn or very young rats, it sets up a male pattern of hormone development, but if progesterone is given at the same time, that doesn't happen. Progesterone prevents the differentiation away from the basic female path into the male specialization. Later in life, a deficiency of progesterone in a woman can again lead to masculinization of some features, such as musculature and facial or body hair. When progesterone is given to men in large doses, it blocks various typically male processes, such as growth of whiskers. In the brain, it has a protective function in both sexes.

Estrogen promotes cell division, and is involved in essentially every tissue, in both males and females. If it is to be called a "female hormone," maybe it also has to be called "a male hormone." It does have to be present for breast development, though it is just one of many factors. In this instance, it is contributing to feminization. In other instances, it seems to contribute to virilization.

At menopause, estrogen excess can promote the production of androgens, in the absence of progesterone, which tends to defeminize the woman. This is often a result of stress, and sometimes is a consequence of hypothyroidism. In situations of this sort, estrogen is seen not to be a feminizing hormone; it is unable to neutralize the male hormones the body produces in response to the estrogen excess.

Footnote*

Since the 1930s, estrogen's toxic potential has become very clear. However, the estrogen industry doesn't want people to understand that estrogen is a shock hormone with pro-aging effects. Histamine mimics estrogen's effects on the uterus, and antihistamines block estrogen's effects (Szego, 1965, Szego and Davis, 1967). Estrogen mimics the shock reaction. Stress, exercise, and toxins cause a rapid increase in estrogen. Males often have as much estrogen as females, especially when they are tired or sick. Estrogen increases the brain's susceptibility to epileptic seizures, and recent research shows that it (and cortisol) promote the effects of the "excitotoxins," which are increasingly implicated in degenerative brain diseases.

Currently, estrogen marketing emphasizes appearance and the danger of osteoporosis. Evidence occasionally turns up implicating estrogen in thinning of the skin and bones.[10]

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References

1. R. R. Maurer and R. H. Foote, "Maternal ageing and embryonic mortality in the rabbit," *J. ReProd Fert* 25, 329-341 1971.
2. G. H. Zeilmaker "Effects of prolonged feeding of an ovulation inhibitor (Lyndiol) on ageing of the hypothalamic-ovarian axis and pituitary gland tumorigenesis in rats," *J. Endocrin.* 43, xxi, 1969).
3. Wise, P. M., "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.
4. Wise, P.M., et al., "Neuroendocrine influences on aging of the female reproductive system," *Frontiers in Neuroendocrinology* 12, 323-356, 1991.
5. M. H. Li and W. U. Gardner, "Experimental Studies on the pathogenesis and histogenesis of ovarian tumors in mice," *Cancer Research* 7, 549-566,1947.
6. W. U. Gardner, "Hormonal imbalance in tumorigenesis," *Cancer Research* 8,397-411,1948.
7. M. H. Li and W. U. Gardner, "Further studies on the pathogenesis of ovarian tumors in mice," *Cancer Research* 9, 532-536,1949.
8. H. S. Kaplan, "Influence of ovarian function on incidence of radiation-induced ovarian tumors in mice," *J. Natl. Cancer Inst.*, 11, 125-132, 1950.
9. Lee, N. C., et al., "Estrogen therapy and the risk of breast, ovary and endometrial cancer," in *Aging, Reproduction, and the Climacteric*, Mastroianni, Jr., and C. A. Paulsen, editors, Plenum, N.Y. & London, 1986. To the extent that oral contraceptives suppress the pituitary gonadotropic hormones, the ovary is protected from the stimulation that can produce cancer. However, the estrogen used to treat menopause doubles the risk of ovarian cancer after ten years. If the estrogen was used for more than 6 years, the risk is tripled.
10. Bauer, D. C., et al., "Skin thickness, estrogen use and bone mass in older women," *Menopause* 1(3), 131-136, 1991. "We found no evidence that estrogen preserves skin thickness; indeed, estrogen use is associated with thinner skin." "Our findings further support an association between skin thickness and bone mass." "Skin thickness and bone mass are related, but skin thickness cannot be used to predict bone mass."

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