BIOLOGICAL ASPECTS OF MENOPAUSE: Across the Lifespan

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KEY WORDS: lifespan approach, age, symptoms, ovary, atresia

INTRODUCTION

Menopause is defined biomedically as the last menstrual period, identified in retrospect after 12 months of amenorrhea (178). Menopause is a biological universal among human females who live through their middle age (32). It is an event that transects the biological and psychosocial trajectories threading through a woman’s life. As an event, menopause is a parameter closing the reproductive phase of life (52, 167), a marker in the linear progression of bone loss with advancing age (123, 129, 156), and an indicator of changing serum lipid profiles (150, 164).

Menopause occurs within what is called the climacteric, the transition from the reproductive to post-reproductive phase of life. Although defined biomedically as an event, menopause is experienced as a process by individual women (68). For example, the physiological transition from reproductive to post-reproductive life is associated with a decline in estrogen levels (77, 92). Over time, this decline may be experienced as a change in skin elasticity (17), altered cognitive abilities (143), lengthened or shortened menstrual patterns (160, 161), or discomforts such as vaginal dryness, night sweats, and hot flashes (35). The decline in serum estrogen levels is just one of a patchwork of hormonal changes associated with menopause. Similarly, menopause—or the
entire climacteric—is just one piece of the dynamic, ongoing physiological and sociocultural process of aging (26a).

Menopause is both a biological aging event (8) and a maturational process in the context of aging (125) that coincides with age-related changes in, for instance, bone density and immune response (148). One challenge of menopause research is to identify physiological changes that are specific to menopause, separate from the other progressive, irreversible, universal processes of aging (75). Another challenge is to differentiate between biological and cultural effects. For instance, hot flashes are measurable, physiological occurrences (73, 79, 80); however, the frequency and severity of hot flashes differ between cultures (3, 10).

In the discussion presented here, menopause will be conceived of as both a process and an event. Menopause will also be envisioned as both a dependent and an independent variable. As an event, the timing of menopause is best modeled as a single outcome from multivariate input. For example, the timing of menopause varies between populations (49, 52, 55, 86, 167, 178) and within populations (for the United States, see 95, 159). Dependent variables related to intrapopulation variation in age at menopause include smoking habits, parity, education, and body mass index (106). As an independent variable, the process of menopause is just one factor contributing to menopausal symptoms such as hot flashes or bone loss. For example, the recent medical emphasis on osteoporosis as a symptom of menopause (96, 177) downplays a myriad of risk factors including white or Asian ethnicity, family history of osteoporosis, lifelong low calcium intake, lack of physical activity in childhood and adulthood, alcohol abuse, cigarette smoking, and high caffeine intake (28, 90).

Cross-species studies identify aspects of menopause that are unique to humans. The macaque (60) and the chimpanzee (50, 51) provide lifespan stage, hormonal, and anatomical points of comparison for the study of menopause. Cross-cultural studies tease apart the human universal (biological) aspects of menopausal symptoms from culture-specific variation. For example, cross-cultural studies have pointed to lifestyle changes (83), parity (11), and nutrition (8) as explanations for iation differences in bone loss and fracture rates in pre- and postmenopausal women.

An understanding of the biological aspects of menopause is relevant for evolutionary comparative work; for biocultural investigations of intra- and interpopulation variation; for informing and framing theoretical discussions in medical anthropology; and for examining menopause in relation to nutritional status, genetics, fertility, and mortality. It is also an appropriate adjunct to the comparative study of menstruation (18a, 129a).

Menopause is a “distinct window” (181) into a long process of ovarian aging. Menopause follows years of exposure to infectious disease, childbear-
ing, changes in marital status, smoking and drinking habits, and fluctuations in nutritional status. The event of menopause cannot be separated from ongoing life. Nonetheless, except for the window of menopause, the long process of ovarian aging is hidden from noninvasive observation. It is not known when, or even whether, there are critical moments in ovarian development and/or aging that determine age at menopause or particular symptom experience. All that can be observed is the cessation of menses at the individual or population level, coupled with hormonal changes.

This review outlines the biological basics of menopause and then places menopause within the context of a dynamic lifespan. The basic tenets of the lifespan approach maintain that, for each individual, aging and development are lifelong processes from birth to death; biological, psychological, and sociocultural trajectories interweave across the life course; the entire lifespan serves as a frame of reference for understanding particular events or transitions; and the life course can be affected by environmental change (16, 134, 144, 147).

This review also points to the gap between population-level studies of menopause and studies carried out at the biochemical, cellular, or organ systems level. Filling this gap between the “students of the whole” and “students of the fragments” (153) offers the most interesting directions for future anthropological research.

