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Reproduction and Adaptation

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8 *The evolution of post-reproductive life: adaptationist scenarios*

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Introduction

In adaptationist scenarios, traits are selected for if they are positively correlated with reproductive success (Fisher, 1930; Price, 1970). It seems counter-intuitive, then, that natural selection would select for a dampening, or complete cessation, of reproductive ability before the end of the somatic lifespan. If the production of offspring is a means by which favorable traits can be passed to future generations, then the continued production of offspring – even the costliest of offspring – would seem to be beneficial. Why was there a phylogenetic shift in female reproductive strategy away from continued egg production in fish, amphibians, and reptiles, to a finite number of eggs that slowly dwindles across the lifespan to the point, in some mammalian species, of follicular exhaustion and low levels of ovarian hormones prior to death? In other words, why is there a menopause?

This chapter reviews the evidence for two categories of adaptationist scenarios. In the first, menopause and post-reproductive life are the direct products of natural selection. In the second, menopause and post-reproductive life are the indirect by-products of natural selection for other traits. A similar differentiation between menopause as either adaptation or epiphenomenon has already been made (Peccei, 2001), but the argument presented here takes a slightly different tack by emphasizing the byproduct scenario as also adaptationist. In the byproduct scenarios presented here, mammalian patterns of early oogenesis (egg production) and lifelong atresia (ovarian follicle loss) are the reproductive strategies that underwent positive selection. Negative selection acted to conserve the patterns of oogenesis and atresia among all mammals by selecting against mutations that would bring about change. When coupled with a lengthened lifespan, the byproducts of these conserved strategies are menopause and post-reproductive life. This chapter does not address why lifespans lengthened in species such as humans, killer whales, and short-finned pilot whales (Foote,

2008). Instead, this chapter asks why the ability to produce offspring was not extended to the end of a longer life.

Female menopause and post-reproductive life

Menopause is clinically and epidemiologically defined as the cessation of menses caused by the loss of ovarian follicular activity (WHO, 1996). It is a universal event experienced by all women who live beyond 60 years of age (Sievert, 2006). After menopause, women can spend more than a third of their life in post-reproductive years. Jeanne Louise Calment, who died in 1997 at the age 122, may have spent 72 years in post-reproductive life! It is the potentially great length of post-reproductive life, rather than the event of menopause per se, that is unique to human females.

Not all mammals menstruate, therefore the definition of menopause must be broadened for cross-species comparisons. In a survey of post-reproductive life among 42 mammals, Cohen (2004) defined menopause as “the irreversible loss of the physiological capacity to produce offspring due to intrinsic biological factors” (p. 734). The definition of post-reproductive life can also be broadened to mean the length of life that exceeds one species-specific inter-birth interval plus two standard deviations of inter-birth interval (Cohen, 2004; Pavelka & Fedigan, 1999).

Varying lengths of post-reproductive life have been observed among an assortment of mammals. Western lowland gorillas have a maximum longevity of 52 years but few give birth past the age of 37 (Atsalis & Margulis, 2006). A study carried out among gorillas in American zoos of fecal progesterone concentrations, daily estrus status, and weekly activity patterns demonstrated that, among 22 females aged 32 or older, five (23%) were not cycling (Margulis *et al.*, 2007). Among chimpanzees in the Mahale mountains of Tanzania, 25 middle aged (18–33 years) females were observed until death. Six were post-reproductive for 5 years or longer, with a mean age at death of 40.2 years (Nishida *et al.*, 2003). Among free-ranging Japanese macaques, all females ceased reproduction after age 25 but lived only an average of 2.1 years past their final birth. Only 3% lived to the age of 26 (Pavelka & Fedigan, 1999). East African elephants, with a maximum lifespan of 60 years, are often cited as an example of animals with post-reproductive life; however, age-specific fecundity (the probability of giving birth to a female calf) is still above 15% for females aged 50–54 (Croze *et al.*, 1981). Short-finned pilot whales and killer whales are much better examples of species demonstrating post-reproductive life (Foote, 2008). Short-finned pilot whales demonstrate an average post-reproductive

lifespan of 14 years (Marsh & Kasuya, 1986). Female killer whales have a maximum longevity of at least 80 and perhaps 90 years, but post-reproductive life is estimated to begin at a mean age of 40.1 years (Olesiuk *et al.*, 1990). See Cohen (2004) for more data on post-reproductive lifespan in mammal species.

