Chapter 13

c0013 Hormones and Reproductive Cycles in Primates

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p0010 **SUMMARY**

p0015 Primates are characterized by long lifespans, slow reproductive processes, and low fecundity. Gonadarche is a late and prolonged process in which the maturation of the hypothalamic-pituitary-gonadal (HPG) axis is followed by a period of 'adolescent infertility.' Ovarian cycles are prolonged, with spontaneous ovulation of one ovum (or several ova, in some species) followed by a spontaneous luteal phase supporting development of the uterine endometrium. Following conception, in the anthropoid primates (monkeys, apes, and humans) an invasive hemochorial placenta supports a prolonged gestation and offers the opportunity for placental endocrine signals to be transmitted directly to the maternal blood. Mothers produce dilute milk over long periods, supporting slow postnatal growth rates. Lactation induces anovulation in most primates through a process linked to the suckling stimulus. Seasonal, energetic, and social factors can all influence the course of puberty, conception, pregnancy, and, to a lesser extent, lactation. Primates experience a long reproductive life, typically with age-related reductions in female fertility and in male androgen production. As much as 25% of the female's maximal lifespan may be postreproductive, with reproductive senescence driven primarily by loss of the follicular pool.

s0010 1. OVERVIEW OF THE PRIMATES

p0020 The order Primates includes roughly 230 extant species in two suborders: the Strepsirhini, comprising the lemurs, lorises, galagos, and pottos (also referred to as prosimians, along with tarsiers); and the Haplorhini, comprising the tarsiers, Platyrrhini (New World monkeys), Cercopithecoidea (Old World monkeys), Hylobatidae (lesser apes; i.e., gibbons and siamangs), and Hominidae (humans and great apes; i.e., orangutans, gorillas, chimpanzees, and bonobos) (Bininda-Emonds et al., 2007; Hartwig, 2007) (Figure 13.1). Primates exhibit tremendous diversity in body size, ranging from the 30 to 60 g mouse lemurs (*Microcebus* spp.) (Yoder et al., 2000) to the roughly 200 kg gorillas (*Gorilla gorilla*) (Smith & Jungers, 1997), and in longevity, ranging from approximately nine years in several prosimians to roughly 60 years in great apes and over 120 years in humans (Anage: The Animal Ageing and Longevity Database, 2009). They occupy a diversity of habitats, from tropical forests to savannas to semideserts, and exhibit a variety of lifestyles, from arboreal to terrestrial, from diurnal to nocturnal, and from largely dispersed and solitary to highly gregarious. Nonetheless, primates as a group are characterized by long lifespans, delayed reproductive maturation, low fecundity, and high investment in each offspring (Zimmermann & Radespiel, 2007).

p0025 In this chapter, we summarize current perspectives on and understanding of reproductive function in human and nonhuman primates, including regarding the hypothalamus-pituitary-gonad (HPG) axis function across the lifespan; pregnancy and lactation; sexual behavior and its hormonal underpinnings; and seasonal, social, and energetic influences on reproduction. Descriptive data on reproductive patterns are available for several hundred primate species and subspecies studied in the wild and/or in captivity (Zimmermann & Radespiel, 2007). In contrast, experimental investigations of reproductive physiology have focused largely on humans and a small number of monkey species, especially the Old World macaques (*Macaca* spp.) and baboons (*Papio* spp.), and the New World squirrel monkeys (*Saimiri* spp.) and marmosets (*Callithrix* spp.). By necessity, we focus largely on the best-studied taxa; however, we also attempt to highlight the diversity among primates (Table 13.1).

2. TESTICULAR FUNCTION AND ITS NEUROENDOCRINE CONTROL s0015

p0030 As in other mammals, the two major functions of the testes — spermatogenesis and androgen production — take place in anatomically and functionally distinct testicular compartments. Spermatogenesis occurs within the seminiferous

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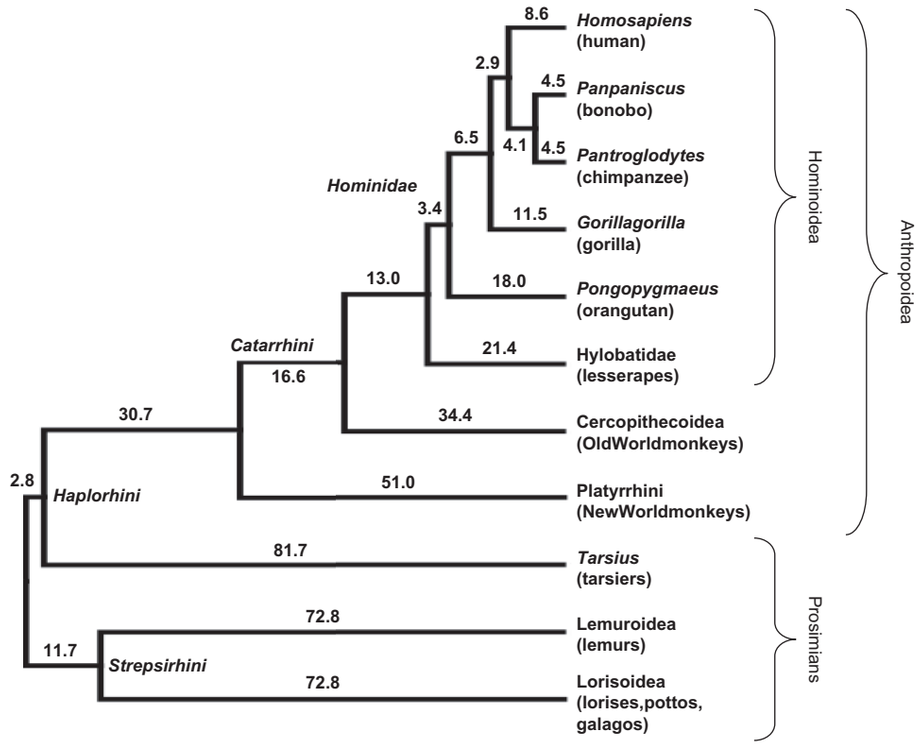


f0010 **FIGURE 13.1** Cladogram showing the major extant primate taxa, with branch lengths in millions of years. Based on Bininda-Emonds et al. (2007).

tubules, whereas androgen production occurs primarily in the Leydig cells of the testicular interstitium. Both processes are controlled by the HPG axis. Therefore, we begin by briefly reviewing this endocrine axis and its control of androgen secretion, and then discuss spermatogenesis and its hormonal control.

s0020 2.1. The Hypothalamic-pituitary-gonadal (HPG) Axis and Androgen Secretion in Males

p0035 In both sexes, gametogenesis and gonadal steroid secretion are ultimately regulated by gonadotropin-releasing hormone (GnRH), a decapeptide synthesized in neuronal cell bodies in the arcuate nucleus of the medial basal hypothalamus and released into the hypothalamic-hypophysial portal blood vessels in a pulsatile manner (see Chapter 2, this volume). The cellular and molecular mechanisms responsible for the generation of GnRH pulses are not yet understood, but appear to involve endogenous oscillations within the GnRH neurons themselves (Terasawa, 2001; Zeleznik & Pohl, 2006; see also Chapter 2, this volume). Stimulatory inputs to the GnRH pulse generator in primates include kisspeptin (Kp), norepinephrine, glutamate, neuropeptide Y (NPY), and nitric oxide, while inhibitory inputs include endogenous opiates, γ-aminobutyric acid (GABA), and corticotropin-releasing hormone (CRH) (Terasawa, 2001; Zeleznik & Pohl, 2006; Plant & Ramaswamy, 2009).

p0040 At the anterior pituitary, GnRH binds to gonadotropes to stimulate synthesis and secretion of two glycoprotein hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). A notable exception to this pattern occurs in at least some New World monkeys (common marmoset (*Callithrix jacchus*), Bolivian squirrel monkey (*Saimiri boliviensis*), Ma's owl monkey (*Aotus nancymaee*)), in which the pituitary secretes chorionic gonadotropin (CG) instead of LH. Correspondingly, the gonads in some or all New World monkeys express a modified form of the LH receptor, in which exon 10 is not expressed and is activated selectively by CG (Gromoll et al., 2003; Müller et al., 2004a; 2004b; Scammell, Funkhouser, Moyer, Gibson, & Willis, 2008). AQ2

p0045 The major function of LH in males is the stimulation of androgen release by the Leydig cells. Correspondingly, testosterone (T) is an important regulator of LH secretion, exerting negative feedback to reduce the frequency of LH and presumably GnRH pulses (reviewed by Tilbrook & Clarke, 2001). Testosterone-mediated feedback in primates is thought to occur primarily at the level of the brain, rather than the pituitary. The neuroanatomical substrates of this feedback, however, are not yet known. Gonadotropin-releasing

hormone neurons in mammals do not appear to contain receptors for androgens, estrogens, or progesterone (P_4); thus, feedback by these steroids must be mediated by other cell populations. To date, the endogenous opiates, GABA, and Kp have all been implicated as possible mediators of androgenic feedback on GnRH in rhesus macaques (*Macaca mulatta*) (El Majdoubi, Ramaswamy, Sahu, & Plant, 2000; Shibata, Friedman, Ramaswamy, & Plant, 2007). Intracellular aromatization of T to estradiol (E_2) within the brain also has been implicated in the feedback regulation of the HPG axis in male primates, as in other mammals; however, studies have yielded inconsistent results (Tilbrook & Clarke, 2001).

p0050 In contrast to LH, the major functions of FSH in males involve development of the gonads, especially production of Leydig cells, and regulation of spermatogenesis, the latter being mediated through actions on Sertoli cells (see AQ3 Section X). Follicle-stimulating hormone also differs from LH in the hypothalamic and gonadal mechanisms regulating its secretion (Plant & Marshall, 2001). Whereas LH release is highly sensitive to GnRH pulse frequency, FSH release is not, so that changes in GnRH pulse frequency alter the ratio of circulating FSH to LH (Zeleznik & Pohl, 2006). The occurrence of a separate, selective hypothalamic FSH-releasing factor has been postulated but has not been confirmed, and seems unlikely to play a significant role in primates (Zeleznik & Pohl, 2006). Moreover, the inhibitory effects of T on FSH secretion, apparently mediated through aromatization to E_2, are less pronounced than those controlling LH release. Instead, the major testicular hormones controlling FSH secretion are inhibin B and activins, glycoprotein hormones produced by the Sertoli cells that inhibit and stimulate, respectively, pituitary release of FSH (McLachlan et al., 2002b).

s0025 2.2. Spermatogenesis

p0055 Spermatogenesis comprises three major processes: mitotic proliferation, which maintains the population of stem cell spermatogonia and produces differentiated spermatogonia and primary spermatocytes; meiotic division, in which each diploid primary spermatocyte gives rise to two secondary spermatocytes and, subsequently, to four haploid sperm, involving development of head and tail structures; and spermiation, or release of sperm into the lumen of the seminiferous tubules (Johnson & Everitt, 2000; Plant & Marshall, 2001; McLachlan et al., 2002b; see also Chapter 5, this volume) (Figure 13.2). In most respects, these processes are similar in all mammals; however, some noteworthy differences have been found between primates and nonprimates as well as among primate species.

p0060 Spermatogonia are classified as either type A (undifferentiated, including stem cell spermatogonia and proliferative spermatogonia) and type B (differentiated spermatogonia). In primates, but not rodents, type A spermatogonia are further divided into two morphologically distinct subtypes: A-pale, which undergo mitotic divisions to produce new type A and type B spermatogonia, and A-dark, which are thought to constitute a pool of reserves that begin to proliferate only under conditions of testicular damage (McLachlan et al., 2002b; Luetjens, Weinbauer, & Wistuba, 2005) (Figure 13.2).

p0065 Beginning at puberty, A-pale spermatogonia, occupying the basal compartment of the seminiferous tubules, undergo a limited number of mitotic divisions to yield type A as well as type B daughter cells. Subsequently, type B spermatogonia undergo one or more mitotic divisions to yield primary spermatocytes. The number of mitotic divisions at each stage differs reliably among species. The duration of the spermatogenic cycle (i.e., the time between consecutive spermatogonial divisions to produce spermatocytes in a single section of seminiferous tubule) in New World and Old World monkeys averages approximately 10 days, with longer cycles reported in chimpanzees (*Pan troglodytes*) (14.4 days) and humans (16 days) (Luetjens et al., 2005).

p0070 As in other taxa, spermatogenesis in primates is governed largely by the Sertoli cells, the only somatic cells present in the seminiferous tubules (Sofikitis et al., 2008). Functions of these cells include forming the blood−testis barrier, maintaining the cytoarchitecture of the germinal epithelium, producing nutrients that provide energy for the germ cells, regulating FSH secretion via secretion of inhibins and activins, and mediating androgenic effects on spermatogenesis through expression of androgen receptors and production of androgen-binding protein.

p0075 In rodents, each cross section of seminiferous tubule contains germ cells in only a single stage of spermatogenesis. A similar pattern is found in prosimian primates. Among great apes and humans, however, most tubular cross sections contain germ cells in multiple stages of spermatogenesis. Monkeys show intermediate patterns, but the proportion of so-called multi-stage tubules is higher in New World than Old World monkeys (Wistuba et al., 2003). The functional significance of these differences, if any, is not clear. Spermatogenic efficiency, defined as the absolute number of germ cells produced relative to the theoretical number, does not appear to vary markedly across primate species or to differ between species with single-stage vs. multi-stage tubules, although efficiency is lower in numerous primate species than in the rat (*Rattus norvegicus*) (Luetjens et al., 2005).

p0080 In rats, FSH and T play critical roles in regulating spermatogenesis, acting both separately and synergistically. Among primates, the relative roles of these two hormones are less clear but differ to some extent from those in rodents (reviewed by McLachlan et al., 2002a; 2002b; Luetjens et al., 2005; Sofikitis et al., 2008).

t0010 **TABLE 13.1 Reproductive and life-history parameters for representative primate species**

