The evolutionary origin and significance of Menopause

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Abstract

Contemporary human females have long life expectancy (81y US), especially relative to age at menopause (51y US). Menopause is a consequence of reproductive aging and follicular depletion (ovarian failure), yielding very low circulating estrogen* serum concentrations and biologically disadvantageous metabolic alterations. Stated in terms of antagonistic pleiotropy, the ongoing hypoestrogenic endocrine environment, beneficial during lactation, results in acceleration of several age-related health conditions following menopause (i.e. late postmenopausal osteoporosis, cardiovascular disease and cognitive decline). In contrast, the complex hypoestrogenic hormonal milieu present during postpartum lactation provides biologic advantages to both mother and newborn. The lactational hormonal milieu causes symptoms similar to those of the late perimenopause and early postmenopause, prompting theories for their biologic selective advantage. The precepts of evolutionary medicine encourage a reassessment of hormone therapy. Based on data presented, the authors propose additional opportunities for disease prevention and morbidity reduction in postmenopausal women.

Keywords

evolution; menopause; aging; lactation; hypoestrogenism; osteoporosis; heart disease

Introduction

Efforts to understand the evolutionary origin and significance of human menopause have engaged anthropologists and evolutionary biologists for decades. The adaptive hypothesis views programmed ovarian failure among humans as offering fitness by favoring females

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*To avoid unnecessary complexity that would obscure the main thrust of our argument, we have used the terms *estrogen* and *estrogenic* throughout, rather than specifying the different compounds involved. For the interested reader, estrogenic refers to the net action of the following estrogens at any time: classical estrogens (estradiol, estrone and estriol), conjugates (e.g. lipoidal estrogens), nonestrogens active at the estrogen receptor level (e.g. progesterone, testosterone, 27 OH-cholesterol) and xenoestrogens (e.g. isoflavonoids, SERMs [selective estrogen receptor modified compounds] and some pesticides such as DDT). Serum estradiol is the primary estrogen measured in human menopause research. Terms for the stages of menopause are those defined by the 2001 Stages of Reproductive Aging Workshop.[1]

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who become infertile years before death.[2] An alternate explanation, the epiphenomena hypothesis, considers menopause a product of antagonistic pleiotropy, favoring early fertility at the expense of late fertility or as the byproduct of an increase in life span or life expectancy.[3] The emergence of significant post-reproductive life expectancy in humans occurred during an evolutionary time when overall life expectancy was short, with death from acute, not chronic, conditions. Paleodemographic data from Australopithecines, Neanderthals, hunter-gatherers and proto-agricultural populations underscore the likelihood of menopause evolving with minimal life expectancy thereafter.[4] Although evolutionary medicine generally seeks to unify emerging health issues and their genetic antecedents, here we focus on diseases appearing during the post-reproductive period that are no longer subjected to the fitness-selecting forces of evolutionary biology.[5,6]

The long post-reproductive life span of women appears to be an evolutionary trait of long standing, although experts interpreting the available paleodemographic data disagree.[4,6–8] Debate centers on when, during the course of human evolution, menopause occurred, but it is likely to have evolved since the time of the last common ancestor.[9] From a Darwinian perspective, the long life spans of women after menopause are not easily explained by the energetic costs of reproduction alone, revealing a capacity for somatic aging to be uncoupled from reproductive aging to some degree.[10] Natural selection would favor females who become infertile many years before death if offspring require exceptional duration and intensity of parental care, as is the case with humans.[2] This adaptation allows extension of maternal nurturing energies well beyond the direct energy costs of pregnancy and lactation. This adaptation is also necessary to enhance survival of human offspring with a prolonged period of dependency (as compared with all other primates).[2,5,10]

The trend toward ever-increasing percentages of individuals reaching life spans beyond 80 or 90 years is a recent phenomenon.[11–13] Current data from more developed nations reveal no survival advantage conferred to younger populations with increasing numbers of octogenarians. Since 1900, achieving very old age is no longer an indicator of greater reproductive fitness, as it was in earlier centuries. Long life spans result from public health measures, socioeconomic factors and cultural customs, with medical and scientific interventions accounting for a small percentage.[14] In the 21st century, the largest population expansion in US women is in those older than 65 years[13], with survival not coupled to prior reproductive or ongoing biologic fitness.

