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Minireview

Menopause in Nonhuman Primates?[1]

Margaret L. Walker[2] and James G. Herndon[3]

Yerkes National Primate Research Center, Emory University, Atlanta, Georgia 30322

ABSTRACT

A gradual alteration in the mechanisms underlying reproduction and fertility characterizes the aging process in human females. These changes culminate in menopause, conventionally defined as a cessation of menstrual cycles that marks the end of reproductive capacity. In fact, a central and defining event in menopause is the discontinuation of ovulation, which is correlated with a number of structural and functional changes in the reproductive axis. Despite several decades of research, a degree of uncertainty remains as to whether nonhuman primates undergo menopause, and whether they are suitable models of human reproductive senescence. We review some of the controversies that have clouded our understanding of reproductive aging in nonhuman primates, including issues of definition, timing, comparability of data from wild versus captive populations, and cross-species comparisons. The existing data support the view that menopause occurs in a number of primate species and is not unique to humans.

aging, ape, climacteric, evolution, hormones, human, menopause, menstrual cycle, monkey, nonhuman primates, ovary, primate, reproductive senescence

INTRODUCTION

As a natural consequence of aging, human females gradually lose the ability to reproduce. This loss in fertility is signaled by a disruption in the normal cyclicity of menstrual periods and eventually the complete cessation of ovulation and menstrual bleeding. The functional and structural changes in the hypothalamic-pituitary-ovarian axis that underlie menopause have been the subject of considerable research [1–4]. For example, in an early study of hormonal changes across the human life span, Sherman and Korenman [5] reported that as females age, intermenstrual intervals increase, a phenomenon thought to result directly from lower serum estradiol (E_2) levels and elevated follicle-stimulating hormone (FSH) concentrations. In addition to endocrine changes, the senescent ovary shrinks in size [6, 7], undergoes vascular changes [8, 9], decreases the rate of folliculogenesis [10], reorganizes morphologically [6], and increases androgen output [11–13]. These alterations in reproductive parameters have been linked to other markers of aging, including diminished bone density [14–16], cognition [17–21], and cardiovascular health [22, 23]. The physiological and behavioral consequences of aging, particularly in postmenopausal females, are far reaching and significant, and as a result, much effort has been devoted to achieving a better understanding of the menopausal process.

Because of their biological similarities to humans, nonhuman primates have been studied in an attempt to find a suitable model for menopause. One impediment to this research has been a paucity of normal aged primates for study. In addition, uncertainties about the life span of various primate species, definitions used to establish the markers of reproductive aging, measurements used to verify menopause, the comparability of data derived from captive versus free-ranging animals, as well as the similarities and differences among species, have hindered progress in our understanding of the biological mechanisms underlying reproductive senescence in primates. The resulting confusion has led to several assertions that menopause is uniquely human [24–26]. Here, we attempt to dispel some of the uncertainties surrounding the comparative analysis of menopause in primates by examining the commonalities and differences in established markers of menopause among primate species. We conclude that menopause is not unique to humans.

DEFINITION OF MENOPAUSE

Perhaps the most salient source of misunderstanding in comparative studies is the definition of menopause, which originated to describe obvious changes that occur in humans. The Oxford English Dictionary defines menopause as the "permanent cessation of menstruation; the period of a woman's life when this occurs..." [27]. This definition draws heavily from the historical characterization of menopause almost exclusively in terms of the termination of menstruation (e.g., "12 months of amenorrhea following the final menstrual period" [28]). From a physiological perspective, however, menopause can be defined as "the cessation of ovarian steroid hormone secretion as a result of the depletion of oocytes and surrounding follicular apparatus" [29]. By the first two definitions, only those species that menstruate—that is, exhibit cyclic vaginal discharge of blood—can experience menopause. The third definition, however, emphasizes the pivotal role of ovarian changes in the termination of reproductive viability, of which the discontinuation of menstruation is only one component. We agree with vom Saal and Finch [30] that an "underlying and unifying framework" for understanding

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[2]Correspondence: Margaret L. Walker, Yerkes National Primate Research Center, Emory University, 954 Gatewood Rd. N.E., Atlanta, GA 30322. FAX: 404 727 1266; e-mail: mlwalke@emory.edu
[3]Correspondence: James G. Herndon, Yerkes National Primate Research Center, Emory University, 954 Gatewood Rd. N.E., Atlanta, GA 30322. FAX: 404 727 1266; e-mail: jim@rmy.emory.edu

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TABLE 1. Average (mean) life span (LS), maximum LS, average age at menopausal onset, and proportion of life spent in a nonreproductive state as a function of currently known average or maximum life spans in a variety of primate species.