	Adrenarche	Age at sexual maturity — males (days)	Age at sexual maturity — females (days)	Ovarian cycle length (days)	Menstruation	Birth seasonality*	Female age at first parturition (years)
Strepsirhini							
Microcebus murinus *(gray mouse lemur)*		243[1]	243[1]	50.5[23]	Absent/covert[9]	Strong[18]	0.67[28]
Daubentonia madagascariensis *(aye-aye)*			882[1]	49.8[23]	Absent/covert[9]	Absent[18]	3.5[28]
Lemur catta *(ring-tailed lemur)*		912[1]	595[1]	39.3[23]	Absent/covert[9]	Strong[18]	2.13[28]
Eulemur fulvus (brown lemur)		548[1]	608[1]	29.5[23]	Absent/covert[9]	Strong[18]	2.41[28]
Varecia variegata (ruffed lemur)		608[1]	604[1]	30[2]	Absent/covert[9]	Strong[4]	2.0[28]
Propithecus verreauxi (Verreaux's sifaka)		912[1]	912[1]		Absent/covert[9]		3.5[28]
Otolemur crassicaudatus (thick-tailed greater galago)		639[1]	495[1]	44.0[23]	Absent/covert[9]	Strong[24]	2.17[28]
Perodicticus potto (Western potto)		547[1]	547[1]	37.9[23]	Absent/covert[9]	Weak[24]	2.03[28]
Tarsius							
Tarsius bancanus (Western tarsier)			920[1]	24.0[23]	Absent/covert[9]	Strong[19]	2.52[28]
Platyrrhini							
Callimico goeldii (Goeldi's monkey)		395[1]	365[1]	23.8[23]	Absent/covert[23]	Weak; possibly bimodal[13]	1.32[28]
Callithrix jacchus (common marmoset)	Absent[29]	382[1]	477[1]	28.6[23]	Absent/covert[9]	Weak; bimodal[13]	1.44[28]
Callithrix pygmaea (pygmy marmoset)		638[1]	684[1]	33.3[33]	Absent/covert[23]	Weak; bimodal[13]	1.88[28]
Saguinus oedpius (cotton-top tamarin)		550[1]	548[1]	22.7[23]	Absent/covert[23]	Weak[13]	1.89[28]
Leontopithecus rosalia (golden lion tamarin)		730[1]	547[1]	18.5[23]	Absent/covert[23]	Weak; sometimes bimodal [13]	2.40[28]
Saimiri sciureus(common squirrel monkey)		1,826[1]	1,003[1]	9.1[23]	Absent/covert[9]	Strong[20]	2.5[28]
Cebus apella(brown capuchin)			1,703[1]	20.0[23]	Slight[9]	Weak[20]	5.64[28]
Alouatta caraya (black howler monkey)		928[1]	1,167[1]	20.4[23]		None/weak[14]	3.71[28]
Lagothrix lagotricha (Humboldt's woolly monkey)		1,520[1]	2,555[1]	25[2]	Slight[9]	Weak[13]	6.29[28]
Ateles geoffroyi (Geoffroyi's spider monkey)		1,826[1]	1,825[1]	25.5[23]	Slight[9]	Weak[14]	6.0[28]
Brachyteles arachnoides (muriqui)			2,738[1]	21.0[23]		Weak[7]	7.5[28]
Callicebus moloch (dusky titi)			912[1]	17[12]	Absent/covert[12]	Weak[12]	3[28]
Pithecia pithecia(white-faced saki)		1,460[1]	775[1]	16-17[25]		Weak[25]	2.08[28]
Aotus trivirgatus (northern night monkey)		730[1]	821[1]	15.6[23]	Absent/covert[9]	Weak[13]	2.40[28]

Gestation length (days)	Interbirth interval (months)	Modal litter size	Age at weaning (days)	Maximum recorded lifespan in captivity (years)	% of lifespan completed at time of last birth‡	Mean body mass – wild adult females (g)	Placentation
							Superficial, epitheliochorial, villous[3]
60[28]	3[28]	2[28]	40[28]	18.2[1]		63[28]	
167[28]	20[28]	1[28]	268[28]	23.3[1]		2,531[28]	
135[28]	14[28]	1[28]	142[28]	37.3[1]	76.7% (C) (*Lemur spp.*)[17]	2,250[28]	
120[28]	24[28]	1[28]	159[28]	35.5[1]		2,228[28]	
139[28]	12[28]	2[28]	90[28]	36[1]		3407[28]	
140[28]	12[28]	1[28]	180[28]	30.5[1]		3,285[28]	
135[28]	12[28]	2[28]	135[28]	22.7[1]		1,110[28]	
195[28]	12[28]	1[28]	150[28]	26.8[1]		836[28]	
							Superficial, epitheliochorial, villous[3]
178[28]	8[28]	1[2]	79[28]	16.3[1]		109[28]	
							Superficial, hemochorial, trabecular[3]
153[28]	9[28]	1[28]	68[28]	22.2[1]		355[28]	
148[28]	6[28]	2[28]	76[28]	22.8[1]	61.7% (C)[17]	334[28]	
137[28]	6[28]	2[28]	90[28]	18.6[1]		101[28]	
168[28]	7[28]	2[28]	50[28]	26.2[1]		404[28]	
129[28]	6[28]	2[28]	90[28]	31.6[1]	48.6% (C)[17]	579[28]	
170[28]	9[28]	1[28]	197[28]	30.2[1]	90.5% (C)[17]	681[28]	
154[28]	22[28]	1[28]	263[28]	46[1]		2,361[28]	
187[28]	11[1]	1[28]	325[28]	32.4[1]		4,606[28]	
224[28]	24[28]	1[28]	411[28]	32[1]		6,303[28]	
227[28]	37[28]	1[28]	786[28]	47.1[1]		7,480[28]	
233[28]	34[28]	1[28]	747[28]	30 (unconfirmed)[1]		8,070[28]	
164[28]	12[28]	1[28]	60[28]	26.2[1]		956[28]	
164[28]	19[28]	1[28]	122[1]	36[1]		1,580[28]	
133[28]	9[28]	1[28]	127[28]	30.1[1]		730[28]	

(*Continued*)

TABLE 13.1 Reproductive and life-history parameters for representative primate species—cont'd

	Adrenarche	Age at sexual maturity — males (days)	Age at sexual maturity — females (days)	Ovarian cycle length (days)	Menstruation	Birth seasonality*	Female age at first parturition (years)
Cercopithecoidea							
Semnopithecus entellus (Hanuman langur)		1,886[1]	1,162[1]	26.8[23]	Overt[9]	Absent/weak[6]	3.66[28]
Pygathrix nemaeus (red-shanked douc langur)			1,460[1]				
Nasalis larvatus (proboscis monkey)			1,460[1]			Weak[22]	4.5[28]
Colobus guereza (guereza)		2,192[1]	1,461[1]			Absent[16]	4.75[28]
Macaca mulatta (rhesus macaque)	Absent[29]	2,007[1]	1,231[1]	26.6[23]	Overt[9]	Strong[27]	3.75[28]
Macaca fascicularis (long-tailed macaque)	Absent[29]	1,544[1]	1,238[1]	29.4[23]	Overt[9]	Weak[27]	3.9[28]
Macaca arctoides (stump-tailed macaque)		2,099[1]	1,186[1]	29[2]	Slight[9]	Absent[27]	3.84[28]
Macaca fuscata (Japanese macaque)		1,369[1]	1,483[1]	28[2]	Overt[9]	Strong[27]	5.54[28]
Macaca nemestrina (pig-tailed macaque)		1,095[1]	1,125[1]		Slight[9]	Weak[27]	3.92[28]
Papio anubis (olive baboon)		973[2]		33.2[23]	Overt[9]	Absent[21]	4.5[28]
Papio hamadryas (hamadryas baboon)	Absent[29]	1,762[1]	1,514[1]	30[8]	Overt[9]	Weak[5]	6.1[28]
Mandrillus sphinx (mandrill)			1,186[1]	39.6[23]		Weak[21]	4[28]
Theropithecus gelada (gelada baboon)		2,190[1]	1,391[1]	35.5[23]	Slight[9]	Weak[5]	4[28]
Cercocebus torquatus (white-collared mangabey)			973[1]	33[2]	Slight[9]	Weak[21]	4.67[28]
Chlorocebus aethiops (vervet)		1,825[1]	1,034[1]	33[23](median)	Slight[9]	Weak[15]	4.88[28]
Cercopithecus neglectus (De Brazza's monkey)		2,555[1]	1,611[1]			Weak[15]	4.67[28]
Erythrocebus patas(patas monkey)		1,400[1]	956[1]	30.6[23]	Overt[9]	Weak[15]	3[28]
Miopithecus talapoin (Angolan talapoin)		2,008[1]	1,395[1]	36[2]	Overt[9]	Weak[15]	4.38[28]
Hominoidea							
Hylobates lar (white-handed gibbon)		1,825[1]	2,555[1]	20.2[23]	Overt[9]	Weak[30]	8.00[28]
Hylobates syndactylus (siamang)		2,190[1]	2,190[1]				7.09[28]
Pongo pygmaeus (orangutan)		2,555[1]	2,555[1]	29.6[23]	Slight[9]		10.65[28]
Gorilla gorilla (gorilla)		4,015[1]	2,829[1]	31.1[23]	Slight[9]	Absent[11]	8.1[28]
Pan paniscus (bonobo)			3,194[1]	42[31]		Weak[10]	13-15[28]

Gestation length (days)	Interbirth interval (months)	Modal litter size	Age at weaning (days)	Maximum recorded lifespan in captivity (years)	% of lifespan completed at time of last birth‡	Mean body mass – wild adult females (g)	Placentation
							Interstitial, hemochorial, villous[3]
192[28]	17[28]	1[28]	354[28]	29[1]	94.1% (FP)[17]	10,470[28]	
210[28]	20[28]	1[28]	330[1]	26[1]		8,180[28]	
166[28]	18[28]	1[28]	246[28]	25.1[1]		9,593[28]	
170[28]	20[28]	1[28]	371[28]	35[1]		8,401[28]	
165[28]	12[28]	1[28]	279[28]	40[1]	66.7% (C)[17], 73.5% (SF)[17]	6,890[28]	
164[28]	13[28]	1[28]	375[28]	39[1]		3,582[28]	
178[28]	19[28]	1[28]	393[28]	29.2[1]		8,400[28]	
173[28]	24[28]	1[28]	453[28]	38.5[1]	67.3% (FP)[17]	8,565[28]	
169[28]	14[28]	1[28]	300[28]	37.6[1]	69.2%(C)[17]	5,657[28]	
180[28]	25[28]	1[28]	592[28]	25.2[28]	92.6% (FP)[17]	13,233[28]	
170[28]	24[28]	1[28]	561[28]	37.5[1]		10,568[28]	
198[28]	17[28]	1[28]	349[28]	40[1]		12,125[28]	
170[28]	24[28]	1[28]	465[28]	36[1]		11,427[28]	
171[28]	13[28]	1[28]		46[1]		5,500[28]	
163[28]	12[28]	1[28]	262[28]	30.8[1]	66.9% (C)[17]	3,020[28]	
167[28]	12[28]	1[28]	393[28]	30.8[1]		3,816[28]	
167[28]	12[28]	1[28]	234[28]	28.3[1]		6,409[28]	
164[28]	12[28]	1[28]	188[28]	27.7[1]		1,560[28]	
							Interstitial, hemochorial, villous[3]
209[28]	30[28]	1[28]	639[28]	56[1]		5,403[28]	
232[28]	50[28]	1[28]	639[28]	43[1]		10,568[28]	
250[28]	72[28]	1[28]	1,273[28]	59[1]	68.1% (C)[17]	36,389[28]	
273[28]	47[28]	1[28]	1,061[28]	55.4[1]	51.9% (C)[17]	80,000[28]	
240[28]	48[28]	1[28]	1,080[28]	55[1]		33,200[28]	

(*Continued*)

TABLE 13.1 Reproductive and life-history parameters for representative primate species—cont'd

	Adrenarche	Age at sexual maturity — males (days)	Age at sexual maturity — females (days)	Ovarian cycle length (days)	Menstruation	Birth seasonality*	Female age at first parturition (years)
Pan troglodytes (chimpanzee)	Present[29]	2,920[1]	3,376[1]	37.3[23]	Overt[9]	Weak[26]	13.6[28]
Homo sapiens (human)	Present[29]	5,110[1]	4,745[1]	29.1[23]	Overt[9]	Weak[32]	14.5[28]

[1]*Data from: AnAge, The Animal Ageing and Longevity Database (http://genomics.senescence.info/species/);*
[2]*Harvey et al., 1987;*
[3]*Mossman, 1987;*
[4]*Richard, 1987;*
[5]*Stammbach, 1987;*
[6]*Struhsaker, 1987;*
[7]*Strier and Ziegler, 1994;*
[8]*Rowe, 1996;*
[9]*Strassmann, 1996;*
[10]*Furuichi* et al., *1998;*
[11]*Watts, 1998;*
[12]*Valeggia* et al., *1999;*
[13]*Di Bitetti and Janson, 2000;*
[14]*Di Fiore and Campbell, 2007;*
[15]*Enstam and Isbell, 2007;*
[16]*Fashing, 2007;*
[17]*Fedigan and Pavelka, 2007;*
[18]*Gould and Sauther, 2007;*
[19]*Gursky, 2007;*

Follicle-stimulating hormone appears to be necessary for proliferation of A-pale spermatogonia, transition of A-pale to B spermatogonia, and spermiation. T, on the other hand, is thought to stimulate late spermatid differentiation, whereas both T and FSH may play roles in suppressing apoptosis in germ cells and in regulating meiotic divisions by spermatocytes. Other hormones that have been implicated in modulating spermatogenesis in primates include LH, insulin, inhibin, activin, follistatin, somatostatin, and estrogens (Sofikitis et al., 2008).