BIOLOGICAL BASICS

Science presently wields technology capable of extending the female reproductive lifespan beyond intrinsic limits, as evidenced by widely publicized success in postmenopausal pregnancies (8a). For most women, however, menopause signals the end of childbearing. Female reproductive aging may relate to uterine aging (110) or to a decline in oocyte quality with age (44, 118); however, once the egg supply is exhausted, natural fertility is terminated (133). Evidence of ovulation and primordial follicles have been found in the ovaries of women older than 50 (24, 122); nonetheless, exhaustion of oocyte stores is central to the onset of menopause. The event of menopause clearly demonstrates that ovarian aging is lifelong, progressive, and irreversible: the incessant loss of oocytes leads to menopause.

Aging changes also occur in the neuroendocrine system. Although menopause fundamentally is an ovarian phenomenon, the ovarian changes cannot be considered out of the context of larger neuroendocrine and immunological systems. Both “pelvic clocks” and “neural clocks” (9) are involved in the onset of menstrual cessation.
Ovarian Follicles

In simple terms, the timing of menopause and onset of menopausal symptoms is determined by the number of eggs present in the ovaries at birth and by the rate of egg loss through ovulation and degenerative processes. More technically, within the human fetus, primordial germ cells exist prior to the differentiation of the gonad. These ovoid, ameboid-like cells migrate to the ovary by the fifth or sixth week of gestation. From the eleventh or twelfth week onward the germ cells (called oogonia at this stage) form oocytes by mitosis (7, 27, 116). Oocytes are undeveloped eggs stored in the ovary. Oocyte formation ceases by the fifth month in utero (7). Although fish, amphibians, and reptiles continue oogenesis throughout adult life (137), most mammals do not (7, 57).

The size of the fetal follicular endowment is species-specific (41, 119, 127, 168) and is probably under genetic control (49). In humans, there are an estimated two million oocytes present at birth (7). This extraordinary number of oocytes may be an evolutionary carryover from ancestors (e.g. fish) that relied on external fertilization (97).

Within the ovaries, at about 16 weeks in utero, oocytes are surrounded by a layer of flattened granulosa cells (116). These are the primordial follicles. Oocytes that remain naked, without a layer of granulosa cells, degenerate (168). Primordial follicles act as a pool from which all developing follicles emerge (20, 127). Primordial follicles can develop further into preantral follicles, then antral follicles (see Figure 1). These more developed follicles contain oocytes encircled by granulosa and theca cellular envelopes (97, 127). Estrogen is produced in the granulosa cells; the rate of hormone secretion increases in proportion to follicle size. Maximum rates of estrogen production are attained just before ovulation in mature (preovulatory) follicles. Following ovulation the follicle becomes a corpus luteum, which secretes large amounts of progesterone (97).

![Diagram of a follicle](Figure 1 Preantral follicle (based on 97:62).)
Follicles at all stages of development are present in the ovaries during the reproductive years. Although follicular development can lead to ovulation, ovulation accounts for very few of the follicles lost across a woman’s lifespan. Instead, 99.9% of all oocytes disappear from the ovary by the process of atresia (degeneration), not ovulation (40, 127). In the human ovaries there are 6.8 million germ cells at the fifth month post-conception. This number declines to 2 million oocytes in the ovaries at birth (7) and to some 390,000 at menarche (19). The greatest loss of oocytes occurs during the fetal and prepubertal periods (27, 59).

The causes and rates of atresia differ by follicular developmental stage (20, 57, 127). Atresia of small follicles originates in the oocyte, which undergoes lysis or phagocytosis (20, 57). Atresia of preantral and antral follicles originates in the granulosa cells, which shrink as cells of the theca layer increase in size (20, 57, 168). Atresia occurs more frequently in the late preantral and antral stages even though there are more follicles in the early stages of development in the ovary at any one time (127).

Cells going through, or about to enter, atresia can be identified microscopically, chemically, and molecularly (27, 61, 158). The process of atresia begins prenatally and continues throughout the lifespan (7, 57). Mathematical models have attempted to determine whether number of follicles at birth or rate of atresia is more important in determining age at menopause (102, 155), whether there is a limiting threshold number of follicles needed to maintain menstrual cycles (119, 133), and whether there is an acceleration of follicle loss as menopause approaches (37). With respect to the latter model, Faddy et al (37) mistakenly argue for an accelerated rate of follicular atresia in women older than 37 based on log transformed data (LR Godfrey, LE Leidy, manuscript in preparation). The actual decline in number slows with age (40, 155).

There are various arguments for a genetic component to age at menopause. Women experiencing premature ovarian failure—before the age of 40—have exhibited Mendelian inheritance patterns (101). X-chromosome monosomy in both mice and women (Turner’s syndrome) is associated with an early age at reproductive failure (49), as is partial deletion of the long arm of the X chromosome (78). Trisomies of chromosome 18 (Edward’s syndrome) and chromosome 21 (Down’s syndrome) are associated with reduced numbers of both non-growing and growing follicles (49). In addition, early age at menopause is related to a genetic deficiency of galactose-1-phosphate uridyl transferase, an enzyme used in the conversion of galactose to glucose (25). In this case the genetic control of the timing of menopause alters the rate of follicular atresia, first in utero, then during the first decades of life, through the accumulation of galactose metabolites, which damage the ovary (72).