Species	Average LS (yr)	Maximum LS (yr)	Menopause onset (yr)	Nonreproductive state	
				Average LS (%)	Maximum LS (%)
Homo sapiens	80[a]	122[b]	50[c]	38	59
Pan spp.	40[d]	60[e]	35–50?[f]	0–8.8	16.7–42
Gorilla gorilla	35[g]	50[h]	40?[i]	0	20
Pongo spp.	30[j]	53[k]	?	0	?
Papio spp.	30[l]	45[m]	26[n]	13	42
Macaca spp.	25[o]	40[p]	25[q]	0	38

[a–q] Reference number: [a][44]; [b][45]; [c][35]; [d][46]; [e][46]; [f][47–49]; [g][50]; [h][50]; [i][51]; [j][52]; [k][53]; [l][54]; [m][55]; [n][56]; [o][42]; [p][57]; [q][40].

female reproductive senescence is needed, and argue that a rigorous definition of menopause, focusing on its essential physiological features, will permit a more meaningful comparison of reproductive senescence across species.

Menstrual bleeding is an easily observable marker of the underlying ovarian and neuroendocrine phenomena that govern reproductive viability in humans (see vom Saal and Finch [30]). However, not all primates exhibit regular patterns of menstrual bleeding [31, 32], and menstruation is only one of many relevant biological events that define reproductive potential. A definition of menopause that encompasses hormonal changes and their anatomical substrates as key determinants of the age-associated loss of fertility provides a more fundamental view of reproductive senescence, inasmuch as studies of primates strongly suggest that ovarian exhaustion is central to this process [30]. The decline of ovarian function is not the only cause of hormonal change, however, and there is evidence in women that other age-associated neuroendocrine alterations may occur independently of ovarian influences [2]. Since not all primates menstruate, and because menstruation is only one facet of the complex physiological mechanism that governs reproductive cyclicity, we believe that a meaningful comparative analysis of female reproductive senescence should focus on the anatomical, physiological and biochemical changes that are essential to the cessation of ovarian cyclicity, regardless of whether menstrual bleeding is present. For these reasons, in the following comparative analysis, we define menopause in primates as the permanent, nonpathologic, age-associated cessation of ovulation. To infer this event, a variety of biological parameters, such as menstrual bleeding, perineal swelling, follicular depletion, and hormonal changes, can be useful. However, it should be emphasized that a change in any *one* of these phenomena cannot be considered an exclusionary criterion for the underlying physiological event.

TIMING OF MENOPAUSE IN THE LIFE SPAN

An important issue regarding comparative research on menopause involves the timing of menopause relative to average (mean) and maximum life span. Humans may be unique among primates in that the females have a long postreproductive survival potential [33]. The mean age at menopause for humans is approximately 50 yr [34–36]; if we consider that the maximum life span for humans is about 122 yr, a human female could spend nearly 60% of her life in a postreproductive state. This issue arises in the debate over whether nonhuman primates experience menopause, and if so, when this event occurs relative to death; one of the prevailing arguments against accepting nonhuman primates as models for human menopause emphasizes this very point [37]. For example, rhesus monkeys (*Macaca mulatta*) cease menstruating at approximately 25 yr of age [38–41]. In captivity, the known maximum life span of rhesus monkeys is around 40 yr [42, 43]. Hence, at most, about 40% of the maximum life span of rhesus monkeys is postreproductive.