Menopause is a mammalian trait

In all vertebrates, primordial germ (stem) cells give rise to *oogonia* (undeveloped eggs) through mitosis (Baker, 1986). A single layer of granulosa cells surrounds each oogonium, and meiosis begins in the nucleus of what is now called an *oocyte* (Guraya, 1998). During meiosis, the full complement of genetic material present in the oocyte is halved, but this process does not happen all at once. Meiosis begins in the oocyte and then stops (meiotic arrest) until ovulation occurs (Crisp, 1992). An oocyte encircled by flattened granulosa cells forms a *primordial follicle*. Primordial follicles do not increase in size, but they live the longest – potentially for 50 years or longer depending on the species. According to Rothchild (2003), the common organization of the follicle in all vertebrates “must mean that it was a specific trait of the common ancestor of all vertebrates – and probably of all chordates” (p. 338).

In most mammals, the primordial follicle develops into a primary and then secondary (pre-antral) follicle. A layer of theca cells surrounds the granulosa cells. Development continues as the follicle becomes an antral (vesicular or Graafian) follicle through the proliferation of granulosa cells and a vesicle that fills with follicular fluid (Figure 8.1). The largest antral follicles are called pre-ovulatory follicles.¹ Antral follicles produce the hormones necessary for communication within the hypothalamic–pituitary–ovarian axis (Rajkovic *et al.*, 2006). In mammals, massive numbers of oogonia and follicles in all stages of development are lost through atresia, “the process by which an ovarian follicle loses its integrity and the egg is lost by means other than ovulation” (Crisp, 1992). Guraya (1985) notes that all follicles appear destined to become atretic, but a few are rescued at a critical point in development through “a complicated web of interactions between the oocyte, granulosa cells, thecal cells, pituitary and hypothalamus” (Rajkovic *et al.*, 2006). Only a few oocytes will ovulate (about 400 in humans) and only a few follicles will become corpus lutea (progesterone-producing glands) (Rothchild, 2003).

¹ Follicular growth is somewhat different in monotremes and non-mammalian vertebrates because of the accumulation of yolk within the oocyte (Rothchild, 2003).

Figure 8.1. Follicles in various stages of development (after Peters & McNatty, 1980, p. 15). Phases one, two, and three refer to stages of loss in Figure 8.2.

Mammals and birds produce a single large population of oogonia only once (Figure 8.2).² In birds, oogenesis ends with hatching (Guraya, 1989). In mammals, oogenesis ceases before or just after birth (Peters & McNatty, 1980). Oogonia, oocytes, and follicles in all stages of development are lost through the process of atresia from the prenatal period, through the pre-reproductive and reproductive periods, into the early post-reproductive lifespan. It appears that at least 34 species of mammals experience the complete exhaustion of follicles prior to death (Cohen, 2004). In mammals, humans in particular, the loss of follicles can result in menopause and post-reproductive life. Post-reproductive life is not an avian characteristic (Ricklefs *et al.*, 2003; Ricklefs, 2008).

In contrast to the bird and mammalian pattern, fish, amphibians, and possibly all reptiles have stem cells which persist throughout the female's life. New oogonia can be produced during each breeding season through mitosis. Atresia of oogonia or follicles is less common in fish and amphibians compared to mammals; almost all oogonia may be ovulated as mature oocytes (Habibi & Andreu-Vieyra, 2007; Rothchild, 2003).³

² Cyclostomes (hagfish and lampreys) and elasmobranchs (rays, sharks, and skates) also follow this pattern of egg production. Possible exceptions to this pattern in mammals include some prosimians (Baker, 1986; Byskov & Hoyer, 1988; Comfort, 1979; Greenwald & Terranova, 1988) and mice (Johnson *et al.*, 2004), in which limited oogenesis may continue.