s0030 3. OVARIAN FUNCTION AND ITS NEUROENDOCRINE CONTROL

s0035 3.1. Overview

p0085 Ovarian cycles in primates, like those in other mammals, comprise (1) a preovulatory (follicular) phase, characterized by follicular maturation, increasing follicular secretion of estrogens, and generally low circulating levels of gonadotropins (GTHs); (2) ovulation, precipitated by midcycle surges in estrogens and GTH secretion; and (3) a postovulatory (luteal) phase, dominated by formation of a corpus luteum (or, in some species, several corpora lutea) from the ovulated follicle(s), luteal production of P_4 (and estrogens), and low pituitary GTH levels (Figure 13.3) (see also Chapter 4, this volume). In all primate species studied to date, but in contrast to numerous other mammals, follicular development, ovulation, and corpus luteum formation occur spontaneously, independent of mating-induced stimuli (Martin, 2007). Primates also tend to have extended ovarian cycles as compared to other mammals, with especially prolonged luteal phases (Johnson & Everitt, 2000). Nonetheless, overall cycle length and duration of the follicular and luteal phases differ markedly among primates. Average cycle lengths tend to range from 30 to 50 days in prosimians, 16 to 30 days in New World monkeys, 24 to 35 days in Old World monkeys, 20 to 30 days in lesser apes, and 25 to 50 days in great apes, including humans (Van Horn & Eaton, 1979; Dixson, 1998; Martin, 2007; Emery Thompson, 2009; Ziegler, Strier, & Van Belle, 2009) (Table 13.1). The New World squirrel monkeys (*Saimiri* spp.), however, have a mean cycle length of seven to twelve days, with a follicular phase of only about five days (Dukelow, 1985).

p0090 As described below, menstruation occurs to some extent in all or most Old World monkeys and apes, and in several New World monkeys (Strassmann, 1996); thus, these species may be said to have a true menstrual cycle. Other species, most notably prosimians, may be considered to have an estrous cycle, as they exhibit distinct cyclical changes in sexual receptivity, with peak receptivity occurring during the periovulatory period (see Section 8). Finally, many New World monkeys exhibit neither

Gestation length (days)	Interbirth interval (months)	Modal litter size	Age at weaning (days)	Maximum recorded lifespan in captivity (years)	% of lifespan completed at time of last birth‡	Mean body mass – wild adult females (g)	Placentation
238[28]	60[28]	1[28]	1,691[28]	59.4[1]	60.0% (C), 80.0% (FP) [17]	31,850[28]	
269[28]	36[28]	1[28]	830[28]	122.5[1]	41.7-50.0%[17]	53,733[28]	

[19]*Gursky, 2007;*
[20]*Jack, 2007;*
[21]*Jolly, 2007;*
[22]*Kirkpatrick, 2007;*
[23]*Martin, 2007;*
[24]*Nekaris and Bearder, 2007;*
[25]*N07 = Norconk, 2007.*
[26]*Stumpf, 2007;*
[27]*Thierry, 2007;*
[28]*Zimmermann and Radespiel, 2007 (if >1 value was provided for a species, the mean of all values for the species was used);*
[29]*Nguyen and Conley, 2008;*
[30]*Savini* et al., *2008;*
[31]*Emery Thompson, 2009;*
[32]*Vitzthum* et al., *2009;*
[33]*Ziegler et al., 2009.*
**Strong: highly predictable and relatively short breeding and birth periods; evidence of altered gonadal function in non-breeding season. Weak: breeding and birth period peaks are seen, but births can occur in any month. Absent: limited or no evidence of breeding or birth peaks.*
‡*C: captive breeding colonies. FP: free-ranging and provisioned. SF: semi-free-ranging and provisioned*

menstruation nor strict estrous cyclicity. For consistency, therefore, we refer simply to 'ovarian cycles' in all female primates.

p0095 Dynamics of primate ovarian cycles, like many other aspects of reproductive physiology, have been characterized most thoroughly in macaques and women. Therefore, the following review focuses primarily on data from these species. We begin by summarizing the cyclical events occurring in the ovary. We then describe cyclical changes in the uterus and other tissues, and finally discuss the neuroendocrine control of primate ovarian cycles.

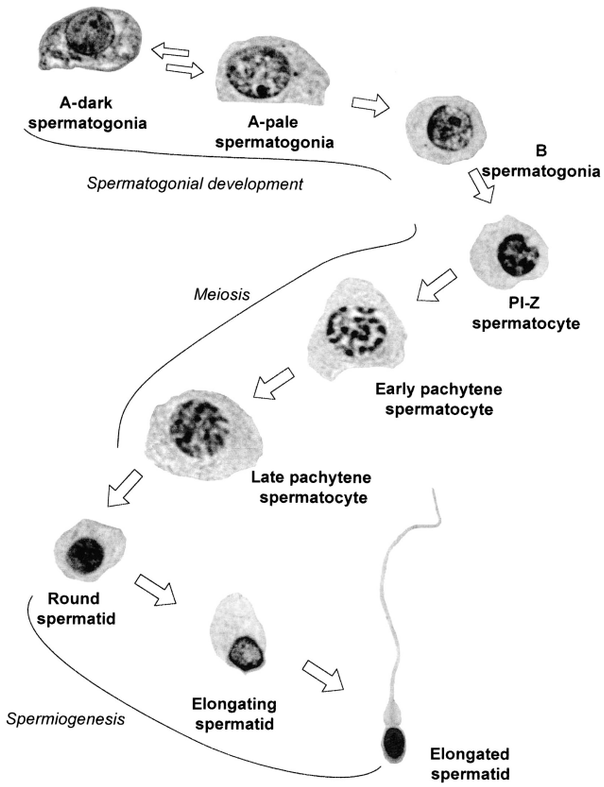
s0040 3.2. Cyclical Changes in the Ovaries

s0045 *3.2.1. Folliculogenesis*

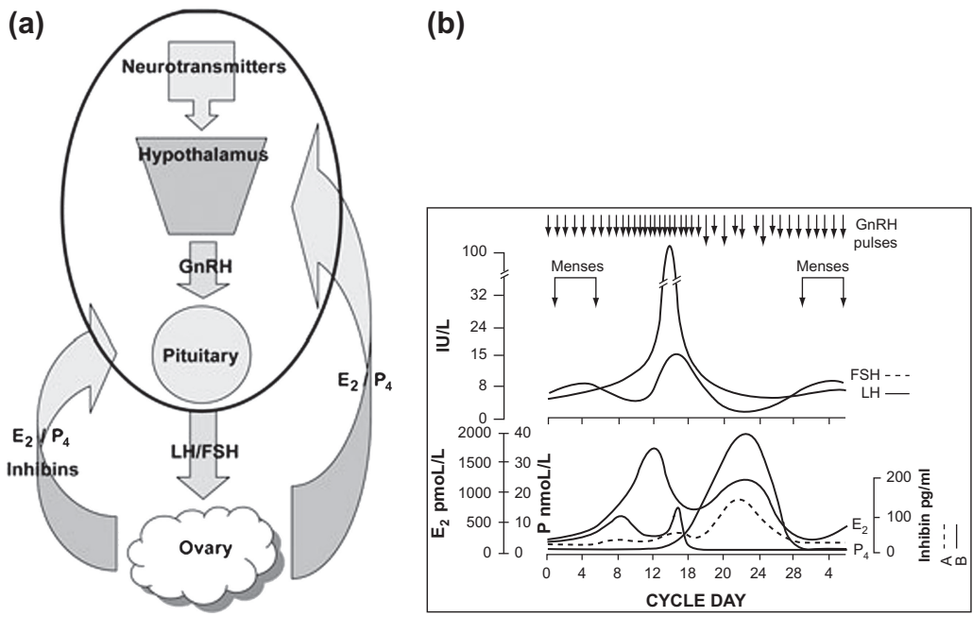
p0100 As in other mammals, primate oogonial germ cells terminate mitotic division and enter their first meiotic division during prenatal development. The resulting primary oocytes become encased in primordial follicles, each consisting of a single layer of spindle-shaped granulosa cells, and abruptly suspend meiosis at the diplotene stage of the first meiotic prophase. Primordial follicles may remain in this state of suspended animation for years or even decades, until they initiate further development to the early antral stage (Johnson & Everitt, 2000).

p0105 Development of primordial follicles into early antral follicles involves growth of the oocyte, formation of a zona pellucida, and growth and proliferation of granulosa cells, followed by formation of the antral cavity and development of the thecal cell layer. This phase of follicular development, which is thought to last approximately 85 days in humans (Gougein, 1986), may occur to a small extent prepubertally (Zeleznik & Pohl, 2006). Beginning at puberty, however, several primordial follicles resume development each day, forming a continuous stream of maturing follicles. Maturation to the early antral stage appears to be independent of gonadotropic stimulation and occurs during all phases of the ovarian cycle. Granulosa cells from preantral and early antral follicles possess receptors for FSH but not LH, whereas thecal cells possess only LH receptors. These immature follicles do not secrete significant amounts of estrogens under basal conditions but can do so if stimulated with FSH for prolonged periods (Zeleznik & Pohl, 2006).

p0110 Maturation of early antral follicles to the preovulatory stage occurs exclusively during the follicular phase of the ovarian cycle, under the control of LH and FSH, and involves expansion of the antral cavity, secretion of follicular fluid into the antrum, expression of LH receptors by the granulosa cells, and follicular secretion of increasing amounts of estrogens and inhibin B. As in other mammals, estrogen production proceeds according to the 'two cell,



f0015 **FIGURE 13.2** Spermatogenesis in the long-tailed macaque (*M. fascicularis*). Arrows indicate the progression of cells through spermatogonial proliferation and differentiation, meiotic division, and spermiogenesis. Dual arrows between A-dark and A-pale spermatogonia indicate the likely transdifferentiation between these cell types (see text for discussion). PI-Z indicates preleptotene-zygotene spermatocytes. Reproduced from McLachlan et al. (2002a), with permission from the American Society of Andrology.



f0020 **FIGURE 13.3** (a) Schematic depiction of the hypothalamic-pituitary-ovarian axis. (b) Hormonal changes across the human menstrual cycle, including relative amplitude (depicted by length of arrows) and frequency (depicted by density of arrows) of hypothalamic GnRH release, and circulating concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E_2), progesterone (P), inhibin A, and inhibin B. GnRH, gonadotropin-releasing hormone. Reproduced from Randolph (2008) with permission from Wiley-Blackwell.

two GTH' model: thecal cells convert C21 steroids to C19 steroids (androstenedione and T) under the influence of LH, and granulosa cells subsequently aromatize these androgens to estrogens under the influence of FSH. Steroidogenesis may be further modulated by several autocrine and paracrine factors, including estrogens, androgens, insulin-like growth factor (IGF)-II, activin, and inhibin; however, the roles of these local factors in follicular steroidogenesis are not well understood (Zeleznik & Pohl, 2006). Follicles the development of which to the early antral stage does not correspond with the slight elevation in circulating GTH levels at the beginning of the follicular phase are unable to mature further, and undergo atresia (Johnson & Everitt, 2000).

p0115 In most primates, only one follicle ovulates in each cycle. This 'dominant follicle' emerges during the mid-follicular phase and inhibits maturation of other follicles by secreting large amounts of estrogens and possibly inhibin B, thereby reducing FSH concentrations below the threshold level required for maturation of early antral follicles. At the same time, the dominant follicle significantly increases its own expression of FSH and LH receptors and develops a markedly denser capillary network than those supplying less mature follicles. Together, these changes ensure continuing GTH support for the dominant follicle, in spite of the declining FSH levels that lead to atresia of other follicles (Zeleznik & Pohl, 2006).

s0050 *3.2.2. Ovulation*

p0120 At the end of the follicular phase, sustained high concentrations of circulating estrogens from the dominant follicle exert positive feedback on the hypothalamus and pituitary (see Section 3.8) to trigger surges in secretion of GnRH, FSH, and, most dramatically, LH. Within several hours, the LH surge stimulates the primary oocyte to complete its first meiotic division. As in other mammals, this division is asymmetric, with half of the chromosomes and almost all of the cytoplasm being inherited by one daughter cell, the secondary oocyte; the other daughter cell, or first polar body, subsequently dies. The secondary oocyte immediately begins its second meiotic division but abruptly becomes arrested again at metaphase (Johnson & Everitt, 2000).

p0125 The LH surge also stimulates final preovulatory maturation and secretory activity of the dominant follicle, including vascularization of the granulosa cell layer, a large increase in the volume of follicular fluid and in follicular size, a transient rise in secretion of estrogens and androgens, and initiation of P_4 secretion. Finally, LH stimulates increased expression of collagenase, prostaglandins, vascular endothelial growth factor, matrix metalloproteinases, and their inhibitors within the follicle, leading to rupture of the follicle and ejection of the oocyte and its surrounding cluster of granulosa cells, the cumulus oophorus, out of the ovary and into the oviduct (Duffy & Stouffer, 2003; Stouffer, Xu, & Duffy, 2007).

s0055 *3.2.3. Corpus luteum formation, function, and regression*

p0130 Luteinization of the dominant follicle in response to the midcycle LH surge involves marked growth of the granulosa cells, proliferation of rough and smooth endoplasmic reticulum, structural modifications in the mitochondria, vascularization of the luteal cells, and increased gene expression (Zeleznik & Pohl, 2006; Stouffer et al., 2007). In humans and macaques, corpora lutea have an intrinsic lifespan of 14–16 days in nonconceptive cycles. During this time, they secrete both steroid and peptide hormones, including P_4, estrogens, relaxin, oxytocin (OXY), and inhibin A, primarily under the influence of LH. Both FSH and prolactin (PRL) have additionally been implicated as luteotropic hormones in primates, but appear to play minor roles in stimulating endocrine activity of corpora lutea in normal cycles (Zeleznik & Pohl, 2006). Interestingly, in a number of New World monkeys, atretic follicles are converted into accessory corpora lutea or interstitial glandular tissue, following luteinization of the granulosa cells or theca interna, respectively. These structures might, in turn, contribute to the extremely high circulating concentrations of estrogens and P_4 characteristic of New World primates (Dixson, 1998). **AQ4**

p0135 The causes of luteal regression in primates are not well understood. In contrast to many nonprimates, this process does not appear to be mediated to a significant extent by endogenous prostaglandins. Moreover, luteal regression does not appear to be determined by the decline in LH pulse frequency that occurs over the course of the luteal phase. Instead, luteal cells are thought to undergo apoptosis, associated with decreases in LH responsiveness and steroidogenic capacity (Brannian & Stouffer, 1991; Nakano, 1997).