It can be difficult to compare life span across species due to differences in living environments, medical care, etc., but another potentially useful measure of longevity is the average life span (usually the mean or median life expectancy). Table 1 depicts current estimates of average (mean) and maximum life span for humans and a selection of nonhuman primates, as well as the approximate age of menopause and the proportion of the average and maximum life spans spent in a nonreproductive state. Species differences in these biological markers are evident, even among the great apes. A schematic representation of interspecies variability in key reproductive parameters is depicted in Figure 1. This diagram underscores the relatively small proportion of the known life span during which humans are reproductively viable compared with either chimpanzees or macaques. These cross-species comparisons provide a conceptual framework for understanding the timing of reproductive senescence in primates, and they support the view that humans have a uniquely extended postmenopausal life expectancy. Postreproductive survival, however, is a separate issue from the existence of menopause per se, as we discuss below in the section on operational definitions.

The timing of the transition into menopause, known as perimenopause, also is highly variable in human females. Age at onset of perimenopause in humans ranges from the mid-30s to the early 50s [12, 35, 61–64]. This wide variability in timing has hindered efforts to understand the mechanisms that control the onset of menopause in humans. In nonhuman primates, the difficulties may be even more pronounced, since reproductive cessation occurs so late in the life span that relatively few

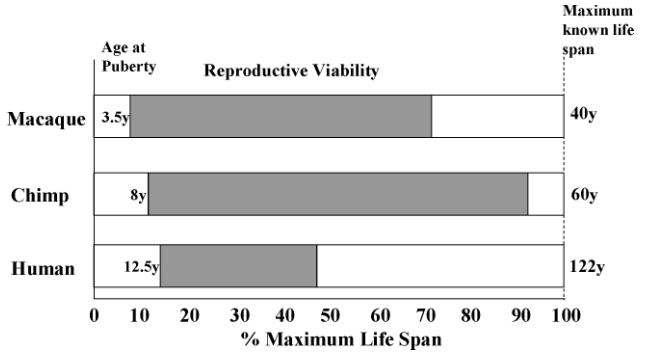

FIG. 1. Reproductive life span in female macaques (*Macaca* spp.), chimpanzees (*Pan troglodytes*), and humans (*Homo sapiens*) depicting approximate ages at puberty, menopause, and maximum life span. The following numbers were used: macaque: 3.5 yr [58], 25 yr [42], 40 yr [57]; chimpanzee: 8 yr [59], 50 yr [47], 60 yr [50]; and human: 12.5 yr [60], 80 yr [44], 122 yr [45].

TABLE 2. Criterion-based operational definitions and dependent variables used to establish the existence of menopause.

Dependent variable	Reference no.
Reduced fertility	[78–80]
Reduced follicle number	[10, 81–85]
Cessation of live births	[78, 79, 86, 87]
Irregular cycles	[12, 49, 51, 65, 88]
Increased cycle length	[47–49, 56]
Species-typical patterns of reproductive senescence > general aging trajectory resulting in post-reproductive life stage	[74]
Age at last live birth	[74]
Interbirth interval (IBI)	[53, 78, 87, 89, 90]
Time lag between last parturition & death (>2 SD of mean life IBI)	[78, 91]
Cycles/year	[48]
Decreased urinary estrone	[41]
Decreased urinary pregnanediol-3-glucuonide	[41, 61]
Decreased serum progesterone	[66, 88, 92]
Decreased fecal progestogens	[51, 93]
Cessation of menses	[38, 40, 41, 47, 56, 79, 80, 94, 95]
Ovarian depletion	[40, 82, 84]
Increased serum/urinary FSH	[47, 65, 66, 88, 95–97]
Reduced fecundity	[71, 86, 87, 90]
Decreased perineal turgescence	[49, 56, 71]
Decreased primordial follicles	[82, 83, 92, 97, 98]
Decreased serum/urinary estrogens	[40, 66, 88, 95–97]
Increased serum/urinary LH	[40, 47, 66, 88, 95]
Decreased IGF1	[99]
Decreased GH	[99]
Paracallosal skin changes	[90]
Vaginal health	[94]
Decreased inhibin B	[66]
Decreased antimullerian hormone	[66]
Increased response to GnRH challenge	[99]
Reversed FSH:LH ratio	[47]
Increased ovarian fibrous tissue	[10]
Duration of effective breeding	[73]
Increased GnRH concentration and decreased/unchanged pulsatile frequency	[2, 100]
Decreased follicular phase length	[5, 62]
Decreased bone mass	[12, 101]
Cessation of sexual behavior	[79, 93]
Increased skeletal turnover	[101]
More than two successive years without a birth	[96]

animals live to ages approaching the maximum. Despite these obstacles, burgeoning data support the existence of a perimenopausal state in nonhuman primates [37, 40, 41, 65, 66], a condition which, by definition, indicates a transitional stage between fertility and age-associated infertility.