³ Guraya (1986) gives a somewhat different perspective, however, noting that "follicles (or oocytes) in various stages of growth in the fish ovary are lost through atresia during any time of the year" (p. 177). Differences in perspective may result from differences among fish. Some

Figure 8.2. Rise and decline in numbers of oogonia, oocytes, and follicles in human, rhesus macaque, and rat, during the prenatal period, at birth, age 3 (approximate life expectancy for rat and age at menarche for rhesus macaque), age 14 (approximate age at menarche for humans – midway between current and historic estimates), age 25 (approximate age at menopause for macaques), and age 50 (approximate age at menopause for humans). (Counts from Baker, 1986; Hansen *et al.*, 2008; Ryan 1981.)

The timing of menopause is determined by: (1) the number of eggs formed in the female ovary during fetal development; (2) the rate of loss of those eggs across the lifespan through the processes of ovulation and atresia; and (3) the threshold number of follicles needed to maintain reproductive function because, in addition to nurturing the oocyte, follicles produce the ovarian hormones critical to the maintenance of fertile cycles (Sievert, 2006). Menopause is a mammalian characteristic because of the pattern of oogenesis (all at once, just once) and the process of atresia across the lifespan to the point of the exhaustion of follicular reserves.

do not demonstrate much follicle loss through atresia (Thorsen *et al.*, 2006), while others do (Bromley *et al.*, 2000; Murua *et al.*, 2003; Murua and Saborido-Rey, 2003). Also, because fish eggs are yolk-rich, atresia may play a role in resource recovery for fish when environmental conditions become unfavorable, rather than the editing or quality-control role suggested here for mammalian atresia (although see Hardardottir *et al.*, 2003 for a mention of quality control in fish).

Menopause is a female characteristic

The shift in the pattern of oocyte production, from continuous output to a single effort, is female-specific. Whereas very few primary follicles are present in 50-year-old women (Novak, 1970), sperm is found in the ejaculate of 48% of men aged 80–90 (Merry & Holehan, 1994). In other words, reproductive senescence is not a programmed universal in men. While there is a universal decline in levels of estrogen owing to the loss of ovarian follicles in females, the evidence of decline in male testosterone is population- and individual-specific (Bribiescas, 1996; Deslypere & Vermeulen, 1984; Ellison *et al.*, 2002; Korenman *et al.*, 1990; Uchida *et al.*, 2002.) There appears to be a loss of circadian rhythm and blunting of the morning peak in testosterone among men; however, age-related declines in reproduction among males is often related to structural changes in the testis, accessory sexual glands, and penis, rather than decline in gonadal hormones or gametes (reviewed in Bribiescas, 2006; Sievert, 2001). Some males continue to produce sperm to very old ages, therefore only females are able to demonstrate a universal menopause and post-reproductive life.

The evolution of menopause: adaptive scenarios

The process of continuous oogenesis worked well for millions of years in fish, amphibians, and reptiles, and continuous spermatogenesis functions pretty well in mammalian males. Why, then, did the pattern of egg production change so that mammalian females make all of their eggs up front, lose them through the process of atresia, and potentially run out of viable oocytes prior to the end of the somatic lifespan? Many have argued that human menopause and/or post-reproductive life is an adaptation, a direct product of natural selection.

Adaptive scenarios apply Darwinian evolution to explain the appearance or persistence of particular traits. For natural selection to occur, three conditions must be met: (1) variation in the trait of interest among individuals in a population, (2) heritability of the variation, and (3) correlation between the variation and reproductive success (Langdon, 2005). Menopause satisfies each of these three conditions.

First, there is species-level and population-level variation in the length of the reproductive span. Across human populations, mean or median ages at menopause vary by about 10 years, from 42 to 52.6 years (Beyene, 1986; DeLille Henderson *et al.*, 2008; Reynolds & Obermeyer, 2005; Thomas *et al.*, 2001). Part of this variation can be explained by methodological inconsistencies (Sievert & Hautaniemi, 2003); however, application of the same methods also yields meaningful differences in the median age at menopause across

populations. Within populations, there is substantial variation among women in age at menopause. This is phenotypic variation upon which natural selection can act, particularly if premature ovarian failure is included in the continuum (Peccei, 1995). For example, recalled ages at natural menopause range from 36 to 56 years in Asuncion, Paraguay ($n = 132$) and 28 to 56 years in Puebla, Mexico ($n = 268$) (Sievert, 2006).