Atresia may be an evolved mechanism that facilitates reproduction by means of relatively small numbers of live offspring. Alternatively, atresia may
be a mechanism whereby products of many follicles are produced to serve a
chosen few (27). In some mammals (e.g. the Canadian porcupine) accessory
corpora lutea are formed from follicles that do not ovulate. The extra corpora
lutea produce progesterone, which maintains pregnancies (126). Similarly in
other mammals, ovarian inhibin is produced by all antral follicles in the ovary,
rather than only the dominant follicle (as with estradiol) (5). Inhibin is an
ovarian hormone that has a negative feedback effect on pituitary follicle stimu-
lating hormone (FSH). Extra inhibin could function to maintain the low levels
of FSH required during the early stages of pregnancy.

Some researchers argue that atresia represents an example of apoptosis (61,
157, 158), which is "an active, genetically governed process whereby cells die
by following what appears to be a controlled, intrinsic program designed for
their demise" (61:2416). Hughes & Gorospe (61), for example, hypothesize
that apoptosis is responsible for the demise of the granulosa cells, which
causes follicular atresia. If cell death is preprogrammed, however, the trigger
for cell death still needs to be explained. Something induces apoptosis. The
trigger may be an imbalance between pituitary and ovarian hormones or it may
have an immunological component.

**Neuroendocrine Aspects of Menopause**

To better grasp the process of atresia, which leads to the cessation of menses
and to symptoms such as vaginal dryness, hot flashes, increasing levels of low
density lipoprotein (LDL) cholesterol, and bone thinning, it is important to
understand the hormonal aspects of menopause.

The hypothalamus, pituitary, and ovaries integrate neural and hormonal
signals into a physiological rhythm that continues for almost 40 years. Begin-
ning with the brain (an arbitrary starting point), the hypothalamus transmits
gonadotrophin releasing hormone (GnRH) in episodic pulses directly to the
anterior pituitary (153). In the anterior pituitary, plasma membrane receptors
for GnRH sense the pulse frequency and amplitude of GnRH (39) and respond
by producing two gonadotrophins, follicle stimulating hormone (FSH) and
luteinizing hormone (LH). FSH and LH are also characterized by episodic
secretion, which continues after menopause (39, 173). Catecholamines (dopa-
mine and norepinephrine), serotonin, endogenous opioid peptides
(encephalins and β-endorphin), and hypothalamic peptides (such as neuropepi-
sin and gastrin) influence the secretion of GnRH, thereby influencing the
secretion of LH and FSH (9, 39, 56, 109, 139, 174). Although FSH and LH are
both stimulated by GnRH, they appear to be under separate regulatory control
as evidenced by higher levels of FSH during the follicular phase of menstrual
cycles (4), an earlier rise in FSH levels prior to menopause (22, 113), and
different effects of endogenous opioid peptides on LH and FSH secretion (39).
Within the ovaries, FSH receptors are present only on follicular granulosa cells, while LH receptors are found on granulosa, thecal, interstitial, and luteal cells. FSH and LH stimulate oogenesis, follicular growth, and the production of estrogen and progesterone (57, 97, 153). Granulosa cells also produce the peptide inhibin (22). Estrogen, progesterone, and inhibin send feedback to the brain, which generally decreases the secretion of FSH and LH (39, 153).

In an ovulatory cycle, FSH levels begin to rise prior to menstruation and continue to rise through the early follicular phase. LH pulses increase in frequency throughout the follicular phase (days 1–14 of the cycle; see Figure 2). Levels of estradiol (the major premenopausal estrogen) and estrone (the predominant postmenopausal estrogen) increase from the mid-follicular to the late follicular phase of the cycle, eventually causing the decline in FSH levels (4, 142). Inhibin levels remain low (5). During the luteal phase (days 15–28), inhibin levels increase (5) while LH and FSH pulse amplitude and frequency decline. Estradiol levels decline from the mid-follicular phase to the end of the luteal phase while progesterone levels increase (4). In reality, it is misleading to speak of days 1–14 and 15–28 because menstrual cycle length varies quite a bit at different points in a woman’s lifespan (77, 161).