Lactation, Endocrine Milieu and Physiology

Nearly all states of endocrine reproductive fitness are estrogen replete, with lactation the only low-estrogen condition associated with successful reproductive effort. Mammalian lactation fulfills the precepts of evolutionary biologic selective pressure, providing mobile, adequate nutrition to enable survival of suckling offspring.[15] Lactation physiology is of particular interest because it is the only low-estrogen state that has resulted from selective genetic evolutionary pressure.[16] In contrast, the menopause has no process of natural selection operating upon it.[2] While the mechanism of lactational hypoestrogenism is different (lactation vs. menopause); many physiologic changes resulting from the estrogen deficiency are similar.

During pregnancy, estrogen, progesterone and prolactin concentrations prepare breast tissue for lactation. Immediately after delivery of the infant, expulsion of the placenta results in a sudden drop in both estrogen and progesterone. Abrupt withdrawal of progesterone in the presence of high prolactin levels initiates lactation. With suckling, prolactin levels continue to be elevated. These high prolactin levels, through their inhibitory impact on gonadotropin secretion, inhibit ovarian function to greater or lesser degrees throughout lactation. Ovarian

suppression results in sustained low estrogen levels until the frequency of suckling diminishes and maternal energy supplies become adequate for further reproduction.[17]

Many maternal symptoms and physiologic alterations result from these lactational hormone shifts that are biologically advantageous for nursing infants at a maternal cost. The low estrogen concentrations during lactation induce many metabolic alterations. We will focus on the metabolism of serum lipoproteins, calcium balance and the resorption of bone, as well as on some alterations of the central nervous system. Although we are concentrating on these specific metabolic alterations, our hypothesis is more complete encompassing other metabolic alterations, menopausal symptoms (e.g. genital atrophy), and immune function. These are included in Table 1 for completeness, but are not discussed further in this manuscript.

Hormonal Effects on Serum Lipoproteins During Lactation

Circulating low estrogen levels during lactation are associated with an increase in lipoprotein lipase enzyme activity[18] resulting in an increase in serum lipoproteins. During lactation, such changes likely serve to increase the fat content of maternal milk, with energetic enrichment being an advantage to suckling infants.

Hormonal Effects on Calcium Balance and Resorption of Bone During Lactation

Approximately 200 mg/day of elemental calcium is lost from the maternal skeleton because of milk production in lactating women.[19] Ample calcium concentrations in human breast milk enhance bone mineralization of offspring at the cost of maternal calcium stores when calcium intake is insufficient.[20] This transfer of calcium results in a 3%–9% loss of bone mineral density (BMD) at the lumbar spine during a 6-month period.[21] Loss of BMD during lactation is greater than the average loss of 1%–2%/yr. observed during the late postmenopause, but approximates the rapid early loss in the late perimenopause and early postmenopause.[21] BMD losses appear greatest during the first 5 months of lactation, with recovery to normal BMD levels after weaning.[21]

Bone density does not always return to pre-pregnant levels, even after resumption of menstruation.[22] Women in whom lower bone mass is likely to persist following lactation are those nursing multiple babies, adolescent mothers, women with inadequate nutrition and women in the later childbearing years who may not be able to regain lost skeletal mass before menopause onset.[23]

Lactation may be a contributing factor for postmenopausal osteoporosis in women whose bone density does not completely recover to pre-pregnancy levels upon weaning, although studies on this topic are inconclusive.[19] Some recent epidemiologic research suggests a higher bone density in women who breastfed their infants compared with women who did not. This is observed in the presence of adequate nutrition, providing there is a sufficient length of time with resumption of menses prior to the onset of menopause.[24]

If lactational bone loss is compared with that occurring during menopause, several variables must be considered. Many researchers fail to define the stage of menopause being studied. For example, late perimenopause and early postmenopause, as defined in the STRAW staging system,[1] are associated with more rapid bone loss than is the late postmenopause. Whereas the normal premenopausal bone remodeling cycle (resorption, reversal, formation, quiescence) occurs over a period of 4–8 months, the remodeling cycle during lactation occurs at twice that frequency: every 3–4 months.[23] During lactation, high prolactin levels prevent gonadotropin-induced ovulation and maintain low estrogen levels, which promote bone resorption. At 6 months postpartum, exclusively breastfeeding women have prolactin

levels that remain elevated,[25] supporting continued transfer of calcium from bone to breast milk.