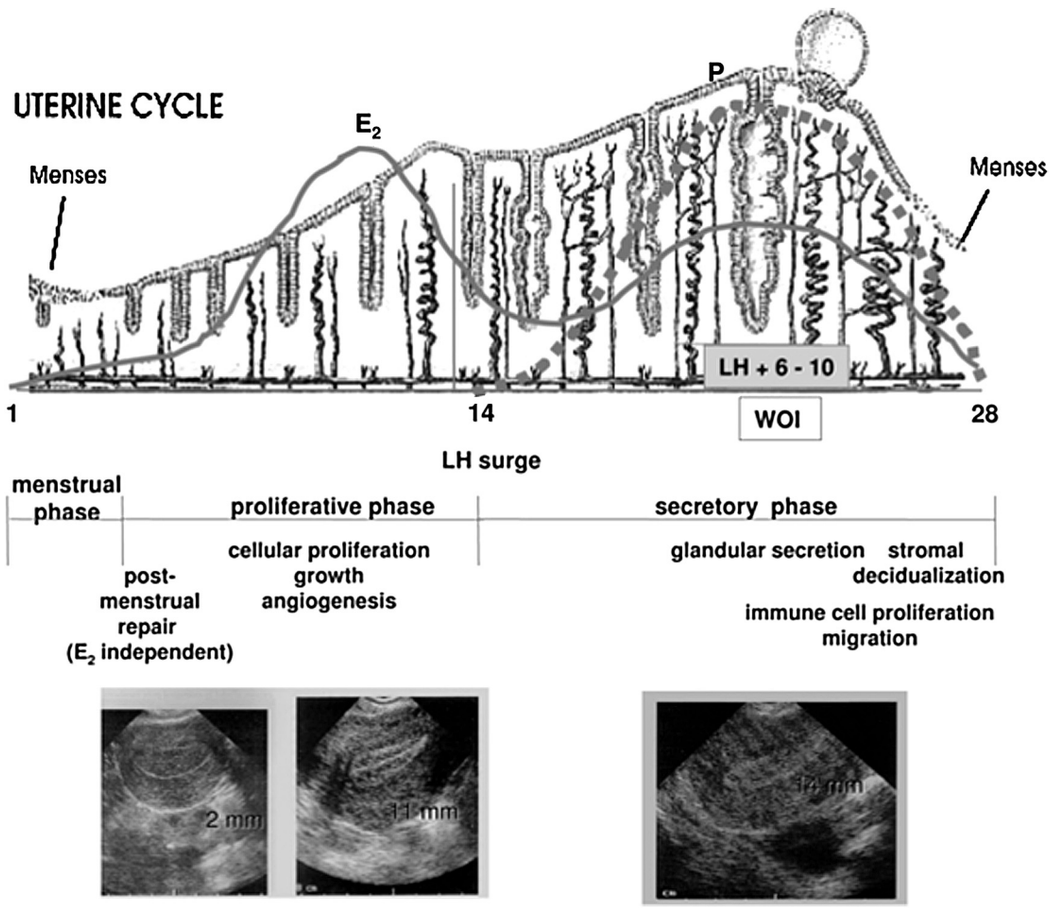
3.3. Cyclical Changes in the Uterus s0060

p0140 Anthropoid primates, along with several additional mammalian species (e.g., Rasweiler & De Bonilla, 1992; Zhang et al., 2007; Wang, Liang, Racey, Wang, & Zhang, 2008), are unique among mammals in undergoing a menstrual cycle – i.e., a cyclical pattern of changes in the nonpregnant uterus characterized by regular sloughing of the endometrium. Menstruation appears to be absent in all prosimians and possibly tarsiers, presumably in association with the noninvasive form of placentation used by these species (Martin, 2007) (see Section 5). Among the anthropoid primates, menstruation occurs in some New World monkeys and apparently in all catarrhines (Old World monkeys, apes, and humans) (Strassmann, 1996). The

functional significance of menstruation is not yet understood. One hypothesis, that it protects females against sperm-borne pathogens (Profet, 1993), has been largely discounted (Strassmann, 1996; Martin, 2007), and an alternative hypothesis, that cyclical shedding and regrowth of the endometrium is energetically less expensive than maintaining the endometrium in a well-developed state across the entire cycle (Strassmann, 1996), has not been confirmed (Martin, 2007). Menstruation has also been suggested to be a nonadaptive consequence of the evolution of an invasive association between the embryo and an adaptive inflammatory reaction of the endometrium (Finn, 1998).

p0145 The uterine cycle in catarrhines comprises four main phases (Figure 13.4). The proliferative phase, corresponding to the mid to late follicular phase of the ovarian cycle, is characterized by increasing growth and vascularization of the endometrium under the influence of estrogens. During this time, edema and proliferation of endometrial stromal cells cause a marked increase in endometrial thickness; increases in size, number, and tortuosity of endometrial glands lead to development of a glandular network; and angiogenesis results in development of an elaborate vasculature. In addition, E_2 induces expression of both estrogen receptors (ERs) and P_4 receptors (PRs) in endometrial cells, thereby performing an obligate priming function for the subsequent secretory phase (Johnson & Everitt, 2000; Hess, Nayak, & Guidice, 2006).

p0150 The secretory phase of the uterine cycle corresponds to the luteal phase of the ovarian cycle. Under the influence of P_4 acting in concert with E_2, the endometrium undergoes additional histological and biochemical changes, including accumulation of glycogen by glandular epithelial cells; synthesis and secretion of glycoprotein-rich fluid into the glandular lumen; cell proliferation, increased capillary permeability, and edema in the stroma; and coiling of the characteristic spiral arterioles. The endometrium is



f0025 **FIGURE 13.4** The menstrual cycle and its endocrine control in catarrhines, including cyclical changes in thickness, vascularization, glandular development, and secretory activity of the endometrium; phases of the uterine cycle and their major cellular events; circulating concentrations of estradiol (E_2) (solid line) and progesterone (P) (dotted line); window of implantation (WOI); and sonograms of the endometrium during the early proliferative, late proliferative, and secretory phases. Reproduced from Giudice (2006) with permission; originally published by BioMed Central. AQ35

receptive to implantation of a blastocyst during a narrow time window, corresponding to six to ten days after the LH surge in women (Johnson & Everitt, 2000; Hess et al., 2006).

p0155 The menstrual phase of the nonconceptive uterine cycle begins at the end of the luteal phase of the ovarian cycle, as luteal regression causes a decline in circulating P_4 and E_2 concentrations. In the absence of steroid support, lysosomal membranes in the endometrium break down, releasing lytic enzymes that degrade cellular elements and extracellular matrix; spiral arterioles constrict, causing ischemia and vascular injury; plasminogen activators are released from the vascular endothelium, leading to production of plasmin and inhibition of clotting; and endometrial cells undergo apoptosis. Whereas the endometrium is resorbed in other mammals, in anthropoid primates the innermost two thirds of the endometrial lining and blood from the ruptured arterioles are expelled through the cervix and vagina as menstrual discharge (Lockwood, Krikun, Hausknecht, Want, & Schatz, 1997; Bergeron, 2000; Hess et al., 2006). By convention, the first day of menstruation is designated day one of a new cycle, corresponding with the beginning of the follicular phase.

p0160 Finally, menstruation is followed by a postmenstrual repair phase lasting several days in the early to mid follicular phase of the ovarian cycle. During this time, the endometrium heals and begins to regenerate its epithelial, stromal, and vascular components. These processes appear to be estrogen-independent and are thought to be initiated by a small population of endometrial stem cells (Bergeron, 2000; Hess et al., 2006).

s0065 3.4. Cyclical Changes in the Oviducts

p0165 In primates and other mammals, the oviducts undergo cyclical changes in histology, secretory function, and muscular activity under the influence of ovarian steroid hormones. During the follicular phase of the ovarian cycle, E_2 stimulates proliferation, hypertrophy and ciliation of epithelial cells, especially in the fimbrial and ampullary portions of the oviducts, as well as secretion of oviductal fluid and spontaneous muscle contractions. These changes peak during the periovulatory period and wane during the luteal phase, when the oviductal epithelial cells undergo atrophy, deciliation, and apoptosis under the influence of P_4, and secretion of oviductal fluid declines. This cyclical series of events is thought to play important roles in facilitating sperm transport, fertilization, early development of the conceptus, and implantation (Johnson & Everitt, 2000; Hess et al., 2006).

s0070 3.5. Cyclical Changes in the Cervix

p0170 The primate cervix undergoes cyclic, steroid-dependent fluctuations in muscular and secretory activity (reviewed by Johnson & Everitt, 2000; Nasir-ud-Din, Rungger-Brändle, Hussain, & Walker-Nasir, 2003; Suarez & Pacey, 2006). During the follicular phase, estrogens stimulate relaxation of the cervical muscles and increased secretion of mucus by the cervical epithelium. Cervical mucus, which contains water, glycoproteins, ions, enzymes, and immunoglobulins, plays key roles in sperm transport and defense of the female reproductive tract against microorganisms. Under the influence of estrogens, the mucus becomes profuse, highly hydrated, and highly penetrable to sperm. These characteristics peak around the time of ovulation, when cervical mucus blocks passage by microbes and abnormal sperm, while guiding normal, motile sperm through the cervix. Subsequently, during the luteal phase, P_4 increases the firmness of the cervix, decreases secretory activity of the cervical epithelium, and alters the quality and quantity of glycoproteins in the cervical mucus, causing secretion of small amounts of thick, viscous mucus that is impenetrable to sperm.

3.6. Cyclical Changes in the Vagina s0075

Primates, like other mammals, undergo cyclical changes in the vagina under the influence of fluctuating estrogen and P_4 concentrations. During the follicular phase, estrogens stimulate increases in mitotic activity, glycogen content, thickness, and keratinization of the vaginal columnar epithelium, with these changes subsiding during the luteal phase (Farage & Maibach, 2000; Poonia et al., 2006). Cyclical changes also occur in the vaginal flora. Although the dominant microorganisms, *Lactobacillus* spp., may remain relatively constant across the menstrual cycle, levels of other microorganisms may fluctuate (Skangalis, Swenson, Mahoney, & O'Leary, 1979; Witkin, Linhares, & Giraldo, 2007). Cyclical changes in the vagina are especially pronounced in prosimians. In many of these species, as in numerous nonprimates, the vaginal orifice is imperforate throughout most of the cycle, opening – and therefore permitting intromission – only during the periovulatory period (e.g., ruffed lemur (*Varecia variegata*), Garnett's greater galago (*Otolemur garnettii*), fat-tailed dwarf lemur (*Cheirogaleus medius*)) (Van Horn & Eaton, 1979; Dixson, 1998). p0175

3.7. Cyclical Changes in the External Genitalia and Sexual Skin s0080

Females of many primate species undergo cyclical changes in coloration and tumescence of the external genitalia and so-called sexual skin, usually found on the rump and anogenital region (reviewed by Dixson, 1983; 1998). In numerous prosimians, the vulva becomes swollen and assumes a pink or red coloration during the periovulatory period. Such changes are greatly exaggerated in many p0180

catarrhines but are virtually nonexistent in New World monkeys.

p0185 Typically in catarrhines, estrogens stimulate tumescence — caused largely by edema — and intensification of the characteristic pink or red coloration of the sexual skin — a consequence of specialized vasculature — during the follicular phase (Dixson, 1983). Swelling and coloration peak during the periovulatory period, corresponding with the female's peak in sexual behavior. Progesterone antagonizes these effects during the luteal phase, so that detumescence occurs shortly after ovulation. Although hormonal control appears to be consistent across species, the location of sexual skin and extent of tumescence and coloration vary considerably. In geladas (*Theropithecus gelada*), e.g., pink or purple, nonedematous sexual skin is AQ5 found on the circumanal, paracallosal, vulval, and clitoral regions, as well as on the lower abdomen. Additionally, white, fluid-filled vesicles develop around the edges of the sexual skin and in a figure-eight pattern on the chest during the periovulatory period (Dunbar, 1977; Dixson, 1998). Other species, including chimpanzees, bonobos (*Pan paniscus*), baboons, red colobus (*Piliocolobus badius*), and mangabeys (*Cercocebus* spp.), exhibit prominent pink swellings of the circumanal, vulval, and clitoral regions. Sex skin tumescence and coloration increase females' attractiveness to males, may facilitate intromission by males, and are thought to have evolved in response to sexual selection (Dixson, 1983; 1998).

s0085 3.8. Neuroendocrine Control of the Ovarian Cycle

p0190 The ovarian cycle in primates, as in other species, is governed by a complex interplay between the gonads, the gonadotropes in the anterior pituitary, and the GnRH pulse generator in the medial basal hypothalamus (reviewed by Johnson & Everitt, 2000; Messinis, 2006; Zeleznik & Pohl, 2006; see also Chapter 2, this volume). During the follicular phase, LH and FSH are released in low-amplitude, circhoral pulses, reflecting negative-feedback effects of estrogens on pulse amplitude but not frequency (see Figure 13.3). At midcycle, when estrogen levels exceed approximately 200 pg/ml for about 48 hours, estrogens trigger positive-feedback surges in GnRH, LH, and FSH, eliciting increases in pulse frequency and/or amplitude. Fully developed GTH surges in women require the presence of small amounts of P_4; however, no such effect is seen in rhesus macaques (Zeleznik & Pohl, 2006). Finally, the luteal phase is characterized by low-frequency, high-amplitude LH pulses, reflecting negative feedback primarily by P_4. In addition to ovarian steroids, inhibin B is secreted by the granulosa cells during the follicular phase, and inhibin A is secreted by the corpus luteum during the luteal phase, possibly exerting negative feedback specifically on FSH release; however, the precise role of inhibins in primate ovarian cycles is not yet clear (Zeleznik & Pohl, 2006; Randolph, 2008). Interestingly, FSH concentrations are elevated during the luteal phase in squirrel monkeys, suggesting that development of antral follicles may occur during this period, and possibly permitting the extremely short (~five-day) follicular phase of these species (Yeoman et al., 2000).

p0195 The sites of positive and negative feedback by estrogens have not been delineated fully in primates (reviewed by Johnson & Everitt, 2000; Messinis, 2006). A variety of experimental approaches have suggested that positive feedback by estrogens at the pituitary alone is sufficient to generate preovulatory LH surges, although GnRH plays an obligate permissive role. Nonetheless, other studies have indicated that hypothalamic release of GnRH increases in response to sustained elevations of estrogens. Negative feedback by estrogens, likewise, may be mediated primarily at the level of the pituitary; however, estrogens reduce pulse amplitude (but not pulse frequency) of GnRH as well as LH, indicating that the negative feedback effects of estrogens are mediated in part at the hypothalamus (Mizuno & Terasawa, 2005; see also Chapter 2, this volume). Negative feedback effects of P_4 on GTH pulse frequency are assumed to occur at least partly within the central nervous system and are mediated, at least in part, by endogenous opioids. In addition, negative feedback effects of both estrogens and P_4 at the level of the brain appear to be mediated in part by Kp (Plant & Ramaswamy, 2009).

