

Hot flashes, energy, and aging

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Around the time that menstruation and fertility are ending, certain biological problems are more likely to occur. Between the ages of 50 and 55, about 60% of women experience repeated episodes of flushing and sweating. Asthma, migraine, epilepsy, arthritis, varicose veins, aneurysms, urticaria, reduced lung function, hypertension, strokes, and interstitial colitis are some of the other problems that often begin or get worse at the menopause, but that normally aren't considered to be causally related to it.

Recently, hot flashes are being taken more seriously, because of their association with increased inflammation, heart disease, and risk of dementia. Around the same age, late 40s to mid-50s, men begin to have a sudden increase of some of the same health problems, including night sweats, anxiety, and insomnia. In both sexes, the high incidence of depression in this age group has usually been explained "psychologically," rather than biologically.

When the estrogen industry began concentrating on women of menopausal age (after the disastrous years of selling it as a fertility drug), "estrogen replacement" therapy was promoted as a cure for the problems associated with menopause, including hot flashes, which were explained as the result of a deficiency of estrogen. However, in recent years, the phrase "estrogen deficiency" has begun to be replaced by the phrase "estrogen withdrawal," because it has been found that women with hot flashes don't necessarily have less estrogen in their blood stream than women who don't have hot flashes.

Associated with this change of terminology, there has been a recognition that changes in the temperature regulating system in the brain, rather than changes in the amount of estrogen, are responsible for the hot flashes, but mainstream medicine has carefully avoided the investigation of this subject. The effects of estrogen on the thermoregulatory system are very clear, but the standard medical view is that the physiology of hot flashes simply isn't understood.

Since the medical literature boldly describes the mechanisms of the circulatory system and the causes of major problems such as heart attacks, high blood pressure, and strokes, it's odd that it doesn't have an explanation for "hot flashes."

But looking at this historically, I think this selective ignorance is necessary, for the protection of some doctrines that have become very important for conventional medicine.

When doctors are talking about diseases of the heart and circulatory system, it's common for them to say that estrogen is protective, because it causes blood vessels to relax and dilate, improving circulation and preventing hypertension. The fact that estrogen increases the formation of nitric oxide, a vasodilator, is often mentioned as one of its beneficial effects. But in the case of hot flashes, dilation of the blood vessels is exactly the problem, and estrogen is commonly prescribed to prevent the episodic dilation of blood vessels that constitutes the hot flash. Nitric oxide increases in women in association with the menopause (Watanabe, et al., 2000), and it is increased by inflammation, and hot flushes are associated with various mediators of inflammation, but, as far as I can tell, no one has measured the production of nitric oxide during a hot flash. Inhibitors of nitric oxide formation reduce vasodilation during hot flushes (Hubing, et al., 2010).

Starting in the 1940s, the doctrine that menopause is the result of changes in the ovaries, involving a depletion of eggs and an associated loss of estrogen production, was widely taught to medical students. By the 1970s, the taboo against discussing menopause publicly was fading, and the mass media began teaching the public that hot flashes are the result of an estrogen deficiency, and that "estrogen replacement" is the most appropriate and effective treatment, and in the next 20 years almost half the women in the US began taking it around the time of menopause. This practice became routine at a time when "evidence based medicine" was being promoted as a new standard, but there was no evidence that women experiencing hot flashes were deficient in estrogen (in fact, there was evidence that they weren't), and there was evidence that hot flashes began when the first menstrual period was missed, which coincided with, and resulted from, a failure to produce a functional corpus luteum, preventing the production of a normal amount of progesterone. But the silly old doctrine of deficiency is often restated by professors, as if there was no doubt about it (for example, Rance, 2009; Bhattacharya and Keating, 2012).

This extremely persistent disregard for important evidence about the nature of menopause and its symptoms was guided by the estrogen industry, which began in the 1930s to call estrogen "the female hormone," disregarding the facts about the biological roles of estrogen and progesterone, because chemicals with estrogenic effects were numerous and cheap, while progesterone was expensive, and had no synthetic equivalents. At the time the pharmaceutical industry began promoting estrogen as the female hormone to prevent miscarriage, it was already well known that it could produce abortion, as well as causing inflammation and cancer, and some of the most famous estrogen researchers were warning of its multiple dangers in the 1930s.

Menopause is a major landmark of aging, and if its meaning is radically misunderstood, a coherent understanding of aging is unlikely, and without an understanding of the loss of functions with age, we won't really understand life. More specifically, the real causes of the many serious problems occurring in association with the menopause will be ignored. Finding the causes of the seemingly trivial hot flash will affect the way we understand aging and its diseases.