Once menses return and estrogen levels rise, bone loss abates.[26,27] Data from nutritionally healthy women corroborate this phenomenon of BMD restoration, showing that multiparity, as compared with low parity or nulliparity, is *not* associated with post-menopausal low bone mass.[28] Unlike lactation-associated bone loss, postmenopausal bone loss has no restorative phase. In addition, menopause is of longer duration than lactation and results in lower bone mass. Lowered bone mass, along with other changes associated with aging, results in measurable increases in fracture risk over time.[29]

Vasomotor Symptoms During Lactation

The low estrogen state is frequently accompanied by vasomotor symptoms (VMS; hot flashes, hot flushes [used interchangeably in this text], and night sweats) in women during the puerperium and postpartum lactation. In this setting, VMS may be integral to positively adaptive endocrinology (as opposed to the negative implications of VMS in post reproductive women). Hot flashes occurring postpartum or during menopause result from alterations in the temperature-regulatory centers of the hypothalamus. The so-called thermoneutral zone narrows in a low serum estrogen environment, making both hot flashes (an exothermic warming phenomenon) and sweating (ultimately a host surface-temperature evaporative cooling phenomenon) more likely.[30] During the hypoestrogenic milieu of lactation, VMS could serve a biologic purpose by elevating maternal skin surface temperature.[31] Such temperature elevations provide radiant heat for infant warming.[31b] Lowering caloric demands for self-warming conserves infant energy for weight gain and reduces metabolic stress on the newborn.[32,33] Therefore, VMS would likely contribute a survival advantage in terms of warming of offspring, and convey some evolutionary biologic advantage.[7]

Insomnia During Lactation

Lactation-associated sleep disorders likely confer biologic advantage. Easy wakefulness and heightened alertness during awakenings result in enhanced nighttime attention to the newborn, increase the frequency of feedings, and promote greater early infant weight gain, especially in the high-mortality neonatal interval. Additional maternal endocrine changes and blunted stress responses serve to enhance lactation adequacy and prevent maladaptive sensitization of infant central nervous system (CNS) programming.[32,34] This stabilization of both basal and stress-induced hypothalamic-pituitary-adrenal activity may be important for maintaining a constant endocrine environment, thereby preventing negative programming effects on the developing offspring. Other aspects of the lactational endocrine milieu likely serve to enhance nurturing behaviors and maternal calm during the low-estrogen state.[35]

Longevity, Demography and Changing Patterns of Disease

Whether a product of natural selection advantage, chance, or constraint as the cause of design complexity, menopause confers some advantages toward survival.[36] In view of suggestions by others, one should consider any claim of adaptation against constraint and pathology as alternatives.[37] The mechanism by which the naturally occurring state of menopause (constraint or pathology) accelerates somatic aging and advances disease risks over time will be explored.

Survival beyond age 65 of a large percentage of the female population is a very recent phenomenon in terms of evolutionary time. The earliest census data for the United States are from Massachusetts, where life expectancy in 1850 (free-living white women) at birth was 40, biased by high rates of infant mortality. If a woman reached age 40, the data predicted

28 additional years of life expectancy, indicating that if one survived infancy and the high mortality of childbearing, then surviving until age 68 was common.[38] This estimate is similar to the maximum 70- to 74-year life expectancy observed in the most fertile women, as reported by Emery Thompson et al.[39] Demographic data do not support life spans beyond the eighth decade as a frequent naturally occurring event.

We can expect the population of US women older than 80 years to increase by more than 15 million over the next three decades.[40] Considering the large number of nursing home-dwelling women at present, these statistics stimulate thoughts regarding possible measures to slow the pace of somatic aging in menopausal women.[41] In less developed nations, women who lived to be very old were a relatively small percentage of those who were biologically fittest.[42] Hunter-gatherer octogenarians were subjected to tests of reproductive fitness and were the most vigorous with respect to later-life somatic fitness.[43] With medical and scientific advances today, surviving to a very old age no longer represents evidence of fitness selection.[44]

Comparative Endocrine Milieu of Reproductive and Post-reproductive Women

The principles of low estrogen menopausal physiology help explain diseases that appear to increase in frequency and severity during the late postmenopause. Low serum estrogen levels in menopause, compared with low levels during lactation, result in very different metabolic and CNS effects.[45] It does not seem logical that VMS and sleep disorders serve any beneficial purpose later in life, although VMS in infant-caring menopausal grandmothers could potentially offer similar warming advantages for grand-offspring survival.