4. PUBERTY

s0090

p0200 In comparison to many other taxa, primates undergo an extended period of prepubertal development, as well as a prolongation of the period of reproductive maturation, known as puberty (see Table 13.1). This period is characterized by morphological, physiological, and behavioral changes driven by maturation and activation of the HPG axis (i.e., gonadarche) and, in some species, of the hypothalamus-pituitary-adrenal (HPA) axis (i.e., adrenarche). An excellent review of puberty in primates can be found in Plant and Witchel (2006).

4.1. Adrenarche

s0095

p0205 Several years prior to gonadarche, humans, chimpanzees, and possibly some other catarrhines undergo remodeling of the adrenal cortices, involving development of the zona reticularis (i.e., the innermost zone of the adrenal cortex) and increased secretion by the zona reticularis of androgens, particularly the weakly androgenic steroids dehydroepiandrosterone (DHEA) and its sulfoconjugate, DHEA-sulfate (DHEA-S). Circulating DHEA and DHEA-S

levels peak during early adulthood in both males and females before declining gradually across the remaining lifespan. In other primates, the development of the zona reticularis and onset of adrenal androgen secretion occur during the prenatal and/or early postnatal period or not at all, and DHEA/DHEA-S secretion declines from high levels in infancy or remains stable throughout life (Campbell, 2006; Nguyen & Conley, 2008).

p0210 In humans and possibly chimpanzees, this pubertal development of the zona reticularis, known as adrenarche, is not associated with changes in secretion of cortisol, corticotropin (ACTH), gonadal steroids, or GTHs, and is not necessary for subsequent reproductive maturation (Auchus & Rainey, 2004; Campbell, 2006). In fact, the only known manifestations of adrenarche in humans are growth of pubic and axillary hair; development of apocrine glands in the skin, which may lead to body odor; and stimulation of sebaceous gland activity, which may cause acne (Auchus & Rainey, 2004). In addition, however, adrenarche has been hypothesized to play a role in maturation of the brain and skeletal system (Havelock, Auchus, & Rainey, 2004; Campbell, 2006), and premature (precocious) adrenarche in girls is associated with subsequent development of several clinical disorders, including polycystic ovarian syndrome (PCOS) and metabolic syndrome (Auchus & Rainey, 2004; Nebesio & Eugster, 2007; Belgorosky, Baquedano, Guercio, & Rivarola, 2008).

s0100 4.2. Gonadarche

p0215 In infant primates, the pituitary and gonads secrete high levels of GTHs (i.e., LH and FSH) and steroid hormones (e.g., T, dihydrotestosterone (DHT), estrone (E_1), and E_2), respectively, for a period of weeks to months. This period of neonatal gonadal activity ends with the onset of the so-called juvenile or prepubertal hiatus, during which GTH levels drop precipitously and the gonads enter a dormant state, especially in males (reviewed by Plant & Witchel, 2006). Gonadal 'reawakening' occurs at the time of gonadarche, which begins anywhere from less than one year of age in several prosimians (e.g., fat-tailed dwarf lemur (*C. medius*) (Foerg, 1982)) to three years of age in macaques and squirrel monkeys, to seven to eleven years of age in chimpanzees, to nine to thirteen years of age in humans (Dixson, 1998; Plant & Witchel, 2006).

p0220 Gonadarche in male primates is characterized by dramatic elevations in circulating concentrations of LH and, to a lesser extent, FSH, reflecting primarily an increase in secretory pulse amplitude. These GTH increases, which are thought to reflect a concomitant amplification of pulsatile GnRH release from the hypothalamus, stimulate an increase in testicular volume (associated with growth of the seminiferous tubules, maturation of Sertoli cells, and proliferation of germ cells), development of Leydig cells, secretion of high levels of gonadal androgens, and initiation of spermatogenesis (Plant & Witchel, 2006). In humans and rhesus macaques, nocturnal elevations (known to be sleep-related in boys) in circulating LH and T levels precede diurnal elevations. The increased gonadal steroid concentrations stimulate development of species-typical secondary sexual characteristics, such as sex-specific facial and genital coloration (e.g., mandrill (*Mandrillus sphinx*)), throat sac and cheek flanges (orangutan (*Pongo pygmaeus*)), and specialized facial or body hair (e.g., hamadryas baboon (*Papio hamadryas*)), as well as the onset of sexual behavior (Dixson, 1998).

p0225 In female primates, as in males, gonadarche is triggered by a marked increase in secretion of FSH and, especially, LH by the gonadotropes, secondary to an increase in hypothalamic GnRH secretion (Watanabe & Terasawa, 1989). The surge in GTHs stimulates the initiation of cyclic ovarian activity, including the first development of Graafian (preovulatory) follicles, increased ovarian steroidogenesis, and, in catarrhines and some platyrrhines, the first menstrual period (menarche) (Plant & Witchel, 2006). Following menarche, the pituitary gonadotropes develop the capacity to exhibit GTH release via positive feedback in response to estrogens, culminating in the first ovulation. Thus, menarche precedes — by approximately a year in rhesus macaques, and by a year or more in humans and great apes — the onset of fertile ovulatory cycles, and is typically associated with a period of 'adolescent infertility,' characterized by anovulatory and irregular cycles (Bercovitch & Goy, 1990; Dixson, 1998). Across puberty, increasing E_2 concentrations stimulate uterine growth and maturation of species-typical secondary sexual characteristics, such as development of the breasts and nipples, and coloration and swelling of sexual skin (Dixson, 1998).

4.3. Neural Control of Gonadarche s0105

p0230 Human clinical cases and studies of nonhuman primates have demonstrated that the 'reawakening' of the gonads at gonadarche is not limited by maturation of the gonads, pituitary, or hypothalamic GnRH neurons. For example, treatment of juvenile rhesus macaques with *N*-methyl-D-aspartate (NMDA), a receptor agonist of the excitatory neurotransmitter glutamate, elicits pulsatile release of GnRH from the hypothalamus, pulsatile release of LH from the pituitary, and gonadal activation, indicating that the GnRH neurons, gonadotropes, and gonads are already mature and capable of adult-like functioning prior to gonadarche (Plant, Gay, Marshall, & Arslan, 1989; Claypool, Kasuya, Saitoh, Marzban, & Terasawa, 2000). Further, developmental changes in neural or pituitary sensitivity to negative feedback by gonadal steroids (the so-called gonadostat hypothesis) do not account for the dramatic rise in GTH release during gonadarche. Instead,

the proximate trigger for gonadarche involves maturation of neural inputs to the GnRH neurons, eliciting the dramatic increase in pulsatile GnRH secretion and, consequently, increases in pituitary secretion of GTHs and stimulation of gonadal endocrine and gametogenic activity.

p0235 Studies in rhesus macaques have implicated several neurotransmitters and neuropeptides in the onset of gonadarche. These include the inhibitory neurotransmitter GABA, which plays a key role in restraining GnRH secretion during the juvenile period but exerts only modest inhibitory effects on GnRH release after the onset of puberty (Terasawa, 2005). Moreover, the developmental decrease in GABA release within the pituitary stalk-median eminence may stimulate a corresponding increase in release of the excitatory neurotransmitter glutamate, which may further elevate GnRH secretion (Terasawa, 2005). Neuropeptide Y has been implicated both in inhibiting GnRH release during the prepubertal hiatus and, paradoxically, in stimulating GnRH release during puberty and adulthood (Plant & Witchel, 2006).

p0240 In the past few years, much attention has focused on the role of the neuropeptide Kp, coded for by the *KiSS1* gene, and its receptor, GPR54 (also known as KiSS1R), in regulating gonadarche in humans and other primates (Plant, 2009). In 2003, two research groups reported that members of consanguineous human families presenting with hypogonadotropic hypogonadism (i.e., impaired gonadal function secondary to GTH deficiency) and absence of puberty had homozygous mutations in the GPR54 gene (De Roux et al., 2003; Seminara et al., 2003). Since then, Kp-GPR54 signaling has been implicated compellingly in the control of hypothalamic GnRH release, pituitary GTH release, and onset of puberty in a number of mammalian species, including rhesus macaques (Roa, Aguilar, Dieguez, Pinilla, & Tena-Sempere, 2008). In macaques, both Kp and GPR54 are expressed in the arcuate nucleus of the medial basal hypothalamus (the site of the GnRH pulse generator), and expression of Kp (and of GPR54, at least in females) increases dramatically at the time of the pubertal increase in GnRH secretion (Plant, 2009). Moreover, pulsatile release of Kp and of GnRH in the median eminence are synchronized in midpubertal female rhesus macaques (Keen, Wegner, Bloom, Ghatei, & Terasawa, 2008), and treatment with exogenous Kp stimulates GnRH release in midpubertal females and pulsatile LH release in castrated juvenile males (Plant et al., 2006; Keen et al., 2008). Importantly, the stimulatory effect of Kp on LH can be blocked by simultaneous treatment with a GnRH receptor antagonist, suggesting that Kp affects the gonadotropes only indirectly, through its effects on GnRH secretion (Plant et al., 2006). Collectively, findings from humans and macaques suggest that Kp plays a critical role in triggering the pubertal increase in GnRH secretion; however, the precise nature of this role is not yet known.

AQ6

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4.4. Timing of Puberty s0110

In spite of recent major advances in our understanding of the neurobiological processes governing primate puberty, the factors that determine the timing of these processes remain poorly understood (reviewed by Plant & Witchel, 2006). Clearly, the determinants of the timing of puberty are multifactorial, involving genetic, physiological, and environmental influences. Genetic factors are estimated to account for 50−80% of the variation in pubertal timing in humans, with mutations in such genes as those coding for the GnRH receptor, GPR54, and leptin leading to pathologically delayed or premature gonadarche; however, the specific genes accounting for variation in pubertal timing among clinically normal individuals remain unknown (Gajdos, Hirschhorn, & Palmert, 2009). p0245

At the physiological level, one hypothesis is that the timing of puberty is governed by an endogenous 'pubertal clock' in the central nervous system, which initiates puberty at a specific age. This hypothesis is not widely accepted, however, in view of such findings as high variability in the age of human gonadarche, both within and among populations, as well as declines in the age of human gonadarche over recent decades (Ebling, 2005; Plant & Witchel, 2006; Euling, Selevan, Hirsch Pescovitz, & Skakkebaek, 2008). p0250

Instead, the timing of puberty has long been thought to be governed by a putative 'somatometer' that measures some index of somatic growth. The somatometer hypothesis is supported by compelling evidence; however, the index of somatic development being monitored is not yet known. In recent years, attention has focused on a possible role of the adipocyte hormone leptin, circulating concentrations of which correlate with body fat mass. Findings in humans and rhesus macaques, as well as rodents, suggest that leptin plays a critical role in the onset of gonadarche. This role appears to be permissive, however, rather than serving as a direct trigger for puberty onset (Ebling, 2005; Plant & Witchel, 2006; Kaplowitz, 2008). Other indices of somatic development that have been implicated in determining the timing of puberty include insulin, growth hormone (GH), ghrelin, and metabolic fuels (Plant & Witchel, 2006; Kaplowitz, 2008; Tena-Sempere, 2008). Strenuous exercise, undernutrition, and chronic disease can all delay the onset of puberty, possibly acting through the putative somatometer (Plant & Witchel, 2006). p0255

Finally, a number of environmental factors are known to modulate the timing of puberty in humans and nonhuman primates. Social influences can advance or delay puberty, as described below. In seasonally breeding species, aspects of pubertal maturation may be gated by seasonal cues such as photoperiod. Female rhesus macaques housed outdoors in the northern hemisphere, e.g., may undergo menarche at p0260

any time of year, but the occurrence of first ovulation is more or less restricted to the roughly three-month breeding season (autumn–winter) and is influenced by patterns of melatonin (MEL) secretion (Bercovitch & Goy, 1990; Wilson, Gordon, & Collins, 1986; Wilson & Gordon, 1989a; 1989b). Similarly, in squirrel monkeys, the onset of ovulatory cyclicity in young females and the first T surge in young males are restricted to the breeding season, presumably in response to photoperiodic cues (Coe, Chen, Lowe, Davidson, & Levine, 1981). Thus, seasonality 'imposes a quantum effect' on pubertal timing, such that gonadarche is more closely dependent on the number of breeding seasons elapsed since an individual's birth than on age *per se* (Plant & Witchel, 2006). Importantly, seasonally related cues do not necessarily govern maturation of the neural processes underlying pubertal reactivation of the GnRH neurons, but instead may play a permissive role in the expression of gonadarche, following this reactivation (Plant & Witchel, 2006).