ASSESSING MENOPAUSE IN WILD VERSUS CAPTIVE ANIMALS

The comparability of data derived from wild versus captive animals is a recurrent issue in studies of nonhuman primates [67]. Although important demographic, behavioral, and anthropological information has emerged from field studies of free-ranging nonhuman primates, data dealing with specific physiological mechanisms that govern the timing of menopause in the wild are understandably scarce. Anecdotal evidence suggests the existence of menopause in wild primates [68–71], but the difficulty in obtaining definitive data under the challenging conditions imposed by naturalistic observation diminishes the impact of these reports. Uncertainty about the subjects' ages (which are often estimated [53]) and the effects of predation pressures [72], limited survivability [73, 74], infant mortality [75], food availability and nutrition [76], and social dynamics [77] are a few of the factors that might compromise the investigation of menopause in free-ranging primates. Because of these constraints, field observations of menopause in nonhuman primates are perhaps best viewed as an important, but limited, complement to data derived from captive animals.

OPERATIONAL DEFINITIONS OF MENOPAUSE FOR COMPARATIVE ANALYSIS

Perhaps much of the misunderstanding of reproductive senescence in nonhuman primates results from the broad array of operational definitions for menopause (see Table 2 for a list of criterion-based operational definitions). While each of the parameters measured has merit as a potential marker of reproductive senescence, a piecemeal approach to defining menopause can often lead to contradictory claims, as illustrated by research on captive chimpanzees. For example, Gould et al. [47] measured urinary and serum hormones for 1 mo, menstrual cycle length and perineal swelling for 12 mo, the effects of a single GnRH challenge, and the status of ovarian follicles in two common chimpanzees (*Pan troglodytes*) and one bonobo (*Pan paniscus*) to provide the earliest evidence of menopause in these species. Graham et al. [81] documented reproductive capacity in chimpanzees throughout life using conception rate, cycle frequency, and cycle length, based on perineal swelling. These studies conclude that chimpanzees do not undergo menopause until around the age of 50 yr. More recently, however, Videan and colleagues [49] measured serum luteinizing hormone (LH), FSH, and E_2, sampled biannually, as well as cycle length and perineal swelling, in 14 common chimpanzees ranging in age from 31 to 50 yr. The authors reported the cessation of perineal swelling in the oldest animals (>44 yr) as well as endocrine profiles similar to those in postmenopausal human females. They conclude that menopause occurs at 35–40 yr of age in chimpanzees. When menstrual cycle length, inferred from perineal swelling and menstrual bleeding, is used exclusively as the dependent variable for defining menopause in chimpanzees, however, Lacreuse and colleagues found little evidence for full menopause in chimpanzees in their 30s, 40s, and 50s, except in one female who continued to cycle until 57 yr of age, 2 yr prior to her death [48].

This definitional dilemma was recently illustrated in a study that dichotomized reproductive aging in chimpanzees using separate but interrelated phenomena: reproductive senescence, defined on the basis of "reduced reproductive performance," and menopause, defined as "species typical patterns of reproductive senescence that significantly exceed the general aging trajectory and result in a postreproductive life stage" [74], thus emphasizing the timing of menopause in the life span as a defining feature, rather than the physiological changes that characterize menopause itself. This somewhat unorthodox definition allows the researchers to suggest that menopause is a singularly human phenomenon.