Across the lifespan, the sequence of hormonal rhythms stays the same, but hormonal levels are modified with age. Specifically, estrogen levels increase with age during the late follicular phase and decline with age during the luteal phase. An age-related decline of corpora lutea causes progesterone levels to fall during the luteal phase (77). The follicular phase of the cycle shortens

![Figure 2](image_url)  
*Figure 2* Summary of hormonal events—normal ovulation cycle (138a). Hormone levels are presented as percent maximum secretion.
FSH levels increase throughout the cycle, particularly during the early follicular phase, despite levels of ovarian estrogen that would be expected to suppress pituitary FSH secretion (141, 142). The increase in FSH, which occurs when women are in their thirties (163), is the result of follicular oocyte depletion, which results in lower inhibin secretion (5, 77). As with menstrual cycle length, hormonal changes also vary greatly with age, ranging from ovulatory cycles with low premenopausal levels of FSH to transient episodes of high levels of FSH and LH (112).

Menopause is characterized by elevated serum levels of LH and FSH, and a reduced level of circulating estrogen (92). In one longitudinal study (132), menopause was characterized by a marked drop in the levels of all steroids except those of adrenal origin. Estradiol declines markedly. Postmenopausal estrone is converted from adrenal and ovarian androstenedione in peripheral tissues such as muscle and adipose (21, 77, 93, 128).

Because it is difficult to separate the changes of aging from those specific to menopause, the trigger for menopause is still debated. The etiology of menopause may lie in age-related changes at the level of the hypothalamus. For example, there are age-related changes in dopamine, norepinephrine, serotonin, and β-endorphin levels (41, 114, 151), and a loss of hypothalamic neurotransmitter receptors may occur with age (109). A reduction in GnRH pulse frequency is associated with a decline in follicular maturation (39). The rise in FSH levels prior to the decline in ovarian steroid levels could be the result of an age-related decrease in sensitivity of the hypothalamic-pituitary axis to ovarian steroids (112, 113). In rats the loss of estrous cycles lies in the failure of the hypothalamic-pituitary system (41, 109). The National Research Council points out, however, that anestrous female rats are different from postmenopausal women:

In the rat, the ovaries appear to be capable of normal or near normal function throughout the lifespan, whereas the ovaries of women cease to function around midlife. ...In addition, the hypothalamic-pituitary system of the rat shows a reduced capacity to secrete gonadotropins, whereas gonadotropin levels in postmenopausal women are increased (117:413).

The primate is a much better model for the human menopause (13, 50, 51, 60, 125).

Based on human and non-human primate observations, many researchers argue that menopause is initiated by the ovary as oocytes are depleted through atresia (54, 77, 92, 97, 127, 133, 141, 142). The loss of oocytes results in a decline in ovarian estrogen and inhibin. Lack of negative feedback increases FSH and, later, LH production (22). As with all aspects of menopause, there are also age-related changes that are independent of oocyte loss. For example,
with increasing age the numbers of theca and granulosa cells decrease, so estrogen and progestogen levels also decline (171).

**Immunological Aspects of Menopause**

At the 1993 meetings of the North American Menopause Society, Anderson (2) pointed out that the immunological changes in T cell immunity and humoral immunity occurring in association with menopause are “only beginning to be appreciated.” Various linkages between neuroendocrine aging and immune system changes with age have been hypothesized (41).

Clues to the etiology of menopause may be found in an examination of premature ovarian failure because, as Cramer et al point out (25:610), the line dividing cases of early menopause from the clinical norm is arbitrary. Biomedical anthropologists, well acquainted with the arbitrary cutoffs that identify clinical diseases, could examine the relevance and meaning of the boundary. For example, Ginsburg’s (46) summary of premature ovarian failure applies equally well to menopause at the age of 50:

In women with premature ovarian failure it is not clear whether fewer primordial germ cells migrate to the germinal ridge in fetal life, whether the rate of multiplication up to the fifth month of intrauterine life is reduced, whether the rate of follicular loss thereafter is greater than normal, or whether there is a combination of all three factors (p.1289).

Another interesting observation concerns the relationship between autoimmune disorders and early menopause. Autoimmune disorders are more common among women (12), and higher rates of early menopause have been observed among women with autoimmune disorders involving the thyroid and adrenal glands, as well as women diagnosed with diabetes, pernicious anemia, myasthenia gravis (36), alopecia, vitiligo, Crohn’s disease (87), and systemic lupus erythematosus (12, 18, 94). In addition, anti-ovarian antibodies have been identified in the serum from women with the diagnosis of Addison’s disease (108) and premature menopause (130, 135). Because of documented relationships between handedness (a measure of cerebral laterization) and various autoimmune disorders, one study examined age at menopause in relation to handedness (85). Left-handed women reported a significantly earlier age at menopause. Other studies have not demonstrated such a relationship (1, 86).