p0265 Recently, endocrine-disrupting chemicals have gained attention as another source of variation in pubertal timing (Wang, Needham, & Barr, 2005; Cesario & Hughes, 2007; Euling et al., 2008; Schoeters, Den Hond, Dhooge, Van Larebeke, & Leijs, 2008; see also Chapter 14, this volume). In humans, pre- and/or postnatal exposure to a number of synthetic or naturally occurring chemicals can advance or delay the timing of gonadarche. For example, correlational findings suggest that puberty in girls may be advanced by *in utero* exposure to the organochlorine dichlorodiphenyldichloroethylene (DDE) (a metabolite of the pesticide dichlorodiphenyltrichloroethane (DDT)), or by exposure to phthalates, a group of estrogenic compounds used to increase the flexibility of plastics (Cesario & Hughes, 2007). On the other hand, puberty in boys may be delayed by exposure to polychlorinated biphenyls (PCBs), industrial chemicals previously used in such products as coolants, flame retardants, and electronic components (Schoeter et al., 2008). Exposure to exogenous, naturally occurring steroids, such as phytoestrogens found in soy products and estrogens used in certain cosmetics and hair-care products, have additionally been implicated in altering the timing of gonadarche (Cesario & Hughes, 2007).

s0115 5. PREGNANCY

s0120 5.1. Overview

p0270 Numerous authors have reviewed the physiology of mammalian pregnancy (Albrecht & Pepe, 1990; Solomon, 1994; Ogren & Talamantes, 1994; Petraglia, Florio, & Simoncini, 1996; Albrecht & Pepe, 1999; see also Chapter 6, this volume). Much of this literature centers upon the best-studied primate species, i.e., humans, and is therefore relevant background to understanding primate pregnancy. In the following discussion, it can be assumed that findings for nonhuman primates are similar to those found for humans, unless otherwise stated.

p0275 Pregnancy presents unique physiological, immunological, and evolutionary challenges due to the combined presence of two or more distinct individuals (mother and fetus(es)) who are inextricably linked. The interface of this exchange between mother and fetus is the temporary organ, the placenta. This review will concentrate on the nature of the primate placenta, emphasizing recent findings on its endocrine nature.

p0280 The placenta develops from the outer cell mass, or trophectoderm, of the developing blastocyst that is in direct contact with the maternal endometrium. The outer cell mass eventually differentiates into two cell types: cytotrophoblasts and syncytiotrophoblasts. These cells form the AQ8 fetal side of the boundary between mother and fetus. This boundary actively controls maternal–fetal exchange of nutrients, oxygen, and fetal wastes through alterations in passive diffusion capacity and active transport capacity. The development, maintenance, and alterations in the placenta as an exchange surface are controlled by autocrine and endocrine signals produced and received by the placenta.

p0285 The form of placentation varies greatly among mammalian taxa (Mossman, 1987; Benirschke, 2010). In the hominoid primates (apes and humans), the entire blastocyst implants into the uterine wall in a relatively invasive process that involves penetration of the maternal endometrial epithelium and invasion of the uterine vasculature (Luckett, 1974; Mossman, 1987; Lee & DeMayo, 2004). Monkeys exhibit superficial implantation, in which there is adherence to the uterine wall by the trophoblast, but without complete endometrial penetration or invasion of the deeper layers of the uterine wall (Luckett, 1974), whereas humans have a more invasive interstitial implantation with complete remodeling of uterine vessels. In all anthropoid primate placentae, however, the fetal trophoblast layer (the chorion) is in direct contact with the maternal blood supply; i.e., hemochorial placentation. It has long been proposed that this most invasive form of placentation evolved from the more shallow, epitheliochorial forms of placentation, but studies based on recent phylogenetic analysis suggest that hemochorial placentation was likely the ancestral form in mammals (Wildman et al., 2006). Hemochorial placentation offers the opportunity for endocrine signals produced by the conceptus – i.e., by the cytotrophoblast and syncytiotrophoblast cells – to be directly transmitted to the maternal bloodstream, offering a means for the placenta to affect maternal physiology in ways that may either increase or decrease fetal and placental growth (Haig, 1996; Rutherford, 2009). What follows is a description of aspects of

autocrine and endocrine signaling in the primate placenta, with an emphasis on those areas that are unusual or unique to this taxonomic group. For broader characterization of the dozens of endocrine/autocrine placental processes that have been identified to date, consult Solomon (1994), Ogren and Talamantes (1994), Petraglia et al. (1996), and Petraglia, Floriom, and Vale (2005).

5.2. Steroids

p0290 The primate placenta interacts in a complex fashion with the maternal and fetal blood supplies to synthesize E_2 and P_4 and to convert cortisol to cortisone. As in other mammals, P_4 acts to alter the endometrial environment to allow implantation, including effects upon the maternal immune system. Progesterone also decreases contractility of the myometrium and inhibits lactation. Estrogens, too, prepare the uterus for implantation, but also play a critical role in the development of the endocrine/autocrine capacities of the placenta.

p0295 Albrecht and Pepe (1999) have proposed that placental estrogens are critical to the functional differentiation of the primate cytotrophoblasts into a syncytiotrophoblast. This differentiation includes an upregulation of 11β–hydroxysteroid dehydrogenase (11β-HSD) and P450 cholesterol side-chain cleavage ($P450_{scc}$); therefore, this differentiation controls the ability of the placenta to synthesize P_4 and to convert cortisol to cortisone (see Figure 13.5).

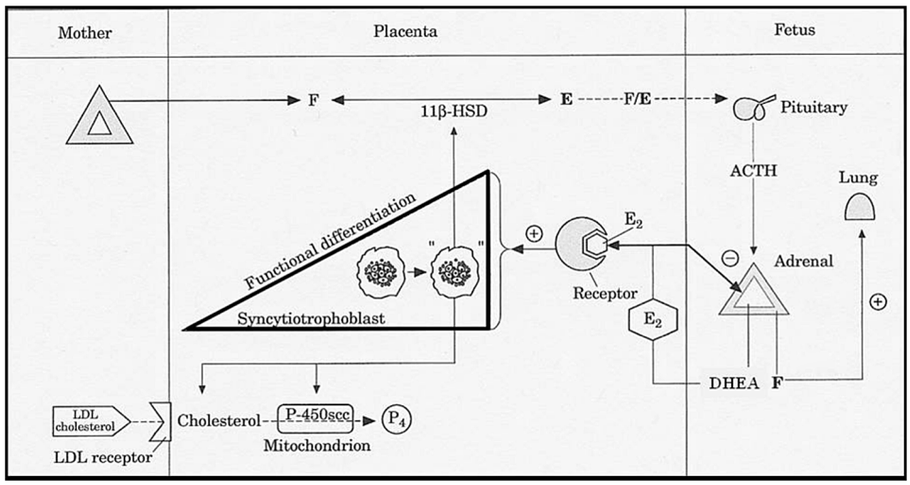
p0300 In primates, placental estrogen synthesis is dependent upon precursors supplied by the fetal adrenal gland. The primate fetal adrenal gland contains a wide inner zone, termed the fetal adrenal zone. This zone involutes rapidly after birth in humans while in rhesus monkeys it disappears more slowly (McNulty, Novy, & Walsh, 1981), but in all primates it disappears before adulthood. The fetal adrenal zone synthesizes DHEA-S, which is then used by the syncytiotrophoblast as substrate for E_2 synthesis.

p0305 At the same time, maturation of the glucocorticoid-producing zones of the fetal adrenal is controlled by fetal exposure to cortisol through the placenta. In midgestation, maternal cortisol is largely passed through the placenta as cortisol and, therefore, inhibits the fetal pituitary's production of ACTH. In late gestation, with more estrogens and, therefore, more 11β-HSD activity, maternal cortisol is converted to cortisone in the placenta, reducing fetal exposure to maternal cortisol and therefore allowing fetal ACTH production to increase. Increased fetal ACTH production leads to maturation of the fetal adrenal capacity to synthesize cortisol (Pepe & Albrecht, 1990; Mesiano & Jaffe, 1997). In this fashion, the placenta supports a timeline of fetal development that is controlled by the pace of developing placental endocrine/autocrine capacity.

5.3. Chorionic Gonadotropin (CG)

s0130

p0310 The syncytiotrophoblast synthesizes CG, a glycoprotein similar to LH synthesized by the pituitary gland. For details on the biochemistry of CG and its relation to LH and other glycoproteins, see Ogren and Talamantes (1994). Chorionic gonadotropin produced by the primate placenta functions to maintain P_4 and estrogen synthesis by the corpus luteum of



f0030 **FIGURE 13.5** Control of functional differentiation of placental syncytiotrophoblast by estrogen (E_2), which upregulates key components of the progesterone (P_4) biosynthetic pathway and the 11β-HSD (hydroxysteroid dehydrogenase)-1 and -2 system, which induces maturation of the fetal pituitary-adrenal axis. Syncytiotrophoblast is a multinucleated tissue of the placenta that produces hormones, depicted here as a drawn circle filled with smaller circles. Quotation marks signify functionally differentiated syncytiotrophoblast that is secreting hormones; e.g., placental lactogen and P_4. F, cortisol; E, cortisone; DHEA, dehydroepiandrosterone. Reproduced from Albrecht and Pepe (1999), with permission. AQ36

the ovary. Therefore, CG is necessary for the early establishment of pregnancy in primates. In most other mammals, maintenance of corpus luteum P_4 production is accomplished through embryonic effects on prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), the primary signal for luteolysis (Niswender & Nett, 1994). In primates and a few other species (e.g., guinea pigs (*Cavia porcellus*)), however, CG acts trophically on the ovary, in the face of waning pituitary LH stimulation, to generate continued steroid production by the corpus luteum (Zeleznik & Benyo, 1994). Recent studies indicate that CG may also play a direct role in altering the character of the endometrium in preparation for implantation.

p0315 Numerous endocrine and autocrine factors have been found to affect CG production *in-vitro*, including cortisol, CRH, triiodothyronine (T_3), thyroxine (T_4), GnRH, interleukin (IL) 6 (IL-6), and IGF-1, which increase CG secretion, and P_4 and transforming growth factor-β (TGFβ), which decrease CG secretion (summarized in Ogren & Talamantes, 1994). However, the specifics of how these interactions may function *in-vivo*, separately or in concert, remain to be determined.

s0135 5.4. Chorionic Somatomammotropins (CSs)

p0320 The placentae of various mammalian taxa produce hormones that have both lactogenic and somatotropic properties. In most taxa, these hormones are derivatives of PRL (Schuler & Kessler, 1992; Soares & Linzer, 2001; Soares, 2004). In primates, however, placental lactogens are coded for by a series of genes that are part of a cluster of GH-like genes. Genetic comparisons among primates suggest that the duplication and possible selection events that led to these GH-like gene clusters occurred separately in Old World and New World primates (Wallis & Wallis, 2002; De Mendoza, Escobedo, Davila, & Saldana, 2004; Li et al., 2005). At least three of the GH-like genes are expressed in the placenta of humans (Kliman, Nestler, Sermasi, Sanger, & Strauss, 1986), rhesus macaques (Golos, Durning, Fisher, & Fowler, 1993), and baboons (Musicki, Pepe, & Albrecht, 1997). It is unknown whether the separate duplications in New World monkeys are also expressed by the placenta.

p0325 Chorionic Somatomammotropin concentrations are correlated with placental weight, but not fetal weight at delivery in rhesus macaques (Novy, Aubert, Kaplan, & Grumbach, 1981). Walker, Fitzpatrick, Barrera-Saldana, Resendez-Perez, and Saunders (1991) report that CS has some direct somatotropic effects on fetal tissues, alters maternal carbohydrate and lipid metabolism, and aids in mammary cell proliferation. Reduced CS expression in human trophoblast is associated with intra-uterine growth restriction *in-vivo* and with hypoxia exposure *in-vitro* (Roh et al., 2006).

5.5. Corticotropin-releasing Hormone (CRH) s0140

p0330 Corticotropin-releasing hormone was first identified as a hypothalamic neuropeptide controlling pituitary release of ACTH and hence affecting adrenal release of glucocorticoids. More recently, it has become clear that CRH (also known as corticotropin-releasing factor (CRF)) is expressed in other tissues and has different functions in those tissues. Most notably, CRH is expressed in numerous brain regions and, in primates, in the placenta. While CRH is produced in the placentae of all anthropoid primates that have been examined (Bowman et al., 2001; Smith, 2005), it is produced at extremely low concentrations or not at all in the placentae of other mammals (Smith, 2005). The pattern of circulating CRH throughout gestation differs between hominoid primates and monkeys: CRH rises continuously during the final trimester in humans and apes, peaking at term, while in monkeys it reaches its highest concentration during midpregnancy, declining thereafter (Goland, Wardlaw, Fortman, & Stark, 1992; Smith, Chan, Bowman, Harewood, & Phippard, 1993; Smith, Wickings, & Bowman, 1999; Power et al., 2006). In contrast with hypothalamic CRH, the secretion of which is inhibited by glucocorticoids, the secretion of placental CRH is enhanced by cortisol, in a positive feedforward pattern that is similar to the glucocorticoid−CRH relation in suprahypothalamic brain regions (Emanuel et al., 1994; Smith, 2005). This difference appears to be due to differential expression of transcription factors, coactivators, and corepressors in hypothalamic vs. placental tissue (King, Smith, & Nicholson, 2002).

p0335 Alterations from the typical CRH trajectory during gestation are often associated with preterm birth in humans, leading to the suggestion that CRH concentration may be a marker of early placentation events that set the stage for the rate of CRH change across gestation and the ultimate timing of parturition (Smith, 2005). Placental CRH may also affect the fetal HPA axis by stimulating fetal ACTH release. *In-vitro* evidence suggests that CRH can directly increase DHEA-S production from fetal adrenal cells, therefore providing additional substrate for placental estrogen production (Petraglia et al., 2005).