If a common occurrence is thought to have some importance in itself, or to relate closely to something of importance, it will be described carefully, and its general features will become part of the common understanding. It's clear that our medical culture hasn't considered the hot flash to be important, because there are still physicians who believe that the hot flash represents a rise of body temperature caused by a sudden increase of heat production, which they sometimes explain as an upward fluctuation of thyroid gland activity. Measurement of body temperature before and during hot flashes has shown clearly that the internal temperature is lowered slightly by the hot flash, as heat is lost from the skin, as a result of vasodilation. Physiologists have been studying the differences in temperature regulation between men and women, and the

effects of hormones on temperature regulation, for more than 70 years, but the medical profession in the United States showed almost no interest in the subject for about 50 years.

August Weismann's doctrine of "mortal soma, immortal germ line," led people to postulate that "primordial germ" cells migrated into the ovary (consisting of "somatic" cells) during embryonic development, and that the baby was born with a supply of germ cells that was used up during the reproductive lifetime, accounting for the decline of fertility with aging. The fact that menstrual cycles ended around the time that fertility ended was explained by the idea that ovulation caused the release of estrogen, and that the absence of eggs caused a failure to produce estrogen, and that the absence of estrogen led to the failure of the cyclical uterine changes. It was all deduced from a mistaken ideology about the nature of life.

Cancer of the endometrium (lining) of the uterus and breast cancer were known to be the first and second cancers, respectively, produced by uninterrupted exposure to estrogen (for example, Lipshutz, 1950). Investigation of the causes of endometrial cancer showed that women with anovulatory cycles, that failed to produce progesterone, or who had a reduced production of progesterone, developed overgrowth of the endometrium, and that these were the women who were later most likely to develop cancer of the endometrium. The peak incidence of endometrial cancer is in the postmenopausal years, resulting from prolonged exposure to estrogen, unopposed by progesterone. The medical belief* that "ovulation produces estrogen," and that the absence of menstruation means an absence of estrogen, has been very harmful to women's health.

Several laboratories, from the 1950s through the 1980s, investigated the causes of age-related infertility. A.L. Soderwall, among others, demonstrated that an excess of estrogen makes it impossible for the uterus to maintain a pregnancy.

Subsequently, his lab showed that neither changes in the eggs nor changes in the uterus could explain age related infertility. Altered pituitary hormone cycles, resulting from changes in the brain, could account for the major changes in the ovaries and uterus.

Other experimenters, including P.M. Wise, V.M. Sopolak and R.L. Butcher (1982), P. Ascheim (1983), and D.C. Desjardins (1995) have clarified the interactions between the ovaries and the brain. For example, when the ovaries of an old animal are transplanted into a young animal, they are able to function in response to the new environment, but when the ovaries of a young animal are transplanted into an old animal, they fail to cycle. However, if the ovaries are removed from an animal when it's young, so that it lives to the normal age of infertility without being regularly exposed to surges of estrogen, it will then be able to support normal cycles when young ovaries are transplanted into it. But if it received estrogen supplements throughout its life, transplanted young ovaries will fail to cycle.

The work of Desjardins and others has demonstrated that free radicals generated by interactions of estrogen and iron with unsaturated fatty acids are responsible for damage to brain cells (Desjardins, et al., 1992). The damaged inhibitory nerve cells allow the pituitary to remain in a chronically active state; in old rats, this can produce a state of constant estrus. Several groups (Powers, et al., 2006; Everitt, et al., 1980; Telford, et al., 1986) have shown that removal of the pituitary gland can greatly extend lifespan, if thyroid hormone is supplemented.

One of the animal "models" used to study hot flashes is morphine withdrawal. The model seems relevant to human hot flashes, because estrogen can stop the morphine withdrawal flushing, and estrogen's acute and chronic effects on the brain-pituitary-ovary system involve the endorphins and the opioidergic nerves (Merchenthaler, et al., 1998; Holinka, et al., 2008).

In young rats, sudden morphine withdrawal caused by injecting the anti-opiate naloxone, causes the tail skin to flush, with a temperature increase of a few degrees, and causes the core body temperature to fall slightly. However, old animals respond to the withdrawal in two different ways. One group responded to the naloxone with an exaggerated flushing and decrease of core temperature. The other group of old rats, which already had a lower body temperature, didn't flush at all (Simpkins, 1994). I think this provides an insight into the reason that menopausal treatment with estrogen can relieve some hot flashes-estrogen treatment might create a flush resistant state similar to that of the cooler old animals in Simpkins' experiment.