All of these studies provide important information on reproductive aging in chimpanzees, but the use of different criteria and dependent variables leaves the question open: do chimpanzees experience menopause, and if so, when? If one adopts the view that reproductive aging is a process and not a singular event, then perhaps the apparently discrepant findings from chimpanzees can be understood more clearly. Falling birth rates [81, 102], follicular depletion [81, 82], and increased anovulatory cycles [71] certainly bespeak a system in decline. With a more comprehensive approach to characterizing reproductive senescence in chimpanzees, one might be convinced that their reproductive system is indeed undergoing

changes that parallel those seen in humans. Rather than dismissing chimpanzees as "poorly suited" [37] models for human menopause, or concluding that chimpanzees fail to exhibit menopause altogether [74, 78, 103], it may be more advantageous to refine and focus our definition of menopause in order to deepen our understanding of age-related changes in reproductive function.

Table 2 depicts many useful criteria for establishing the presence of menopause, although most are by no means definitive. For example, cycle irregularity could foretell the onset of menopause, but it could also result from social, pathologic, or environmental factors that influence the reproductive system independent of aging. The same could be said for hormonal correlates of menopause (e.g., growth hormone [GH], inhibin, insulinlike growth factor 1, etc.), because these endocrine indices may describe a correlate of the menopausal state without providing irrefutable documentation of menopause per se. What is evident from Table 2 is that many criteria are available for examining menopause, and some have more merit than others.

ACROSS-SPECIES COMPARISONS OF MENOPAUSAL SIGNS

With the rapid expansion of the aged human population, interest in the mechanisms underlying reproductive senescence has grown rapidly, along with a concomitant evolution in opinion regarding menopause in nonhuman primates. Originally, menopause was considered to be a uniquely human phenomenon, as there was little scientific support for the existence of menopause in other primates [24, 104]. However, as record keeping and research tools improved, evidence began to mount that menopause does, in fact, occur in a number of nonhuman primate species (see below), and that these animals can be useful for expanding our understanding of the mechanisms underlying menopause in humans.

Great Apes

*Chimpanzees (*Pan *spp.).* Some of the earliest work on reproductive senescence in the great apes was that of Gould and colleagues [47] in three chimpanzees (two *P. troglodytes* [48 and 50 yr] and one *P. paniscus* [>40 yr]). This study reported similar menopausal signs in chimpanzees and in humans, particularly with regard to gonadotropin levels, FSH:LH ratios, and ovarian histology. In more recent work on a larger number of subjects, Lacreuse and colleagues [48] showed that many aged chimpanzees (*P. troglodytes*) continue to menstruate into their 50s. These workers also reported that cycle length in female chimpanzees increased from the age of 20 yr onward. Increasing cycle length with age has also been noted by Videan et al. [49], who supplemented this observation with hormonal data from biannual samples. They concluded that menopause occurs in this species at approximately 35–40 yr of age, a finding that concurs with data from wild chimpanzees in which 28% were found to cease cycling after the age of 30 [71].

Another analysis of chimpanzees in the wild, however, found that healthy chimpanzees remain reproductively viable well past the age of 40 yr [74]. The authors suggest that menopause occurs as a byproduct of ill health in this population. This conclusion was drawn from observations of a truncated (i.e., mortality-selected) distribution of wild chimpanzees, as the rate of survivability to 40 yr of age was only 7%. It should not be surprising that females who survive in the wild (or even in captivity) to advanced age are reproductively robust. Perhaps long-lived animals represent extraordinary females who manifest behavioral and constitutional traits that enhance health and survivability. In such females, a continuation of reproductive function, albeit at a diminished level, might simply be considered a marker for overall good health. This observation does not necessarily undermine the contention that female chimpanzees undergo menopause, but rather suggests that the onset of menopause may simply be delayed in relatively healthy, long-lived animals. In fact, chimpanzees show a number of other similarities to humans in terms of reproductive aging; both species show an increase in fetal loss as a function of advancing age [102, 105, 106], and the age-related depletion of ovarian follicles follows a remarkably similar trajectory in chimpanzees and humans [82]. Although some specifics regarding the precise timing of menopause-associated events remain uncertain, it seems clear that reproductive aging is remarkably similar in female chimpanzees and humans.