Vasomotor symptoms affect a large majority of post-industrial menopausal women, with some estimates as high as 90%. Although all women are not equally affected, about one-third of affected women have very severe symptoms causing multiple nighttime awakenings, severe night sweats and disturbed cognitive function (Figure 1).[46,47] These studies are reported from present-day sedentary populations and are not representative of hunter-gatherers.[48] Menopausal symptoms at every stage are decreased in very physically active women as compared with those who are less active.[46,48]

Because hunter-gatherers are extremely vigorous and active even through the late menopause years, they are likely to have been among the least bothered by menopausal symptoms, as evidenced by data on sleep disorders in women from less developed nations as compared with sedentary women in post-industrial countries.[48] Compensatory mechanisms that diminish VMS occur in 80% of postmenopausal women, and appear to occur in most women 10 years after the final menstrual period.[46,46b] Although hypoestrogenic symptoms of menopause (urogenital atrophy, vaginal dryness) are highly prevalent, these symptoms seldom are associated with severe disease or disability. Recent assessments are divided as to whether VMS may signal the presence of cardiovascular disease (CVD) in menopausal women. Recent data from the Women's Health Initiative (WHI) suggest that persistent VMS are a marker of subclinical CVD.[49] This analysis showed that women most likely to suffer a cardiovascular event (heart attack or stroke) when given either oral estrogen or oral estrogen/progestin therapy were those in late menopause *with persistent VMS*.[49] Women whose symptoms abated after the typical 4–5 years (Figure 1) had much lower risk when similarly treated. CVD is the major cause of mortality for US women, equal in number to the sum of the next four causes of death, thus refining our risk factor analyses may assist in efforts aimed at CVD risk reduction.[50]

Lipids and Cardiovascular Disease

In contrast to the Paleolithic-era diet of hunter-gatherer populations, the high-glycemic-index and high-fat diets characteristic of populations in more developed nations result in adverse cardiovascular risk factors and higher rates of disease.[51] In menopausal women, a more sedentary lifestyle and higher body-fat content result in higher circulating serum lipoprotein concentrations.[50] Plasma lipoprotein elevations caused by increased lipoprotein lipase activity in the presence of low serum estrogen levels, common in menopausal women, further increase risk.[52–54] In the menopause, low serum estradiol levels are associated with a sustained rise in total cholesterol, low-density lipoprotein cholesterol, and triglycerides and a concomitant fall in high-density lipoprotein cholesterol—a more atherogenic lipid/lipoprotein profile.[52–54]

Although not universally demonstrated in cross-sectional studies, longitudinal data document a small but statistically significant elevation in diastolic blood pressure (BP), in the range of 0.48 mmHg for diastolic BP across the menopause transition in conjunction with low serum estrogen levels.[54] Other adverse effects of low serum estrogen are a rise in cardiospecific C-reactive protein (C-CRP), a marker of vascular inflammation in the coronary circulation. Elevated C-CRP is recognized as a marker for increased risks for CVD and thrombus formation. Low serum estrogen levels cause increases in arterial tone, with a rise in BP in both primates and humans.[45] Increases in arterial tone also result in vascular luminal narrowing, requiring greater pressures to maintain adequate blood flow to vital organs. Increased arterial pressures over time increase vascular injury and formation of atheromata, and contribute to higher rates of plaque rupture, myocardial infarcts and peripheral vascular disease.[55,56]

Primates rendered menopausal in the laboratory exhibit adverse changes in CVD risk markers that are similar to those in human females with premature, surgical or spontaneous menopause.[45,52–59] A comparison of premenopausal and postmenopausal women aged 40–55 showed that, regardless of age stratum, CVD was more common in the postmenopausal group than in the premenopausal group.[57] Similarly, the degree of CVD increases the earlier hysterectomy/oophorectomy is performed.[58,59] The cumulative effects of dyslipidemia, when compounded by abnormal serum inflammatory markers and hypertension, result in elevated risks for atherosclerotic CVD, stroke, renal disease and dementia in menopausal women.

Bone Metabolism and Chronic Disease

In late postmenopause, the prolonged hypoestrogenic milieu causes a decline in BMD over time, with no rebound compensatory phase of bone formation as occurs after lactation ends in reproductively fit women. Resultant late postmenopausal skeletal fractures, particularly those of the hip, cause higher rates of disability and death. One-year mortality rates after this injury range from 15% to 20%.[60] A prospective study on the socioeconomic aspects of proximal femur fracture demonstrated that approximately 50% of patients who lived independently before hip fracture were unable to regain their independent lifestyle subsequent to the fracture.[60,61] The inexorable demineralization of bone following diminished ovarian estrogen synthesis, as in late postmenopause, is biologically disadvantageous.