It has been known for a long time, from studies in animals and people, that estrogen lowers body temperature, and that this involves a tendency to increase blood flow to the skin in response to a given environmental temperature, that is, the temperature "set-point" is lowered by estrogen. Besides increasing heat loss, estrogen decreases heat production. These physiological effects of estrogen can be seen in the normal menstrual cycle, with progesterone having the opposite effect of estrogen on metabolic rate, skin circulation, body temperature, and heat loss. This causes the familiar rise in temperature when ovulation occurs. Occasionally, young women will experience hot flashes during the luteal phase of their menstrual cycle because of insufficient progesterone production, or at menstruation, when the corpus luteus stops producing progesterone.

Estrogen increases the free fatty acids circulating in the blood, and this shifts metabolism away from oxidation of glucose to oxidation of fat, and it also reduces oxidative metabolism, for example by lowering thyroid function (Vandorpe and Kühn, 1989). These changes are analogous to those of fasting, in which metabolism shifts to the oxidation of fatty acids for energy, causes decreased body temperature, and in some animals leads to a state of torpor or hibernation.

Despite decreasing oxidative metabolism, estrogen stimulates the adrenal cortex, both directly and indirectly through the brain and pituitary, increasing the production of cortisol. Cortisol, by increasing protein turnover, can increase heat production, but this effect isn't necessarily sufficient to maintain a normal body temperature. It increases blood glucose, mainly by blocking its use for energy production, but the glucose is derived from the breakdown of muscle protein. It allows some glucose to be stored as fat. Sudden increases in the amount of glucose can lower adrenaline, and chronically excessive cortisol tends to suppress adrenaline. Cushing's syndrome (produced by excessive cortisol) commonly involves flushing and depression, both of which are likely to be related to the decreased action of adrenaline.

While the biological changes occurring at menopause and during hot flashes are very similar to some of the direct actions of estrogen, and although the menopause itself is the result of prolonged exposure to estrogen, very large doses of estrogen can, in many women (as well as in morphine addicted rats), stop the flushing. In some of the published animal experiments,

effective doses of estrogen were about 2000 times normal, and in some human studies, the dose was 30 times normal. By blocking the production of heat, the estrogen treatments might be creating conditions similar to those in Simpkin's cooler old rats, which failed to flush during morphine withdrawal. Menopausal estrogen treatment is known to lower temperature (Brooks, et al., 1994).

Since the Women's Health Initiative publicized the dangers of estrogen, there has been some interest in alternative treatments for hot flashes. Since a reduced production of progesterone has been associated with hot flashes for several decades, it isn't surprising that it is now being tested as an alternative to estrogen. Recently, 300 mg of oral progesterone was found to be effective for decreasing hot flashes, and a month after discontinuing it, the hot flashes were still less frequent than before using it (Prior and Hitchcock, 2012). Previously, transdermal progesterone was found to be effective (Leonetti, et al., 1999).

One of the things progesterone does is to stabilize blood sugar. In one experiment, hot flashes were found to be increased by lowering blood sugar, and decreased by moderately increasing blood sugar (Dormire and Reame, 2003).

Hypoglycemia increases the brain hormone, corticotropin release hormone, CRH (Widmaier, et al., 1988), which increases ACTH and cortisol. CRH causes vasodilation (Clifton, et al., 2005), and is more active in the presence of estrogen. Menopausal women are more responsive to its effects, and those with the most severe hot flashes are the most responsive (Yakubo, et al., 1990).

The first reaction to a decrease of blood glucose, at least in healthy individuals, is to increase the activity of the sympathetic nervous system, with an increase of adrenaline, which causes the liver to release glucose from its glycogen stores. The effect of adrenaline on the liver is very quick, but adrenaline also acts on the brain, stimulating CRH, which causes the pituitary to secrete ACTH, which stimulates the adrenal cortex to release cortisol, which by various means causes blood sugar to increase, consequently causing the sympathetic nervous activity to decrease. Even when the liver's glycogen stores are adequate, the system cycles rhythmically, usually repeating about every 90 minutes throughout the day.