Second, a number of studies have measured heritability of age at menopause. Estimates of heritability range from 63% among British twins (Snieder *et al.*, 1998), to estimates of 72–87% for Dutch singleton sisters and twins (de Bruin *et al.*, 2001), 31–53% for Australian twins (Treloar *et al.*, 1998), and 40–50% for US mother–daughter pairs (Peccei, 1999).

The third condition, the correlation between the timing of menopause and reproductive success, is harder to measure (Shanley *et al.*, 2007), but has become the subject of five adaptationist scenarios. These scenarios can be summarized as aging eggs, aging mothers, the grandmother hypothesis, energy conservation, and the prevention of reproductive cancers.

Aging eggs

Menopause may have been selected for in order to ensure that old eggs are not fertilized (Hrды, 1999; O'Rourke & Ellison, 1993; Pollard, 1994). As noted above for mammals, oogenesis and the first division of meiosis occur when the female is still a fetus. In humans, pre-ovulatory meiotic arrest can last for 15 to 50 years while oocytes wait in the ovary. This wait time is related to an age-related increase in risk of chromosomal abnormalities (Kohn, 1978; Martin, 2008) and fetal loss (Forbes, 1997; Holman *et al.*, 2000; Wood, 1994). Older oocytes may accumulate injuries “because selection pressure cannot act to maintain vigor of surviving cells in a nongrowing population” and because oocytes can be exposed “within their leaky follicle walls” to damaging toxins (Gosden & Faddy, 1994:271).

Also, as women age, the ovarian reserve declines so that there are fewer primordial follicles to choose from and, thus, an increased risk of chromosomal abnormalities in the oocytes that are selected to develop and ovulate (Freeman *et al.*, 2000; Kline & Levin, 1992; Kline *et al.*, 2000). Menopause may function to prevent the ovulation and fertilization of abnormal oocytes.

Aging mothers

Menopause ensures that mothers are young enough to survive pregnancy, delivery, and the infancy of their offspring (Pollard, 1994; Peccei, 1995; Shanley

et al., 2007). The demands of motherhood are heightened by the extreme altriciality of human infants (Williams, 1957), and, as shown among the Ache foragers of eastern Paraguay, offspring survivorship is low when mothers die in the first 5 years of the child's life (Hill & Hurtado, 1991).⁴

With menopause, women cease childbearing early enough to allow the last child to remain dependent, perhaps for 15 to 16 years (Lancaster & Lancaster, 1983). This adaptationist scenario implies that maternal death, more than paternal death, threatens the survival of the youngest offspring owing to differential parental investment (Gaulin, 1980; Kuhle, 2007).

From a different perspective, menopause protects older women from the demands of pregnancy and childbirth. With increasing age, women are at greater risk of complications from pregnancy (reviewed in Sievert, 2001) which, untreated, would result in death. Using data from pre-industrial Quebec, Pavard *et al.* (2008) explain menopause with models that include an increase in maternal mortality at older ages. However, using data from The Gambia, Shanley *et al.* (2007) concluded that "increasing mortality risk of giving birth at older ages was not sufficient on its own to select for menopause."

The grandmother hypothesis

Many authors have looked beyond aging eggs and aging mothers to the extended family and argued that menopause and post-reproductive aging were selected for by the evolutionary benefits gained through grandmothing (Volland *et al.*, 2005). The general idea is that, during human evolution, females gained more, in terms of inclusive fitness, by investing in their grandchildren than they would have gained by continuing to produce children of their own (Alexander, 1974; Dawkins, 1976; Hamilton, 1966; Williams, 1957). Postmenopausal grandmothers were selected for because they served as reservoirs of knowledge, provided toddler care and attention, produced surplus calories (Hrdy, 1999; O'Connell *et al.*, 1999),⁵ and may have been the first birth attendants when hominins moved from solo to assisted births. Hawkes *et al.* (1997) argue that if a grandmother fed a weaned but still dependent grandchild, then her daughter could have more children more quickly. The fecundity of the daughter benefits the reproductive success of the grandmother.