*Orangutans (*Pongo *spp.).* Data on menopause from other great apes are much scarcer. Early reports from captive orangutans documented the endocrine characteristics of the menstrual cycle and illustrated similarities to the human cycle [107]. However, this work did not extend to an evaluation of aged females. An analysis of archival data examining live births and interbirth intervals across the life span showed a significant age-specific decline in fertility in captive orangutans (*Pongo pygmaeus*) [78]. Research on wild Sumatran orangutans (*Pongo abelii*) failed to document menopause, as inferred from increased interbirth intervals in animals whose ages were estimated [53]. However, data from wild animals are difficult to interpret because of countervailing factors, such as female rank, infant mortality, uncertain age, and ecological issues such as food availability. Rather than assuming that this species represents a "decoupling of reproductive and somatic aging" [69], it may be more pragmatic to focus on improving measurement techniques and methodologies used to assess menopause in the wild.

*Gorillas (*Gorilla gorilla*).* Relatively little is known about reproductive senescence in female gorillas (*Gorilla gorilla*). Early work described the reproductive physiology of this species, correlating perineal tumescence with circulating hormones and reporting a pattern of cyclic hormone secretion similar to that in humans [108]. Cycle length (28–38 days) and urinary FSH levels also have been established in gorillas [109], with the authors concluding that this species provides a suitable model for human reproduction. More recently, fecal hormone determinations in two captive female gorillas (>40 yr old) revealed protracted luteal phases (as indicated by progestogen peaks and cyclic irregularities) typical of aging human females [51, 93]. An age-related decline in fertility was reported in wild mountain gorillas from the Virunga Volcano area in central Africa, although no evidence of a period of protracted postreproductivity in these females was found [89]. The paucity of data on gorillas and other great apes underscores the need for further research on reproductive senescence in this group of closely related species.

*Baboons (*Papio *spp.).* Baboons have been studied extensively with regard to reproductive physiology because they are similar to humans in both menstrual cycle characteristics [56, 110, 111] and pregnancy [112–114]. Data regarding the occurrence of menopause in baboons (*Papio* spp.), however, are relatively meager. Based on menstrual cycle length (inferred from perineal turgescence), increased cyclic variation begins at approximately 19 yr of age, whereas total cessation of cycling occurs at ~26 yr in captive baboons [56]. This finding supports an earlier report of menopause occurring in the mid-20s in this species [115]. Data from a wild troop of baboons confirm this

conclusion, as inferred from age-related reductions in fecundity and increases in interbirth intervals [90]. Additional studies of wild baboons have reported increased cyclic variability with age and a complete loss of fertility by the age of 25 yr [116]. Thus, there is reasonably compelling evidence that baboons undergo age-linked alterations in reproductive function that are similar to those in humans.

Macaques

*Rhesus monkeys (*Macaca mulatta*).* Reproductive senescence has been more thoroughly characterized in rhesus monkeys (*Macaca mulatta*) than in any other species of nonhuman primate. An early study of two captive rhesus monkeys found evidence of menopause, based on menstrual bleeding, in females older than 25 yr of age [38, 39]. Hodgen et al. [88] extended this observation with supporting endocrine data. They reported that a subset of animals older than 22 yr exhibited elevated gonadotropin concentrations and basal progesterone (P_4) and E_2 concentrations characteristic of human menopause. However, these original studies are difficult to interpret, because rhesus monkeys breed seasonally, and in controlled laboratory environments they exhibit natural anovulatory cycles that could be mistaken for menopause [117–120]. Furthermore, in a laboratory environment during the summer months, ovulatory cycles with abnormal luteal phases can occur [121, 122]. Summer corresponds to the nonbreeding season in outdoor-housed animals that are exposed to seasonal variations in daylight [123–127]. Because of seasonal variations in endocrine and menstrual parameters, it can be difficult to distinguish seasonal acyclicity and amenorrhea from reproductive senescence in captive females. This concern was addressed in two studies [40, 41] that documented menopause in female rhesus monkeys. Based on menstrual bleeding and serum E_2 and LH levels analyzed over a 12-mo period, as well as ovarian histology, Walker [40] found evidence for menopause in six females ranging from 26 to 34 yr of age. This finding was corroborated by Gilardi et al. [41] in a group of 20- to 29-yr-old females using menstrual data and urinary steroid hormone levels. In this study, 13 animals with a mean age of 24 yr were considered to be perimenopausal, and two animals with a mean age of 29.5 yr were fully menopausal [37]. Shideler et al. [65] also examined the interaction of seasonality and aging by focusing on endocrine parameters. They confirmed earlier findings regarding the approximate age range for menopause, and reported a monotonic pattern of FSH secretion in these females. In addition, the anovulatory cycles characteristic of the nonbreeding season were found to immediately presage the onset of menopause. These observations were supported recently by Downs and Urbanski [66], who found that age-related changes in plasma FSH levels forecast menopause (no episodes of menses for $\geq$12 mo). Postmenopausal females showed diminished levels of circulating E_2 and P_4 and elevated FSH and LH. They further reported significant declines in anti-Mullerian hormone and inhibin B in postmenopausal females when compared to younger animals [66], indicating that these endocrine parameters may reflect changes in ovarian dynamics associated with menopause.