Sympathetic nervous activity typically causes vasoconstriction in the skin and extremities, reducing heat loss, but the small cycles in the system normally aren't noticed, except as small changes in alertness or appetite. With advancing age, most tissues become less sensitive to adrenaline and the sympathetic nervous stimulation, and the body relies increasingly on the production of cortisol to maintain blood glucose. Many of the changes occurring around the menopause, such as the rise of free fatty acids and decrease of glucose availability, increase the sensitivity of the CRH nerves, causing the fluctuations of the adrenergic system to cause larger increases of ACTH and cortisol. Estrogen is another factor that increases the sensitivity of the CRH nerves, and unsaturated fatty acids (Widmaier, et al. 1995) and serotonin (Buckingham, et al., 1982) are other factors stimulating it. Serotonin, like noradrenalin, rises with hypoglycemia (Vahabzadeh, et al., 1995), and estrogen contributes to hypoglycemia, by impairing the counterregulatory system (Cheng and Mobbs, 2009).

With the reduced vasoconstrictive effects of the sympathetic nerves, and the increased activity of CRH, cyclic vasodilation under the influence of cortisol will become more noticeable. With the onset of menopause, and in proportion to the number and intensity of symptoms (on the Greene Climacteric Scale), the daily secretion of cortisol was increased (Cagnacci, et al., 2011).

Once the ideologically based doctrine of menopause as estrogen deficiency is discarded, it's possible to see its features as clues to the ways in which "stress" contributes to the age-related degeneration of the various systems of the body--not just the reproductive system, but also the immune system, the nutritive, growth, and repair processes, and the motivational, emotional, and cognitive processes of the nervous systems. The changes around menopause aren't the same for all women, but the ways in which they vary can be understood in terms of the basic biological principles of energy and adaptation that are universal.

Each type of cell and organ is subject to injury, and in some cases these injuries are cumulative. In the healthy liver, which stores glycogen, toxins can be inactivated, for example by combining with glucuronic acid, derived from the stored glucose. With injury, such as alcoholism combined with a diet containing polyunsaturated fats, the liver's detoxifying ability is reduced. Even at an early stage, before there is a significant amount of fibrosis, the reduced activity of the liver causes estrogen to accumulate in the body. Estrogen's valuable actions are, in health, exerted briefly, and then the synthesis of estrogen is stopped, and its excretion reduces its activity, but when the liver's function is impaired, estrogen's activity continues, causing further deterioration of liver function, as well as injury of nerves such as Desjardins described, and the systemic energy shifts and stress activations mentioned above.

Besides lowering the liver's detoxifying ability, stress, hypoglycemia, malnutrition, hypothyroidism, and aging can cause estrogen to be synthesized inappropriately and continuously. With aging, estrogen begins to be produced throughout the body--in fat, muscles, skin, bones, brain, liver, breast, uterus, etc. Polyunsaturated fats are a major factor in the induction and activation of the aromatase enzyme, which synthesizes estrogen.

Increased synthesis of estrogen, with aromatase, and decreased excretion of it, by the liver and kidneys, are only two of the processes that affect the influence of estrogen during aging. Cellular stress (chemical, mechanical, hypoxemic, hypoglycemic [Clere, et al., 2012; Aguirre, et al., 2007; Zaman, et al., 2006; Saxon, et al., 2007; Tamir, et al., 2002; Briski, et al., 2010]) increases estrogen receptors (which activate CRH and the stress response). The presence of estrogen receptors means that estrogen will be bound inside cells, where it acts to modify those cells. Before estrogen can reach the liver to be inactivated, it must be released from cells. Ordinarily, the cyclic production of progesterone has that function, by destroying the estrogen-binding proteins. Progesterone also inhibits the aromatase which synthesizes estrogen, and shifts the activities of other enzymes, including sulfatases and dehydrogenases, in a comprehensive process of eliminating the presence and activity of estrogen. At menopause, when the ovary fails to produce the cyclic progesterone, all of these processes of estrogen inactivation fail. In the absence of progesterone, cortisol becomes more active, increasing aromatase activity, which now

becomes chronic and progressive. The decrease of progesterone causes many other changes, including the increased conversion of polyunsaturated fatty acids to prostaglandins, and the formation of nitric oxide, all of which contribute to the tendency to flush.

*The limits of the belief system or consciousness of US medicine are nicely defined by the topics included in the Index Medicus, which was published from 1879 to 2004, by the Surgeon General's Office of the U.S. Army, the American Medical Association, and the National Library of Medicine, at different times. If you look up any important topic in physiology or biochemistry in an index of scientific publications such as Biological Abstracts or Chemical Abstracts, and then look for the same subject in the Index Medicus, you will find some startling differences--long delays and antagonistic attitudes. At first the discrepancies seem ludicrous and hard to account for, but I think they can be explained by recognizing that the editors of medical journals consider science to be their enemy.

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