In a test of the grandmother hypothesis, using data from historic Canadian and Finnish farming communities, Lahdenperä *et al.* (2004) showed that

⁴ However, there is a very low probability of a woman dying within the first 5 years after a birth until she is very old. Shanley *et al.* (2007) found a similarly low probability of being orphaned using 1950–1975 data from The Gambia.

⁵ This is not true among the Ache of Paraguay (Kaplan *et al.*, 2000).

post-reproductive women gained two extra grandchildren for every 10 years that they lived beyond age 50. In Finland, both sons and daughters who had a living, post-menopausal mother had children sooner, at shorter intervals, and more of those children reached adulthood (Lahdenperä *et al.*, 2004). Other studies have also demonstrated an increase in reproductive success among offspring because of grandmothers in historical Tokugawa, Japan (Jamison *et al.*, 2002), rural Gambia (Sear *et al.*, 2000, 2002; Shanley *et al.*, 2007), and historic Germany (Volland & Beise, 2005).

However, some of these same studies have shown that only maternal grandmothers have a positive effect on the survival of grandchildren (Jamison *et al.*, 2002; Volland & Beise, 2002; Volland *et al.*, 2005), whereas paternal grandmothers and grandfathers are associated with an increased risk of infant death. Using data from Atenas, Costa Rica, Madrigal & Meléndez-Obando (2008) showed that the longevity of maternal grandmothers was negatively correlated with number of grandchildren. Among non-human species, Packer *et al.* (1998) found no evidence among lions or baboons for contributions of grandmothers to grandchild fitness. Finally, although a significant proportion of contemporary women in hunting and gathering societies do live beyond menopause (Hawkes, 2007), the lifespan was much shorter for earlier hominins, not just because of infant and child mortality but because of the harshness of everyday life. In this case, the potential for a grandmother effect is unlikely to have had much of an impact.

Energy conservation

Roberta Hall (2004) suggests that high metabolic costs are associated with reproduction, therefore menopause evolved as an opportunity to save energy. Just as menstrual bleeding may save the energy required to maintain an enriched endometrium (Strassman, 1996), menopause may have evolved so that energy spent in menstrual cycling could otherwise be used to support offspring survival.

Prevention of reproductive cancers

Risk factors for breast cancer include early menarche, delayed childbirth, and the low parity patterns characteristic of contemporary Western societies. Each of these factors increases a woman's exposure to periodic elevations in levels of estrogen which, over time, increase the risk of breast cancer (Kelsey *et al.*, 1993; Eaton & Eaton, 1999). Without menopause, women would continue to be exposed to high, cyclic levels of estrogen into the seventh or eighth decades of life. Menopause is, therefore, adaptive within the context of contemporary

industrialized societies because it lowers the risk of breast cancer and other estrogen-dependent cancers which can occur before the end of the fertile period and hence directly reduce reproductive success.

The evolution of menopause: byproduct scenarios

In contrast to the adaptive scenarios reviewed above, menopause can also be understood to be the byproduct of (1) a conserved mammalian pattern of oogenesis and follicular atresia coupled with (2) a lengthened lifespan. This is true not just for humans but for killer whales, short-finned pilot whales, and other mammals as well (Cohen, 2004; Foote, 2008). Instead of focusing on menopause and post-reproductive life as direct products of natural selection, the following adaptationist scenarios use evidence from cross-species studies of ovarian physiology to construct menopause and post-reproductive life as neutral byproducts of natural selection.

In mammals, many more oogonia are produced shortly before, or at the time of birth, than will ever develop and ovulate. Almost all oogonia, oocytes, and follicles are lost through the degenerative process of atresia. The loss occurs in three phases – prior to birth, prior to puberty, and prior to menopause (Figure 8.2). Authors who present log-transformed counts of follicles in relation to age have argued for acceleration in the rate of atresia as menopause approaches (Gosden & Faddy, 1994; Gougeon *et al.*, 1994; Hansen *et al.*, 2008; Richardson *et al.*, 1987); however, when untransformed data are used, as in Figure 8.2, one can see that fewer follicles are lost with age (Leidy *et al.*, 1998). Each phase of oocyte and follicle loss is detailed below. The outcome, or byproduct, of this pattern of oocyte production and loss is the eventual depletion of all viable ovarian follicles in some long-lived species, resulting in menopause and post-reproductive life.