Few data from free-ranging rhesus monkeys exist. One exception is a study of provisioned, free-ranging monkeys by Johnson and Kapsalis that factored survivability into the assessment of the likelihood of reaching menopause [79]. The authors reported a median age of menopause $>$27 yr, but in a manner similar to Emery Thompson et al. [74], they concluded that reproductive senescence was highly correlated with general overall health. Perhaps in wild female primates, age-related declines in overall health may preclude the reliable observation of true menopause in many animals.

Studies of the neuroendocrine axis also reveal changes associated with somatic aging. Gore and colleagues [100] examined four aged rhesus monkeys (age range, 26.9–30.6 yr) that were implanted with intracranial push-pull cannulae for the measurement of pulsatile GnRH concentrations. The researchers found that aged animals continue to secrete GnRH in a pulsatile fashion, although absolute levels of this hormone are higher than in younger females. Similarly, whereas circulating levels of GH and GH pulse amplitude decline with age in monkeys, pituitary responsiveness to GHRH and GHRP-2 (GH-releasing peptide 2) is similar in young and aged monkeys [99]. Pulsatile LH release, however, is significantly higher in aged females, as is pulse amplitude [99]. These studies support the view that neuroendocrine changes in senescent monkeys are consistent with those found in humans [128–131].

Ovarian changes underlying menopause in rhesus females also have been characterized [40, 84, 97]. For example, gonadotropin stimulation produces significantly fewer oocytes in older (age range, 16–26 yr) rhesus monkeys, a finding reported earlier in humans [132]. When evaluated over much of the life span (from ages 1 to 25 yr), ovarian morphology changes substantially, with increasing evidence of atretic follicles and fewer primordial follicles in aged animals [84]. These studies indicate that rhesus monkeys undergo ovarian changes as a function of aging that are similar to those seen in humans [133, 134] and chimpanzees [82].

*Pigtail macaques (*Macaca nemestrina*).* Few data exist describing the relationship between aging and reproduction in pigtail macaques (*Macaca nemestrina*). Two studies of ovarian changes concur that there is a decline in folliculogenesis with age. Graham et al. [81] examined ovaries from this species and reported a reduction in developing follicles after the age of 20 yr, and Miller et al. [83] extended this work by reporting a bilateral, linear decrease in primordial follicles up to the age of 12.5 yr (the oldest age analyzed). Observations from archival data show an age-associated decline in fertility, and in one group, 26% of the females ceased reproductive activity prior to death [78]. Whereas no endocrine data are available to clarify the mechanisms underlying these changes, it seems evident that pigtail macaques undergo a process of reproductive senescence consistent with menopause.