Low serum estrogen concentrations lead to accelerated rates of bone resorption, with reductions in bone mass; this phenomenon occurs in both lactating and menopausal women. Lactation-related fractures are rare. Multiple factors may account for this phenomenon, but the precise mechanisms are not known. Younger age, higher bone density, a shorter duration of accelerated bone resorption (compared with menopause) and other neuromuscular factors

are likely protective, rendering the nursing mother's skeleton relatively resistant to falls and fracture.[62] Frailty, which increases risk for falls and fractures, is very rare in lactating women but quite common in elderly women with osteoporosis.[63] The human costs of osteoporosis due to prolonged low serum estrogen levels are substantial. Approximately 50% of women older than 50 will have an osteoporosis-related fracture at some time during their remaining lifetime.

The sustained loss of muscle mass, collagen and elastin seen in late postmenopause results in frailty, a second phase of accelerated bone loss.[63] These underlying alterations in menopausal bone, muscle and connective tissue physiology are disadvantageous, decreasing self-sufficiency and independence as women age. Growing demands for assisted living services reflect the cumulative impact of loss of vigor in aging sedentary women.[41]

With an evolutionary medical perspective, one might organize the data regarding lactational and menopausal physiology, and their disparate short- and long-term effects on cardiovascular and skeletal health, as shown in Table 1.

Paradigm Reassessment

There is a paucity of evidence to demonstrate that menopause has a genetic evolutionary contribution for humans over time. Women living beyond their own reproductive fitness may improve maternal-infant care by providing additional hunter-gatherer labor and reliable food and water and by playing midwifery roles that lower infant and maternal mortality rates. There does not appear to be a genomic advantage to menopause per se, other than shortening the reproductive life span to allow for more rapid generation times, enhancing adaptability and lengthening the time of protection and provisioning support of grand-offspring. Selective advantage depends on traits carried by offspring and on the "grandmother effect."[64] In these cases, the selective advantage is not related to post-reproductive adaptation and does not contribute inheritable genetic alterations or novel metabolic responses to the loss of estrogen.[2,16]

Sociological and scientific advances allow humans to experience new challenges and opportunities with respect to longevity. With current life expectancy approximating 80 years, we ask the question: Is it possible for a large percentage of women to be very old and also be very healthy without specific "normalizing" physiologic interventions? The human genome was selected in past environments far different from those of the present. Cultural evolution now proceeds too rapidly for genetic accommodation—resulting in dissociation between our genes and our lives. The mismatch between inherent biology and sedentary lifestyle fosters increasing prevalence of degenerative diseases and chronic illness.[65] We must develop an overall conceptual framework to better characterize differences between ancient and modern life histories and relationships to the emergence of disease patterns. Through such analysis, one can create a unifying approach upon which to base consistent, compelling and effective recommendations for reduction in disease burdens for individuals and across populations of women.[7]

Conclusion

From these examples, we conclude that low serum estrogen's "natural" biologic advantage—its selective evolutionary purpose—is likely restricted to postpartum lactation. Decades of sustained estrogen deprivation, with attendant disadvantageous cardiovascular and musculoskeletal physiology, result in greater rates of diseases and declining vigor in women. As Austad stated, "Assuming the human body has been physiologically adapted to the conditions extant during the vast majority of human history, it may be well worth pursuing how the signs and symptoms of menopause are affected by dietary, exercise, and

reproductive hormone regimes mimicking those of the late Paleolithic era."[4] Adopting evolutionary premises in our approach to menopause, we view it as a state of human existence upon which evolutionary biologic pressures no longer operate. An evolutionary medicine perspective creates a radical shift in our thinking on the biodemography of this aspect of aging in women. Through the study of evolutionary medicine, we are called upon to create new approaches to menopausal health care in order to lower morbidity rates associated with accelerated somatic aging.