Phase one: the rapid pre- and neonatal decline

As Figure 8.2 illustrates, millions of oogonia are produced by mitosis at the beginning of human female life. Production begins during the eleventh or twelfth week and continues until seven million oogonia and oocytes are present in the ovaries by the fifth month in utero (Baker, 1986; Crisp, 1992). Across species, the peak number of oogonia and oocytes is roughly correlated with the length of the lifespan, e.g. 100,000 in the rat, more than 3 million in the macaque, and 7 million in the human female (Figure 8.2, Baker, 1986). The numbers of oogonia produced are high, not unlike the numbers of oogonia seen

in fishes (Martin, 1985); however, mammalian oocytes are not spawned and oocyte reserves are depleted primarily through atresia, not ovulation. While mammals may appear to have evolved an inefficient pattern of oocyte overproduction and loss, once the reproductive system was in place, the cost of producing many eggs was not much higher than the cost of producing a few (Ghiselin, 1987). Why was there a selection for this pattern of oogenesis and atresia?

In humans, during the fifth month in utero, and for the remainder of the pregnancy, oocytes are lost through atresia at a rate of about 1 million per month (Rothchild, 2003) until the neonate is born with approximately 2 million primordial follicles (Baker, 1986). This pattern, characteristic of all mammals, may have been selected for as a reproductive filtering mechanism (Wasser & Place, 2001) to reduce the number of eggs with developmental errors, such as naked oocytes (oocytes without surrounding granulosa cells, Crisp, 1992) or excessive chromosomal abnormalities (Baker, 1986). During the early phase of oocyte production, the transition from mitosis to meiosis takes place (Rothchild 2003). The first stage of meiosis involves duplicating and halving the number of chromosomes within the oocyte. Crossing over also occurs, which is when chromosomes exchange homologous pieces (Baker, 1986). This exchange increases the risk of chromosomal mutations. During the prenatal period, oogonia that have not become part of a primordial follicle and entered meiosis will die via apoptosis (programmed cell death) (Parker & Schimmer, 2006).

Atresia, the shrinking and loss of early oocytes within small follicles, can be described as an editing function that was selected for as a means to increase the likelihood of producing viable offspring from the primordial follicles that remain (Guraya, 1985). A substantial initial production of oocytes allows for a large margin of error in the establishment of the pool of viable follicles. Except in the case of environmental stress (Habibi & Andreu-Vieyra, 2007), fish and amphibians don't generally "clean" the pool of developing oogonia and primary oocytes (see note 3). But mammals are K-selected creatures by comparison – K-selected species invest more heavily in fewer offspring, and each offspring has a relatively high probability of surviving to adulthood. It makes sense that an animal which ovulates fewer oocytes, and invests more in offspring through lactation, more carefully removes abnormalities early in the process of reproduction.

Phase two: the less rapid postnatal pre-reproductive decline

From birth to the onset of puberty, the loss of follicles in the human ovary slows to a rate of 12,000 per month (Rothchild, 2003) and the female enters puberty with approximately 400,000 follicles (Baker, 1986). Because ovulation does

not occur during childhood, all follicles that enter the growth phase during this period are destined to degenerate (Peters & McNatty, 1980; Rajkovic *et al.*, 2006). Atresia during this phase is not caused by the shrinking of the oocyte, as in phase one, but caused by the degeneration of follicles surrounding the oocyte. More specifically, granulosa cells of most early antral follicles undergo apoptosis, which results in follicle death (Rajkovic *et al.*, 2006). As noted above, atresia can happen during any stage of follicle development (Figure 8.1). Some of this loss may be caused by defects that arise when granulosa cells start to proliferate, or by problems that occur when oocytes start to grow (Rothchild, 2003).