*Japanese macaques (*Macaca fuscata*).* Both captive and free-ranging Japanese macaques (*Macaca fuscata*) experience reproductive decline and a period of infertility prior to death as well. Studies of free-ranging animals indicate that fertility rates diminish with age, and that by the age of 25 yr, females cease to reproduce [135–137]. Some captive females have been found to maintain normal menstrual cycles (based on periodic menses) despite loss of fertility [98], a finding similar to that in humans [138]. This decline in fertility may result from a suboptimal uterine or hormonal environment, fetal chromosomal abnormalities, or simply less sexual behavior. Luteinizing hormone levels are higher in aged females [98], and an E_2 challenge elicits an LH surge, suggesting that this neuroendocrine mechanism is intact, as is the case in humans [139]. The ovaries of aged *Macaca fuscata* also show evidence of decline, as judged by increased sclerosis and abnormal follicles [98]. Although Pavelka and Fedigan [91] concluded that reproductive termination in Japanese macaques does not model human menopause, they used a nonclinical definition for the cessation of reproduction based on a strict classification using the time lag between last parturition and death. They conclude that "reproductive termination" is a certainty by the age of 25 yr in

Japanese macaques, but are reluctant to call this "menopause" because of its timing in the life span of the animal. As discussed above, this concern begs the issue by focusing on the timing of the event within the life span rather than the underlying physiological process of menopause per se. The key point is that the similarities in reproductive senescence in humans and Japanese macaques greatly exceed the differences.

*Barbary macaques (*Macaca sylvanus*).* Data from the Barbary macaque (*Macaca sylvanus*), though sparse, parallel those from other macaque species. Paul et al. [87] reported an age-related decline in fertility and an increase in interbirth interval, concluding that reproduction in *Macaca sylvanus* terminates at appropriately 25 yr of age. The authors indicate that a postreproductive period of greater than 5 yr is not uncommon in the Barbary macaque.

*Other macaques (*Macaca *spp.).* Studies from other species of the genus *Macaca* generally confirm that senescent macaque females experience a period of waning fertility and cessation of ovulation characteristic of menopause. As summarized in Paul et al. [87], despite individual variability, the postreproductive life span of macaque females can range up to 8 yr. These authors cite the observations of reduced fertility in crab-eating macaques (*Macaca fascicularis* [140]), bonnet macaques (*Macaca radiata* [141]), and toque macaques (*Macaca sinica* [142]). A recent analysis of *Macaca fascicularis* [96] substantiated earlier observations in this species by demonstrating a postmenopausal neuroendocrine pattern similar to that in humans (elevated FSH and androgens, diminished estrogens).

*Tamarins (*Saguinus *spp.)*

Little research has examined aging and reproduction in New World primates. Two subspecies of tamarins (*Saguinus oedipus* and *S. fuscicollis*) were found to experience reduced fertility at approximately 17 yr of age, based on plasma and urinary hormone measurements [92]. However, ovarian histology of older females suggests that large luteal masses continue to process steroids, despite the absence of normal folliculogenesis. This phenomenon would distinguish these animals from Old World primates and humans, although further research on reproductive senescence in New World primates is clearly needed.

CONCLUSIONS

Menopause is a naturally occurring process in which the permanent cessation of ovulation is associated with a variety of physiological and structural changes in aging female primates. One obstacle to the acceptance of nonhuman primates as models of human menopause has been the tendency to focus on differences rather than commonalities. For example, it is apparent that the onset of reproductive decline occurs relatively later in the life span of nonhuman primates than of humans, resulting in a more protracted postreproductive period in humans [33, 143, 144]. Although postreproductive survival is important from an evolutionary standpoint, menopause is fundamentally a physiological process, and a gradual decline and eventual cessation of female reproductive capacity, based on a host of criteria, appears to be a consistent feature of aging in every primate species that has been examined.

We draw the following conclusions:

1. The multitude of definitions for menopause has contributed to a general confusion about its occurrence among nonhuman primate species. A uniform definition would facilitate our understanding of the way in which menopause reflects species-specific patterns of reproductive senescence.
2. We define menopause in primates as the permanent, nonpathlogic, age-associated cessation of ovulation. Menopause is associated with concomitant structural and functional changes, including (in species that exhibit menstrual bleeding) the termination of menstruation.
3. Whereas humans have a uniquely extended postmenopausal life expectancy, other primate species do experience a postreproductive period. The length of this period is not necessarily related to the existence of menopause per se.
4. Many of the apparent discrepancies in reports regarding the occurrence of menopause in nonhuman primates may be accounted for by environmental and social factors that distinguish captive versus wild animals, and by a paucity of data from sufficiently powered studies.
5. By almost any generally accepted definition, several species of nonhuman primates experience menopause.

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