US physicians and public health officials specializing in post-reproductive health care are concerned about the expanding number of aging women whose longevity will lead to exponential growth in the population of dependent elderly. Analyzing the fundamental underlying physiology that characterizes the postmenopause reveals many characteristics that are biologically disadvantageous when sustained over time. Correcting the underlying cause of the pathophysiology could lessen morbidity during late postmenopause in modern Western cultures. An evolutionary medicine perspective calls for reassessing the current approach that discourages the use of estrogen support in menopause. A methodical evolutionary medical inquiry may generate options that not only lengthen disease-free life spans but also improve quality of life.[7]

Future Directions and Research Opportunities

Careful examination of the inherent self-preserving physiologic and evolutionarily selected mechanisms for homeostasis during and following lactation may provide new insight into the prevention of disease following menopause. Furthering our understanding of energy conservation during lactation may provide opportunities for reduced caloric consumption and its attendant longevity benefits following menopause, with similar salutary effects. Perhaps the hormonal milieu present during and immediately following lactation, an environment that restores skeletal integrity, could be harnessed later in life to prevent osteoporosis, fracture and other infirmities so prevalent in aged women.

The profound similarities between the metabolic changes during lactation and those following menopause bring several research opportunities into focus. Lactation evokes rapid, self-regulating, compensatory mechanisms for its metabolic changes (typically within a few years), with few, if any, attendant long-term health effects. Similar metabolic changes following the final menstrual period result in well-documented adverse lifelong health consequences in late postmenopause (e.g. CVD, osteoporosis and fractures). Hormone therapy has been shown to reduce risk for many of these hypoestrogenic consequences when started early in the menopausal transition. These principles could stimulate a research agenda and, ultimately, a shift in public policy. We need to better characterize differences between ancient and modern women's life histories, identify which of these factors affect the development of disease and ultimately integrate epidemiologic, mechanistic and genetic data with evolutionary principles to create a unifying concept on which to base persuasive, consistent and effective recommendations.
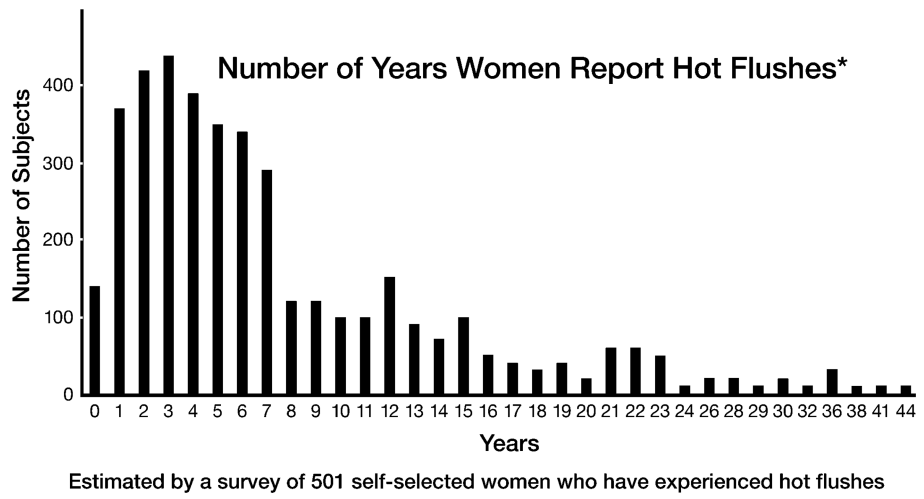
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Number of Years Women Report Hot Flushes*

Estimated by a survey of 501 self-selected women who have experienced hot flushes

Figure 1.
Hot Flushes May Continue Years After Menopause

Table 1

Responses to Falling Sex Steroids

Adaptive During Reproductive Era	Affected Cell Systems	Maladaptive in Menopause
Maintenance of capillary blood flow to critical organs	Arterial tone increased	Cardiovascular disease, hypertension
High blood fat or milk	Lipoprotein lipase (?)	Cardiovascular disease, arteriosclerosis
Mobilization of calcium for milk	Remodeling cycle favors bone loss	Osteoporosis, fracture
Discarding of genital skin, bulk and elasticity	Organ turgor (genital and sexual skin)	Scarring and genital atrophy
Radiant warming of suckling newborn	Vasomotor control, changes in thermoneutral zone set-point	Hot flushes, night sweats
Increased vigilance	Sleep pattern alterations	Sleep disorders
Affective and cognitive changes, decreased immune brain barrier	Central nervous system alterations	Memory deficiency, impaired cognition, dystrophies
Pro-inflammatory (?) anti-inflammatory during puerperium (reversed when estrogen is high)	Immune response to insult and foreign antigens	Failure of immune privilege (?), CNS vulnerability and cancer