5.6. Leptin s0145

p0340 Leptin was originally identified as a peptide, produced by adipocytes, that acts upon centers in the brain controlling satiety, energy state, and reproductive functions. Leptin is also produced by the placenta in a number of mammalian taxa; however, placental leptin production is significantly higher in primates than in other mammals. In addition, the distribution of leptin secretion to maternal vs. fetal compartments differs between rodents and primates (Henson & Castracane, 2002; Power & Tardif, 2005). In

humans, 95% of placental leptin is released into the maternal circulation, suggesting that placental leptin acts mostly on maternal physiology and directly on the placenta rather than acting directly on the fetus (Hauguel-De Mouzon, Lepercq, & Catalano, 2006). Primate pregnancy can be considered a hyperleptinemic state, as leptin concentrations increase early in pregnancy and remain increased over nongravid concentrations until parturition. Local placental effects of leptin include enhancing CG production (Chardonnens et al., 1999) and enhancing synthetic processes (mitogenesis, amino-acid uptake, synthesis of extracellular matrix proteins and metalloproteinases) (Castellucci et al., 2000; Jansson, Greenwood, Johansson, Powell, & Jansson, 2003); i.e., regulation of placental growth. In the mother, it is proposed that the primary function of increased leptin concentration is to enhance mobilization of maternal fat stores. This may be of particular importance in humans, who produce fetuses with a relatively and absolutely larger amount of adipose tissue than other mammals, including other primates (Kuzawa, 1998).

6. LACTATION

Lactation is one of the defining characteristics of mammals. Milk synthesis and secretion by mammary cells into the alveolar lumen is a continuous process that requires PRL (Neville, 2001). However, PRL's influence on the process is modified by the effects of milk removal from the lumen on diffusion and transport processes. Release of OXY from the posterior pituitary causes contraction of myoepithelial cells surrounding the ducts and alveoli, forcing milk out into the nipple, where it can be accessed by the infant (Neville, 2001). If this neuroendocrine 'let-down' reflex is impaired, more milk remains in the lumen. Milk remaining in the lumen generates local factors that adjust milk secretion. In this way, the process of milk production is driven to a large extent by milk demand.

Compared to other mammalian taxa, primates produce milk that has low caloric density (i.e., high water content) and relatively low protein content (Oftedal, 1984; Milligan, Gibson, Williams, & Power, 2008). These features form part of a lactation strategy that involves frequent nursing throughout the day and night, combined with a relatively long period of exclusive milk feeding of young; i.e., weaning at a relatively late age.

Another unusual feature of lactation in most primates is the occurrence of a prolonged lactation-induced anovulatory period, termed lactational amenorrhea in primates that undergo menstrual cycles. Lactation has suppressive effects on folliculogenesis and ovulation in nonprimate mammals; however, the extent to which lactation and subsequent pregnancy are spaced apart by lactation is particularly striking in primates (McNeilly, 1994). It is well established that the suckling stimulus, rather than milk production *per se*, is the driving force behind lactational effects on the ovary. The suckling stimulus results in impaired hypothalamic GnRH release that, in turn, causes impaired pulsatile LH release from the pituitary (Weiss, Butler, Dierschke, & Knobil, 1976; McNeilly, 1994). Given this fact, it is perhaps not surprising that lactational infertility is greatly lengthened in one of the few mammalian orders providing regular and routine infant access to suckling. Primates are one of only two mammalian eutherian lineages (the other being Edentates) in which infants are routinely physically carried. In most primate species this transport is performed mostly by the mother and, as mentioned previously, frequent bouts of suckling throughout the day and night are a typical primate nursing pattern.

Early on, it was proposed that the hyperprolactinemia of lactation might suppress ovarian activity by inhibiting GnRH secretion, given the links between suckling stimulation and elevated PRL release (Freeman, Kanyicska, Lerant, & Nagy, 2000). However, the effect of PRL manipulation on time to resumption of ovulation in lactating macaques is variable (Maneckjee, Srinath, & Moudgal, 1976; Schallenberger, Richardson, & Knobil, 1981), and the correlation between circulating PRL concentration and duration of amenorrhea in lactating women also has been inconsistent (McNeilly, 1994; Tay, Glasier, & McNeilly, 1996). Further evidence that elevated PRL is not a driving force behind primate lactational anovulation is the case of the New World marmosets and tamarins. This is the only group of primates studied so far that does not display lactation-induced anovulation, with most individuals in a captive setting ovulating within 9–20 days following parturition. However, they display the same lactational hyperprolactinemia seen in other primates (McNeilly, Abbott, Lunn, Chambers, & Hearn, 1981).

Central OXY administration inhibits LH release in ovariectomized rhesus macaques (Luckhaus & Ferrin, 1989), but in marmosets OXY increases pituitary release of CG, the primary pituitary luteotropic hormone of New World monkeys (O'Byrne, Lunn, & Coen, 1990). Thus, central OXY effects may in some way mediate GnRH-induced LH/CG release from the pituitary and therefore may be tied to lactational anovulation/amenorrhea. More studies are required to define how such a mechanism might work. Opioids and dopamine also have been proposed as possible signals linking the suckling stimulus to GnRH suppression; however, the factors mediating this link remain unclear (McNeilly, 2001).

7. REPRODUCTIVE AGING

Primates, in common with many other mammals, display an inverted-U shaped pattern relating female fertility parameters to age (e.g., Caro et al., 1995; Smucny et al., 2004). Anovulation, insufficient luteolysis, and impairment

of gestational and lactational processes are all more common at the beginning and end of reproductive life (Atsalis & Margulis, 2008a). The extent to which late-life reductions in fertility are specifically due to aging neuro-endo-reproductive systems is, however, quite variable and often unclear. For example, Wright, King, Baden, and Jernvall (2008) report that aged female sifakas (*Propithecus edwardsi*), a Madagascar lemur, have decreased infant survival, but this effect is attributed to the females' aging dentition and resulting inability to support lactation. Thus, reduced fertility in old age does not, in and of itself, demonstrate impaired neuroendocrine or gonadal function.

p0375 Reproductive senescence will be used here to describe the process through which the HPG axis ages, resulting ultimately in cessation of function. Knobil and Neill (1994) provide an excellent overview of the process of reproductive senescence in laboratory rodents, and Wise (2006) provides a thoughtful perspective, comparing what is known regarding reproductive aging in rodents to that of women. Recent findings on nonhuman primate reproductive senescence, along with commentary, are found in Atsalis and Margulis (2008a). Female reproductive senescence differs among mammalian taxonomic groups. For example, in primates, the loss of the follicular pool is the primary event shaping the end of reproductive life, whereas, in rodents, striking variation is seen in the size of the follicular pool remaining at the end of reproductive life as well as at maximum lifespan (Wise, 2006).

p0380 Within primates, human females are unusual in experiencing follicular depletion relatively early in the maximal lifespan, resulting in an extended period of altered hormonal environments. These alterations stem from the declining negative feedback signals from the ovary (reduced circulating estrogens, P_4, and inhibin), resulting in elevated GTH concentrations for a time, followed by declining GTHs. These hormonal changes are believed to affect disease risks (Wise, 2006). The risk associated with bone loss due to decreasing estrogenic activity on osteoblasts is well described; however, cardiovascular effects continue to be hotly debated.

p0385 With increasing numbers of older nonhuman primates available for study, it is now clear that monkeys and apes also experience follicular depletion and associated hormonal alterations (Hodgen, Goodman, O'Connor, & Johnson, 1977; Graham, 1979; Tardif, 1985; Tardif & Ziegler, 1992; Shideler, Gee, Chen, & Lasley, 2001; Schramm, Paprocki, & Bavister, 2002; Atsalis & Margulis, 2008b; Videan, Fritz, Heward, & Murphy, 2008). However, the stage of life at which this occurs is generally later than that observed in humans (see Table 13.1). Atsalis and Margulis (2008a), in reviewing the data on monkeys and apes, conclude that 'potentially up to 25% of a female's life can be post-reproductive.' This claim is made in reference to maximal lifespan; in comparison, a human female living the maximal lifespan (now around 120 years) will spend around 58% of her life in a postreproductive state. When compared to average lifespan, as opposed to maximal lifespan, most nonhuman female primates will die at or before the point at which reproductive senescence begins. These comparisons have been controversial and will continue to be refined, given the oft-made claim that human female reproductive aging is unique and may be driven by indirect fitness advantages to postreproductive women providing resources to grandchildren; i.e., the grandmother hypothesis (Hill & Hurtado, 1991; Hawkes, 1997; Alvarez, 2000; Peccei, 2001a; 2001b).

AQ15

p0390 Male primates, in common with many other male mammals, display decreases in circulating T concentrations with age (Ellison et al., 2002; Hardy & Schlegel, 2004; Tardif et al., 2008). Data from men and male rodents indicate reduced GnRH pulse amplitude with age, though LH concentrations do not decline. Old marmoset males have lower excreted T and appear to be hyper-responsive to exogenous GnRH stimulation. These findings, taken together, suggest that age-related changes in hypothalamic function may be important drivers of reduced T concentration with age.

8. SEXUAL BEHAVIOR s0160

8.1. Description of Sexual Behavior s0165

p0395 Compared to other mammals, sexual behavior in primates is noteworthy for its flexibility — not so much with respect to the behavioral patterns used in courtship and copulation, but in the relative independence of these behaviors from hormonal control, especially in females. Here we describe the behavioral patterns commonly exhibited during primate courtship and copulation, and then discuss of the role of steroid hormones in regulating these behaviors. For a comprehensive review of these and other aspects of primate sexual behavior, see Dixson (1998).

p0400 Most primate species exhibit fairly stereotyped dorsoventral mounting postures, similar to other mammals (Dixson, 1998; Campbell, 2007). Numerous variations are seen, however; e.g., the male and female may sit, stand, or hang from tree branches while mating, and may even copulate while suspended upside-down (e.g., aye-aye (*Daubentonia madagascariensis*)). Males use a variety of methods to stabilize themselves against females, including single- and double-foot clasp mounting, in which the male uses one or both feet to grip the female's ankles or legs (e.g., macaques, baboons); the leg-lock, in which a male positions his legs over the female's thighs (e.g., spider monkeys (*Ateles* spp.); brown woolly monkeys (*Lagothrix lagotricha*)); and manual grasping of the female's hips or waist (e.g., tamarins (*Saguinus* spp.); owl monkeys (*Aotus*

spp.)) (Dixson, 1998). Ventro-ventral copulation is seen in a number of apes, and two species, human beings and bonobos, exhibit even more varied repertoires of copulatory positions.

p0405 Primate species differ markedly in the number and duration of intromissions prior to ejaculation (Dixson, 1998), although the most common pattern involves a single, brief intromission. For example, pygmy marmosets (*Cebuella pygmaea*) exhibit a single intromission lasting four to ten seconds and involving only several quick pelvic thrusts (Soini, 1988). In contrast, muriquis (*Brachyteles arachnoides*) perform an extended intromission, lasting an average of four minutes and consisting of a prolonged immobile period followed by five to ten pelvic thrusts and ejaculation (Milton, 1985), whereas rhesus macaques perform a series of up to twenty or more brief mounts, each lasting one to fourteen seconds, with two to fifteen pelvic thrusts per mount (Shively, Clarke, King, Schapiro, & Mitchell, 1982). Males and females often separate immediately or shortly after ejaculation, but in several species the male may remain intromitted for up to two minutes (stumptail macaque (*Macaca arctoides*) (Goldfoot et al., 1975)) or even several hours after ejaculation (thick-tailed greater galago (*Otolemur crassicaudatus*) (Eaton, Slob, & Resko, 1973)), suggesting the possibility of a genital lock.

p0410 Male primates use a variety of behaviors to initiate sexual interactions with females, including eye contact; specialized facial movements or expressions; approaches toward or following of the female; visual, olfactory, or oral investigation of the female's genitalia or sexual skin; and specific locomotor patterns (Dixson, 1998). Female sexuality, as described by Beach (1976), can be divided into three major components: attractivity (the female's attractiveness or stimulus value to a particular male), proceptivity (the female's behavioral role in initiating copulation), and receptivity (the female's willingness to copulate). Attractivity in primates may be based on both behavioral and nonbehavioral stimuli from females, including proceptive behaviors, sexual skin swellings in many Old World monkeys and apes, and olfactory cues in many prosimians and New World monkeys. Proceptivity is often a particularly striking aspect of primate sexual interactions. Females use a number of behaviors to arouse males' interest and solicit mating, including facial displays, specific body postures such as the 'sexual present' (presenting the anogenital region to the male), specialized vocalizations, and touching or even mounting the male (reviewed by Dixson, 1998). Sexual receptivity is manifest in stereotyped lordotic postures in at least some prosimian species, whereas female anthropoids do not exhibit lordosis. Consequently, receptivity in anthropoids is typically inferred from females' patterns of permitting, avoiding, refusing, or terminating mount attempts by males (Dixson, 1998).