**BIOBEHAVIORAL FACTORS ASSOCIATED WITH MENOPAUSE**

The entire female lifespan—fetal, prepubertal, and reproductive—ultimately determines the cessation of menses by influencing the environment of the
ovary. The range in variation in age at menopause and onset of symptoms is familial in two ways. Genetically, parents pass to their daughter the parameters for number of oocytes and/or rate of atresia. Behaviorally, a mother’s activity while pregnant affects the ovarian store her daughter possesses at birth (49). From birth until menopause the environment and behavior of the individual affects her own ovarian stores. “Extensive epigenetic influences” (41:569) result in variation in age at menopause and symptom experience between and within populations.

Age at Menopause

Age at menopause is defined as age at last menstrual period after at least 12 months of amenorrhea (70, 165, 178). Cross-sectional, retrospective, and longitudinal studies have consistently placed the median age of menopause at 49–51.5 years among women in relatively well-nourished populations of industrialized societies (49, 52, 53, 55, 86, 167, 178). In contrast, average age at menopause is 43–47 years among women in New Guinea (175), India (138), Pakistan (166) and the Philippines (47). Age at menopause is of interest in relation to fertility (176), mortality (145, 146), and morbidity. Late age at menopause is associated with increased risk of endometrial and breast cancers (31, 81).

Problems in menopause research and cross-study comparison have been reviewed elsewhere (14, 52, 55, 69, 107). For example, comparisons of mean age at menopause between populations are confounded by error in recalled age at menopause (23). A cross-sectional status quo approach, such as probit analysis (42), avoids error in recall. Probit analysis computes the proportions of women who are or are not menstruating at each age to construct the median age at menopause—the age at which 50% of the population ceased menstruating. From a lifespan perspective, a major limitation in cross-sectional or retrospective studies is the measure of cause and effect at the same point in time, which may result in an erroneous association between variables.

The patterns of constancy or change in variables such as smoking habits, body weight, or marital status may be important in relation to the process of atresia. Smoking is associated with a significantly earlier age at menopause (65, 71, 86, 88, 106, 120, 124, 172). Body size is less clearly associated with age at menopause. In many studies lean women appear to experience a natural menopause slightly earlier than heavier women (15, 67, 89, 95, 120). Marital status, for unexplained reasons, is related to the onset of menopause. Married women report a later age at menopause than do single women (15, 120). Women of higher income status have also demonstrated a later age at menopause than do women with lower incomes (131, 149).

Menopause is later among women who use estrogen replacement therapy during the 12 months preceding the last menstrual period (160). Most studies
have found no demonstrable relationship between age at menarche and age at menopause (120, 159, 170), although an inverse relationship has been found in poorly nourished populations (52, 53) and among women with a history of mumps (26).

Menstrual cycle length and regularity has a significant relationship to age at natural menopause (149, 170). Several studies have shown a later age at menopause with increasing numbers of pregnancies (64, 86, 120, 170), although other studies have shown no significant association between age at menopause and parity (15, 48, 131). Mothers of multiple births (i.e. twins) have a significantly earlier natural menopause than do women who have given birth to a single offspring (179).

Other variables associated with menopause include blindness (84) and living at high altitudes (7a, 66, 131). There is no difference in age at menopause between urban and rural women (76, 131). Nor is there an association between age at menopause and the use of oral contraception (15), months spent breastfeeding (48), miscarriages (120, 170), or abortions (120).

The influence of biobehavioral and reproductive factors on the timing of menopause may be the result of an altered rate of atresia. This places menopause within the context of a dynamic lifespan. For all of the above variables, the questions to be asked go beyond cross-sectional vs longitudinal study design. Specifically, when is diet, a marriage, or a two-pack-a-day smoking habit important? What are the threshold numbers of years? Do biobehavioral factors have more of an effect when there are many oocytes present in the ovary, or when there are few?

**Symptom Experience**

The same process of follicular decline responsible for the timing of menopause is also responsible for what have been called the symptoms of menopause.1 As was pointed out above, the follicle, which nourishes the oocyte, is also the major site of estrogen production in the body. The decline in follicle number across the lifespan eventually results in lowered levels of circulating estrogen. As estrogen is withdrawn from estrogen-responsive tissues, symptoms may be acute (e.g. hot flashes or night sweats), or they may develop slowly (e.g. urogenital atrophy) (171). The symptoms of menopause include changes in the vagina, cervix, uterine ligaments, and skin. There is decreased pubic hair, loss

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1 Symptoms are defined as “any perceptible change in the body or its functions that indicate disease or the kind or phases of disease” (154). To use the word symptom thus implies that menopause is a disease or, more precisely, an endocrinopathy (104, 163). It may be more accurate to refer to hot flashes, vaginal dryness, and night sweats as discomforts; to point out that increasing LDL levels are symptomatic of future cardiovascular disease; and to argue that bone thinning is a risk factor for osteoporosis. However, in literature, research funding, and clinical treatment, the biology of menopause remains tightly bound to the medicine of menopause.
of subcutaneous fat, bone loss, and increased risk of cardiovascular disease (58, 115, 171). There is some evidence of altered cognitive ability (143). Although related to lower levels of estrogen, hot flashes, night sweats, and vaginal dryness (35) are far from universal (3).