From an adaptationist point of view, pre-pubertal follicular development and loss may be part of a physiological trade-off that benefits early fertility at the expense of later reproductive decline. Waves of developing and degenerating follicles during pre-reproductive life may help to initiate regular cycles. As levels of FSH increase, more follicles reach late antral size and are capable of hormone production. Repetitions of cyclic ovarian follicular growth and atresia may eventually contribute to ovulatory cycles (Vihko & Apter, 1981). Alternatively, atretic follicles can become steroid-producing interstitial tissue in the pre-pubertal ovary. This tissue may contribute to the development and maturation of a dominant follicle, or to ovarian communication with the hypothalamus and pituitary (Baker, 1986; Guraya, 1985).

When a physiological trait has beneficial effects early in the lifespan, but deleterious effects later in the lifespan, this is known as antagonistic pleiotropy (Wood *et al.*, 2001). Waves of follicle development and degeneration may be necessary prior to puberty to prime the hypothalamic-pituitary-ovarian axis, and to ready the female for ovulation during the reproductive period. The cost, however, is a loss of follicles, contributing to the eventual exhaustion of ovarian reserves, menopause, and post-reproductive life in long-lived species.

Phase three: the least rapid decline during the reproductive period

From puberty to menopause, approximately once per month, the human female may ovulate one oocyte. In addition, she will lose follicles through the process of atresia at an average rate of approximately 700 per month across the reproductive span (Rothchild, 2003). The rate of loss varies across species (Peters & McNatty, 1980), but it appears that the follicular depletion rate among chimpanzees is almost identical to that of humans (Jones *et al.*, 2007). During this third phase of follicle loss, as in phase two, the follicles rather than the oocytes degenerate. Although atresia occurs in follicles at all stages of development, it occurs more frequently in the advanced stages of follicular growth (Guraya, 1985; Rolaki *et al.*, 2005). Follicle loss continues until few primary and early

vesicular follicles remain in the postmenopausal ovaries (Mossman & Duke, 1973).

One adaptationist scenario for a process of atresia that depletes ovarian reserves could be described as: many produced to serve a chosen few (Crisp, 1992). An ovarian follicle serves two functions: it can nurture an oocyte to maturity and ovulation, and/or produce the hormones needed for successful reproduction.

During each ovulatory cycle, a group of primordial follicles begins to grow, with as many as 50 reaching a diameter of 1 mm or more in the follicular (early) phase of the cycle. Three or fewer follicles grow to a diameter of 8 mm by midcycle. The follicle destined to ovulate grows to 20 mm in diameter or more (Hunter, 2003). As these follicles mature (Figure 8.1), they produce hormones such as estrogen and inhibin. These hormones help to maintain regular cycles at early adult ages – another example of antagonistic pleiotropy (Wood *et al.*, 2001). The development of many ovarian follicles maintains regular cycles; this is the benefit. However, only one follicle will be rescued from atresia for ovulation, and the loss of non-ovulatory follicles can be viewed as a deleterious trait at later ages when older women run out of the ovarian follicles needed for fertility.

The same hormonal changes that induce ovulation (e.g. the surge in FSH) may also induce atresia among the non-ovulatory follicles (Guraya, 1986), perhaps to prevent the full maturation of too many follicles (Rolaki *et al.*, 2005). Although talking about fish, Guraya (1986) observes that follicular atresia limits the number of eggs that require maternal investment in vitellogenesis (formation of yolk), maturation, and ovulation. In humans, the degeneration of non-ovulatory follicles results in singleton births. In other mammals, the general pattern of oogenesis and atresia can allow for flexibility in litter size in relation to environmental conditions so that, for example, a deer mouse can produce two to eight offspring per litter in any given year. In birds which are determinant layers (who lay a fixed number of eggs) the number of eggs is controlled by either the number of follicles maturing, or by follicular atresia and yolk resorption when the clutch is complete (Sadleir, 1973).