Hot flashes and night sweats occur during the perimenopause, which is a time of hormonal flux that is defined as the interval from just before the last menstrual period until a full year after it (178). The perimenopause is more difficult to define than is menopause. Irregular menses begin on average at age 45.5 (160), but the range is 41–59. Hot flashes may begin several years before the cessation of menses; osteoporosis may not be visible for decades after. Also, symptoms such as vaginal dryness and dyspareunia (pain with intercourse) increase with advancing age, although hot flashes lessen in frequency and intensity (73). For all symptoms of menopause, the effects of aging and lifestyle need to be taken into account before menopause is identified as causal.

Especially with regard to psychological symptoms, endocrine changes need to be disentangled from lifespan stage to assess whether symptoms such as anxiety or depression (105) are associated with menopause. The rise and fall of the diagnostic category involutitional melancholia (169) is a good example of a culture-bound syndrome. This is a depressive psychosis once thought to occur among women ages 40–60 because of the hormonal changes of menopause. It was removed from the psychiatric nosology in 1979 when studies failed to show that rates of depression were any higher, or of a distinct pattern, among menopausal women compared to nonmenopausal women (169).

The most obvious place for anthropologists in the study of menopausal symptoms is in the realm of cross-cultural comparisons to identify the biological vs cultural components. For example, studies carried out in Greece and Mexico (10), Newfoundland (30), Israel (29), Indonesia (43), Japan (91), Ghana (82), South Africa (33), Pakistan (166), Nigeria (6), Canada, and the United States (3) demonstrate different frequency rates for hot flashes among women in these populations.

Avis et al (3) suggest that the academic and clinical community should accept the normality of the menopause transition and explain the deviance of symptoms. In doing so, however, it is important not to abandon a biocultural approach in the pursuit of menopause as a normal or biologically uneventful life transition.

Consider the pathophysiology of hot flashes. Hot flashes are related to pituitary LH pulses, increases of plasma epinephrine, and decreases of noradrenaline (73, 79, 80). Symptomatic women have lower levels of serum estrogens than do asymptomatic women (73). Visible signs of hot flashes are reddening of the skin accompanied by profuse sweating (171). Peripheral temperature rises 4–5°C in fingers and toes (73, 79). For cross-cultural re-
search and studies of intrapopulation variation, it is extremely interesting that women can demonstrate the peripheral temperature changes without feeling the flush. Clinicians conclude that asymptomatic women are evidence that the objective parameters are more reliable indicators of vasomotor instability than are the subjective sensation of hot flushes (73:55). Anthropologists should go even further to question why the threshold of sensitivity to universal physiological change differs so dramatically between women and between populations.

Just as there is a need for a lifespan approach in considering the timing of menopause, there is also a call for the lifespan approach in considering bone loss leading to osteoporosis (28, 129, 180). Consider the similarity between ovarian aging and the following description of bone loss: “The risk of a woman experiencing an osteoporotic fracture within her lifetime depends upon 2 factors: the peak bone mass achieved and the rate of bone loss after the menopause” (171:16). Taking a lifespan approach involves considering childhood activity levels, participation in college sports, lifelong calcium intake, and exposure to sunshine, in addition to the endocrine changes of menopause.

Menopause is also associated with increases in total cholesterol, triglycerides, and LDL cholesterol, and with reductions in high density lipoprotein cholesterol. These changes are seen in longitudinal study (164) and are independent of age and body mass index (150).

THE GAP BETWEEN LEVELS OF BIOLOGICAL ORGANIZATION

Follicular atresia eventually results in both the cessation of menstruation and the low estrogen environment associated with various menopausal symptoms. Because ovarian decline through atresia is hidden from view, the best we can do at the level of whole individuals or populations is to make observations through the window of menopause; assay hormone levels in blood, urine, and saliva; and identify attributes that may have altered the rate of atresia across the lifespan. The rate of follicular atresia is fastest during the fetal and prepubertal stage (27, 59). Of interest, then, are fetal impacts, such as history of a malnourished or smoking mother, and effects of prepubertal nutrition or infectious disease. Body weight at age 18, for example, is more strongly associated with age at menopause than is body weight at the cessation of menses (140). Cramer et al (26) hypothesize that age at menopause is earlier among women with a history of mumps because the infection may damage the ovaries, causing premature depletion of oocytes.

During the reproductive years, attention should be directed toward physiological changes (e.g. pregnancy, weight gain) and behaviors (e.g. smoking) to assess impact on rate of atresia. For example, smoking may result in an earlier
menopause because of effects on the central nervous system or liver metabolism (65, 88, 100, 120), through hypoxic effects on the ovaries (49), or through the destruction of primordial oocytes (103).

While looking across the lifespan for health-related behaviors and patterns of physiological change associated with the timing of menopause or symptom experience, investigations should be informed by a biological understanding of what turns menstrual cyclicity off. The process of atresia is still not well understood. Some hypotheses involve apoptosis (61, 157, 158); others point to ovarian toxicants (27, 155). Farookhi (38) suggests that atresia is an inflammatory response. Most other hypotheses target specific hormonal triggers (141). Factors that appear to influence the rate of follicular atresia include genetics, age, stage of reproductive cycle, pregnancy, lactation, hypophysectomy (removal of the pituitary), unilateral ovariectomy, exogenous hormones, chemical messengers, nutrition, and ischemia (local obstruction of blood flow) (57). Guraya (57) concludes that even though the basic biochemical or endocrinological aspects of follicular atresia are still unknown, it is apparent that the process of atresia is regulated by the interaction of gonadotrophins and steroids. In particular, the process of atresia appears to be affected by the imperfect balance or lack of these hormones, at least in the mammalian ovary. Elevated estrogen levels (63, 168), intra- and extra-ovarian androgen, prolactin (57), and altered FSH and LH levels (57, 59, 136) all have been implicated in increased rates of follicular atresia. Epidermal growth factor has been implicated recently in oocyte atresia (99).

Observations made at the level of whole individuals suggest underlying biological mechanisms for atresia (74). Similarly, hypotheses developed from an understanding of physiological systems can be tested in survey populations. Atresia begins in the fifth month in utero and continues for 40 or 50 years; therefore, one might expect that longitudinal studies are the best method for studying menopause (69).

**Longitudinal Studies**

The changes of menopause have been approached longitudinally by endocrinologists, epidemiologists, and anthropologists. Sherman & Korenman (142) conducted one of the first studies on hormonal correlations of the menstrual cycle. Fifty complete menstrual cycles in 37 women were examined. Women with regular menstrual cycles were grouped by age: 18–30 (n = 10), 40–41 (n = 5), and 46–51 (n = 6). Endocrine profiles were collected for cycles lasting 20–54 days. The authors demonstrated that FSH levels were increased dramatically throughout the cycle among the women ages 46–51, while LH levels remained indistinguishable from levels in younger women. During the early follicular phase, estradiol levels were the same in women ages 46–51 as among younger women, but the mid-cycle peak and luteal phase concentration
were significantly lower among the older women. Endocrine profiles, menstrual history, and reproductive history were reported for the women studied.

Metcalf et al (112) measured FSH, LH, and estrogens in weekly urine samples from 31 women, ages 36–55, who had recently experienced a change in menstrual cyclicity. Samples were obtained from each woman for 14 to 87 weeks. The hormone patterns observed varied widely. For example, in 14 women, both FSH and LH concentrations rose temporarily to postmenopausal levels in association with high estrogen levels; in 18 women, there was a temporary elevation of LH, but not FSH, into the postmenopausal range. Ovulatory cycles were observed to within 16 weeks of the last menstrual period. Medical, reproductive, and contraceptive information was provided, along with body weight.

Trevoux et al (162) also carried out a longitudinal study that demonstrated wide inter- and intra-individual variation. Their longitudinal study covered 13 years, from 6 years before to 7 years after the last menstrual period (n = 483). From 2 to 7 endometrial biopsies were obtained (n = 388) for comparison and correlation with progesterone, estradiol levels, and menopause status. Information on medical history and HRT use was provided.

In another study, Rannevik et al (132) conducted a prospective 7-year analysis of serum hormone levels in 30 women, ages 48 and 49. Data collection included clinical and biochemical indices of health, height, weight, and use of hormonal supplementation. Also prospectively, Longcope et al (92) followed 88 women, ages 45–58, for 2.5 years. As with the above studies, menstrual characteristics, mean age and weight, general health, and use of hormone replacement were reported.

One of the problems encountered in attempting to bridge physiological and population levels of biological organization is that each level brings its own methodological baggage. For example, hormonal sampling problems include diurnal and menstrual variation in hormone levels, laboratory expense, and the particular disadvantages of sample source, whether it be urine, blood, or saliva. Even so, the inter- and intra-individual variation reported in the above longitudinal endocrine studies raises questions about the impact of biobehavioral variables beyond height, weight, and general health. Biobehavioral variables (e.g. smoking or alcohol intake) have been shown to have hormonal impact (45). Endocrinological investigations should cross boundaries between levels of organization; gather more biobehavioral data when carrying out hormonal assays in large study populations; and compare assay results among women who vary in symptom experience, body shape, body size, and behavior. For example, do smokers have higher levels of FSH at an earlier age in relation to declining inhibin levels caused by oocyte damage?