A pool of developing follicles also provides atretic follicles that can contribute interstitial cells to the ovary. These cells may secrete steroid hormones needed for the growth, differentiation, and maturation of normal follicles (Guraya, 1985). Atretic follicles can also be luteinized to produce progesterone (Bysskov, 1979). For example, in the rabbit there is a quantitative relationship between the number of corpora lutea and the ability of the female to retain eggs within the uterus (Adams, 1966). In the African elephant, as many as 40 corpora lutea may be present to help maintain a pregnancy (Hogarth, 1976). In the porcupine, the accessory corpora lutea function exactly as the corpus luteum, growing during early pregnancy and remaining as accessory glands for more than one year (Mossman & Duke, 1973). In humans there is no

physiological evidence that accessory corpora lutea have the same secretory function as the normal glands (Guraya, 1985); however, their presence suggests a conserved pattern of cellular change.

The overarching point of these byproduct scenarios is that if a female produced only the eggs necessary for ovulation, e.g. if the human female produced only 400 eggs, she may not be able to produce as many offspring because (1) some of the eggs would be defective. Humans cull five million oögonia and oocytes prior to birth. (2) There would be no extra follicles to produce hormones during the pre-pubertal period, when waves of developing and degenerating follicles may be necessary to prime the hypothalamic–pituitary–ovarian axis. And (3) there would be no accessory follicles available to produce the hormones necessary to maintain fertile ovulatory cycles. The mammalian pattern of one-time oögenesis and follicle loss is cumbersome, and may not be an improvement over the continuous oögenesis practiced by fish, amphibians, and reptiles, but the system works. In fact, it works well enough to resist changes that would accommodate a longer lifespan with continued reproduction.

Conclusions

When it comes to explaining the evolution of menopause and post-reproductive life, there is more than one adaptationist perspective. Except for the mother and grandmother hypotheses, most of the scenarios described above have not been empirically tested. Most of the scenarios require the appearance of a long lifespan prior to or concurrent with the selection of post-reproductive life. This chapter did not address possible reasons for the evolution of a longer human life. Instead, longevity was accepted as a given in order to focus on ovarian physiology – something that is too often omitted from evolutionary arguments about menopause.

Many researchers argue that human post-reproductive life is so uniquely long that menopause and post-reproductive life should be explained as the direct result of natural selection; however, the processes that result in menopause – limited, one-time oögenesis and the loss of oocytes through atresia – are not human characteristics, but typical of all mammals. The genes regulating apoptosis (programmed cell death) involved in the mechanism of atresia have been well conserved across mammalian species (Rolaki *et al.*, 2005).

Cohen (2004) points out that any hypothesis about the evolution of post-reproductive life must address the physiological processes that are set in motion far earlier in the lifespan than at the point at which reproduction or menstruation ceases. A focus on ovarian physiology does just that. The human (or whale) lifespan lengthened. Why did the ovary not accommodate the change with continued oögenesis or a slower rate of atresia?

One could argue that menopause and post-reproductive life result from a lack of selective pressure to prolong reproduction, even within the context of an extended lifespan. It may be that because the process of atresia is comprised of many sub-traits (Guraya, 1985; Hsueh *et al.*, 1994; Rolaki *et al.*, 2005; Tapanainen & Vasikivuo, 2002), one small change may lead to negative consequences for other sub-traits. There are so many factors involved in the process of atresia, that the alteration of any one factor (e.g. estrogen production, progesterone production, gonadotropin receptors and responsiveness, IGF binding protein expression, cathepsin-D activity, expression of gap junction protein connexin-43, granulosa cell attachment to the basement membrane) may unbalance the system. Rather than positive selection, menopause may be the result of negative selection (Johnson, 2007), which acts to maintain the status quo of follicular atresia even as the lifespan of a species lengthens. The increase in lifespan set the stage for a human menopause and long post-reproductive life because the pattern of oögenesis and atresia did not change.

In summary, natural selection can be applied to explain menopause and post-reproductive life among human females through two categories of adaptationist scenarios. Some argue that menopause and post-reproductive life have been selected for directly. Alternatively, it can be argued that menopause and post-reproductive life are the neutral byproducts of a highly conserved mammalian pattern of oögenesis and atresia, coupled with a lengthened lifespan. In humans, short-finned whales, killer whales, and other mammals, the lengthened lifespan uncovered the exhaustion of female eggs. Menopause and post-reproductive life were the result.

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