An example of a population-level longitudinal study is Treloar’s Menstruation and Reproductive History Study, which was initiated in Minnesota in
1934 (140, 159–161, 170). This study was the first to show the variability in cycle length experienced by women immediately prior to menopause (161). Data collected included menstrual, contraceptive, reproductive, and medical history (140). Data on exogenous factors (e.g., smoking), which may have influenced age at menopause, were not included (170). In 1975, questionnaires were mailed to current and previous study participants to collect data on weight at current age and recalled weight at age 18. Analyses demonstrated that women who were heavier at age 18 had a later menopause than did leaner women (140). Sherman et al concluded that “the nutritional factors that influence menopausal age are exerted early in life” (p. 317). However, the investigators did not examine the effect of weight change across the lifespan. Instead of exploiting the dynamic potential of a longitudinal data set, the authors used the data as if they were cross-sectional. Weight change affects the hormonal milieu of the ovary (128) and may thus affect age at menopause and symptom experience.

The dynamic nature of biological change is better illustrated by the New England Research Institute’s longitudinal study (3, 14, 106), which collected demographic data on age, marital status, number of children, smoking habits, medical and menstrual history, symptoms, and use of hormone replacement therapy. Data were collected premenopausally (baseline) and at the first 9-month follow up. Menstrual status was monitored through five years of follow-up of 2570 women (106). Change in variables such as weight or marital status was not monitored (14). The study showed the central role of smoking in influencing age at menopause, and that smokers have not only an earlier menopause, but also an earlier and shorter perimenopause (106). Other longitudinal population surveys include the Manitoba Project on Women and Their Health in the Middle Years (70) and the South-East England Longitudinal Study (62).

To consider only one level of biological organization is to forfeit valuable insight. For example, a negative aspect of focusing on only endocrine relationships is that menopause is construed as pathological, a disruption rather than a natural lifespan change. At the other extreme, considering the symptoms of menopause strictly from the level of the individual or population does not help explain why the symptoms of menopause vary. Bridging these levels of organization may yield meaningful answers to questions raised at all levels.

Symptoms can be studied in association with neuroendocrine changes (80) or clinically through changes in core temperature (i.e., esophageal, rectal, or tympanic membrane) or peripheral temperature (i.e. forehead or fingers and toes) (111, 152). Symptoms can also be examined at the level of populations by checklist (3). For example, Beyene (10) found that among the Mayan Indians of Yucatan, Mexico, menopause occurs at a relatively early age, 41–45, and is not accompanied by hot flashes. In addition, elderly Mayan women
do not typically experience osteoporotic fractures (98). Because of these findings, Martin et al (98) examined Mayan women for endocrinological and bone-density differences. They found that endocrine changes were not significantly different from those reported in the United States. In fact, estrogen levels were at or below levels expected for United States populations. Also, bone demineralization was shown to occur despite the lack of fractures. They conclude that the same endocrine events, menopause and bone loss, can result in different clinical manifestations.

CONCLUSIONS

Getting at the how and why of human variation calls for an understanding of biology at more than one level of organization. For this reason, across different levels of organization, a lifespan approach is ideal for gaining a clearer understanding of the timing of menopause and symptoms of menopause, including bone loss and changing serum lipid levels. The study of menopause, osteoporosis, and heart disease can be used to illustrate how events early in life have later effects, how sociocultural and biological components interact, and how patterns of change may be as important as cross-sectional measures.

The lifespan approach is enhanced by longitudinal research, but it is important to point out that lifespan and longitudinal are not synonymous. The lifespan approach can also inform cross-sectional studies. Questions can be designed to allow for the interweaving of biological and sociocultural trajectories, to encourage an understanding of the effect of change in body size, smoking habits, or activity levels.

In a discussion of demographic and physiologic studies of reproduction, Ellison pointed out that “it is valuable to push both forms of inquiry forward without ceding ascendancy to either, in the expectation of benefiting from the dialectic that emerges” (34:934). This integration of different levels of biological organization has been demonstrated in studies of reproduction (34b; see also 34a). For example, Wood et al combined demographic and endocrinological data to examine low rates of fertility among the Gainj of highland Papua New Guinea (175).

The process of follicular atresia leading to menopause is hidden within layers of physical body. Less tangibly, the consequences of follicular atresia are confounded by cultural expectations with regard to menopause and lifestyle practices. For example, women may not experience symptoms such as hot flashes despite measurable, physiological change (73, 98). Similarly, women may not evidence osteoporotic fractures despite postmenopausal bone loss (98). The biological aspects of menopause have been investigated by teams of researchers who have approached the perimenopausal transition from endocrinological and epidemiological angles. Broader insight may be gained
by integrating the two approaches to consider how follicular atresia is influenced across the lifespan by endocrinological and lifestyle variables. The menopausal transition provides a rich opportunity for researchers to bridge levels of biological organization in holistic and comparative study.

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