8.2. Hormonal Influences on Sexual Behavior s0170

As in other male mammals, sexual behavior in male primates, including men, is clearly influenced by androgens. Male sexual behavior tends to correlate with circulating androgen concentrations both across the lifespan and, in seasonal breeders, across the annual reproductive cycle (Dixson, 1998). Castration generally decreases frequencies of sexual behavior, especially intromission and ejaculation, whereas T replacement reverses these effects. Both men and monkeys, however, exhibit pronounced interindividual variation in their responses to castration: while some individuals show rapid declines in, or complete obliteration of, sexual behavior following castration, others show a more gradual cessation of sexual behavior, and still others continue to exhibit virtually normal sexual behavior even years later (Hull, Wood, & McKenna, 2006). Testicular androgens do not, therefore, appear to be essential for the expression of male sexual behavior, in at least some individuals. p0415

The mechanisms by which androgens influence sexual behavior in male primates are not fully understood. In rodents, activational effects of androgens are mediated by intracellular aromatization of androgens to estrogens within the brain and subsequent binding to ERs. In primates, little evidence exists to support a critical role of aromatization in male sexual behavior; however, this issue has been addressed in only a small number of primate species, and therefore remains unresolved (Dixson, 1998; Wallen, 2005; Hull et al., 2006). Finally, P_4 inhibits male sexual behavior in both men and macaques (Hull et al., 2006). p0420

Female sexual behavior in nonprimate mammals is typically exhibited only during the periovulatory period and is critically dependent on stimulation by ovarian steroid hormones. Prosimians appear to follow a similar pattern: females are sexually receptive during a limited period around ovulation — in some cases, only several hours — and ovariectomy abolishes female sexual behavior (Van Horn & Eaton, 1979; Dixson, 1998). In contrast, sexual behavior in anthropoid primates is characterized by its emancipation from strict regulation by gonadal hormones: females may engage in sexual activity at any point in the ovarian cycle, during pregnancy, or even following ovariectomy or menopause (Dixson, 1998; Campbell, 2007). Although such findings demonstrate that the expression of sexual behavior in female primates is not *dependent* upon gonadal hormones, other evidence indicates that female sexual behavior can, nonetheless, be *influenced* by them. In many New World monkeys, Old World monkeys, and apes, females show periovulatory peaks in copulatory behavior, associated with increases in proceptivity, attractivity, and, to a lesser extent, receptivity (Dixson, 1998). Moreover, ovariectomy decreases, and estrogen replacement restores, sexual behavior in a number of species. Again, proceptivity p0425

often shows a clear relationship with hormonal status in these studies, whereas effects on receptivity are much less pronounced (Dixson, 1998).

p0430 In contrast to estrogens, progestogens tend to reduce receptivity, proceptivity, and attractivity in female primates. Finally, androgens of ovarian and/or adrenal origin have been implicated in stimulating both receptivity and proceptivity in female primates, especially rhesus macaques and women; however, findings have been mixed, and the role of ovarian or adrenal androgens in female sexual behavior remains unclear (Dixson, 1998; Johnson & Everitt, 2000). A particularly controversial issue has been whether estrogens and other steroid hormones influence female sexual activity through peripheral (e.g., sexual skin, olfactory cues) and/or central (i.e., brain) actions. Current evidence suggests that estrogens act peripherally to enhance attractivity, whereas estrogens, progestogens, and androgens may all act centrally to modulate receptivity and proceptivity (Dixson, 1998).

p0435 The relationship between the ovarian cycle and sexual behavior in female primates may be influenced profoundly by the environment, especially the social environment. For example, orangutans and rhesus macaques show a pronounced peak in copulatory frequency during the periovulatory period under conditions in which females can control access to males, but not when females and males are 'forced' to interact in free-access pair tests (Wallen, 1990; Dixson, 1998). Similarly, periovulatory peaks in proceptivity and copulation are much more pronounced in rhesus macaques tested in a grouped (multi-female, single-male) situation than when males and females are tested as isolated pairs (Wallen, 1990). Such findings may reflect the use of sexual behavior for nonreproductive functions, the relative abilities of males and females to control sexual interactions under different environmental conditions, and increased agonistic interactions among females of some species (e.g., rhesus macaques) during sexual interactions with males (Wallen, 1990; Dixson, 1998). Wallen (1990) has interpreted such findings as evidence that 'hormones influence the sexual motivation required to initiate sexual activity in social circumstances requiring social effort.' Clearly, in contrast to rodents, in which ovarian steroids are essential for both sexual motivation and sexual performance (i.e., lordosis), ovarian (and possibly adrenal) steroids are not necessary for copulation in female anthropoid primates but may be one of several important factors influencing sexual desire.

AQ16

s0175 9. ENVIRONMENTAL INFLUENCES ON REPRODUCTION

s0180 9.1. Reproductive Seasonality

p0440 Seasonal changes in the environment have long been known to affect reproduction in mammals. Outstanding comparative reviews of both proximate and ultimate aspects of mammalian reproductive seasonality are provided by Bronson (1989) and Malpaux (2006). For mammals in temperate regions, with strong circannual variation in both day length and temperature, the time of year at which various reproductive activities (mating, pregnancy, lactation) occur is often quite predictable, with dramatic differences in HPG function in breeding vs. nonbreeding seasons. Mammals adapted to tropical regions might be expected to have less striking reproductive seasonality, and that is the case with primates. The majority of primate species are restricted to tropical regions, macaques and humans being the best-studied exceptions. Primates exhibit an amazing array of seasonal patterning (see Table 13.1), ranging from predictable, relatively narrow breeding seasons, to seasonal, but quite variable, birth peaks, to no evidence of any seasonality. A comparison of these examples suggests that phylogeny is a poor predictor of these traits. While most prosimians are strongly seasonal and apes are generally not seasonal, the degree of seasonality in New World and Old World monkeys ranges from strong to nonexistent in a manner that is not explained by phylogeny within these groups.

p0445 Two primate genera with strongly seasonal patterns are the Central and South American squirrel monkeys (*Saimiri*) and the northernmost macaques (*Macaca*), such as rhesus macaques and Japanese macaques (*M. fuscata*). In these species, females either ovulate irregularly or fail to ovulate altogether during the nonbreeding season. Studies have suggested both central changes in GnRH pulsatility (Hendrickx & Dukelow, 1995) and direct changes in ovarian function (Hutz, Dierschke, & Wolf, 1985) as possible factors in seasonal anovulation of female rhesus macaques, but the exact mechanisms have not been fully elucidated. In squirrel monkeys, reductions in FSH secretion appear to underlie the seasonal shift from an ovulatory to an anovulatory pattern (Kuehl & Dukelow, 1975).

p0450 In both squirrel monkeys and rhesus macaques, males also display a seasonal pattern of T production, with peaks occurring as the mating season commences. Both squirrel monkey and macaque males display T-supported characteristics that arise during the breeding season. Male squirrel monkeys undergo weight gain of around 14%, caused largely by retention and deposition of water along the arms, shoulders, and back (Jack, 2007), as well as increases in testicular volume of 150% (Wiebe et al., 1984). During the nonbreeding season, male rhesus macaques display reduced LH pulsatility, reduced diurnal rhythms in pulsatility, regression of seminiferous tubules, and few spermatocytes or spermatids. In the months leading into the mating season, LH pulsatility increases, seminiferous tubular diameter increases, and spermatogenesis commences (Wickings & Nieschlag, 1980; Wickings, Marshall, & Nieschlag, 1986). Breeding males also display skin reddening, likely related to increasing T production.

AQ17 AQ18

p0455 The roles of specific environmental cues in generating these neuroendocrine changes in squirrel monkeys and rhesus macaques remain obscure; however, changing day length cues do not appear necessary, as the patterns are retained in controlled day length conditions (Wehrenberg & Dyrenfurth, 1983).

p0460 Circannual variation in the tropical environment is most strongly tied to rainfall that, in turn, generates seasonal variation in food availability. Where there is birth seasonality, births usually occur in the dry season; however, there are exceptions (e.g., Struhsaker & Leland, 1987). As a result of long gestation and lactation periods, primates cannot limit all reproductive investment to a single circannual period. For example, if weaning of infants is to occur during a period of relative food abundance, then other aspects of the reproductive cycle, such as mating and gestation, may occur during periods of relative food scarcity. Numerous attempts have been made to model the manner in which selective pressures may have shaped these responses, but no single model explains the wide variation seen in primate breeding schedules (Van Schaik & Brockman, 2005).

p0465 It is possible that some seasonal patterning results from alterations in physical activity or food availability. In women, e.g., high levels of physical activity are associated with suppressed ovarian function (Jasienska & Ellison, 2004). The increased day range lengths and home range sizes seen in some primate species during times of scarcity (Hemingway & Bynum, 2005) may inhibit HPG axis activity through altering energy balance or stress (See Section 9.3).

s0185 9.2. Social Influences on Reproduction

p0470 Primates exhibit a broad diversity of social systems, including a dispersed, relatively solitary lifestyle; social monogamy and nuclear family units; single-male, multi-female groups; and multi-male, multi-female societies, some of which may undergo complex fission/fusion patterns. In each of these social configurations, reproductive function of females, and in some cases males, may be modulated by salient social cues. The nature and magnitude of these socioendocrine effects, as well as the behavioral or sensory cues eliciting them, vary markedly among species, sexes, and social systems. In general, though, both males and females often exhibit enhanced activity of the HPG axis in response to interactions with or cues from unrelated, opposite-sex adults, and inhibition of HPG activity in response to same-sex adults, especially those of higher dominance status. Such effects may influence the course of reproductive maturation in adolescents, or may alter or even abolish fertility in fully mature adults. Below we describe some of the best-studied examples in each sex.

9.2.1. Males s0190

9.2.1.1. Social influences on reproductive maturation in males s0195

p0475 In several primate species, the timing and/or trajectory of reproductive maturation in males is reported to be influenced by the social environment. Most commonly, adolescent males of high dominance status, or those with high-ranking mothers, have been found to undergo earlier puberty and to have higher circulating or excreted T concentrations and larger testes, compared to lower-ranking males. Among captive rhesus macaques, e.g., both plasma T concentrations and testicular mass (either absolute or corrected for body mass) in adolescent males tend to correlate with the males' dominance status, especially at the outset of the mating season (Bercovitch, 1993; Dixson & Nevison, 1997). Moreover, adolescent males with high-ranking mothers or from high-ranking matrilines have higher plasma T levels and heavier testes, and may attain puberty earlier, than those with lower-ranking mothers (Dixson & Nevison, 1997; Mann, Akinbami, Gould, Paul, & Wallen, 1998).

p0480 Similar patterns have been described in semi-free-ranging mandrills, in which adolescent males that were relatively high-ranking for their age had higher circulating T levels, larger testes, and greater development of secondary sexual characteristics (sexual skin coloration and activity of the sternal scent gland) than lower-ranking adolescents (Setchell & Dixson, 2002). In free-ranging baboons (*Papio cynocephalus*), the onset of puberty, as determined by the age of testicular enlargement, was significantly correlated with maternal rank, with sons of high-ranking females undergoing testicular enlargement up to a year earlier than sons of low-ranking females (Alberts & Altmann, 1995). Interestingly, the age at testicular enlargement is also advanced in sons of high-ranking males if their father remains in the same social group during the son's juvenile development (Charpentier, Van Horn, Altmann, & Alberts, 2008b).

p0485 Social modulation of male reproductive development is especially pronounced in the orangutan. In both wild and captive populations, adolescent males living in proximity to fully adult males often, but not always, exhibit delayed development of secondary sexual characteristics, including cheek flanges, laryngeal sac, beard and mustache, musky odor, and large body size (Kingsley, 1982; Maggioncalda, Sapolsky, & Czekala, 1999; Setchell, 2003). Such 'developmentally arrested' adolescents are fertile and may sire offspring; however, they appear to be sexually unattractive to females and may commonly force copulations (Utami, Goossens, Bruford, De Ruiter, & Van Hooff, 2002). These males exhibit significantly reduced urinary concentrations of T, DHT, LH, cortisol, and PRL (but not FSH), as compared to adolescents undergoing development of

secondary sexual characteristics (Maggioncalda et al., 1999; Maggioncalda, Czekala, & Sapolsky, 2002). The precise role of adult male orangutans in suppressing reproductive maturation in adolescents has not been tested experimentally; however, anecdotal evidence from both captive and free-living orangutans indicates that, after the removal or disappearance of a nearby, fully developed adult male, arrested adolescents may rapidly resume sexual development and attain full maturation within several months, even after a period of developmental arrest lasting 20 years or more (Maggioncalda et al., 1999; Utami, 2000, cited in Setchell, 2003).

s0200 9.2.1.2. Social influences on reproduction in adult males

p0490 Reproductive function of adult males can be influenced by both intrasexual and intersexual stimuli in a wide variety of primates. Typically, interactions with or cues from other adult males dampen activity of the HPG axis, while interactions with or cues from adult females have stimulatory effects. These two classes of socioendocrine effects may interact with each other and with responses to other environmental cues (e.g., photoperiod) in complex ways.

p0495 One of the best-studied examples is the gray mouse lemur (*Microcebus murinus*), a small, nocturnal, relatively nonsocial prosimian (reviewed in Perret, 1992). In captive, mixed-sex social groups, middle- and low-ranking males engage in very little sexual behavior and exhibit low circulating T concentrations during the annual mating period, as compared to dominant males. Moreover, circulating levels of sex hormone-binding globulin are elevated in middle- and low-ranking males, further reducing the bioavailability of T to the tissues. Circulating cortisol concentrations do not differ among high-, middle-, and low-ranking males but are elevated in all group-housed males, as compared to socially isolated males, suggesting that social housing *per se*, but not necessarily subordination, is stressful.

p0500 Circulating T levels in male gray mouse lemurs are modulated by a chemosignal found in the urine of socially dominant or isolated males (Perret, 1992). Interestingly, response to the male chemosignal varies across the annual cycle (Perret & Schilling, 1995). During the onset of photoperiodic stimulation (i.e., long days, as would occur at the outset of the breeding season), exposure to urine from an isolated or dominant male reduces T levels in other males. During continued exposure to long day lengths (i.e., later in the breeding season), exposure to male urine delays testicular regression and the decline in T levels that would normally result from photorefractoriness. Finally, during exposure to inhibitory short days (i.e., the nonbreeding season), exposure to male urine stimulates testicular recrudescence and markedly elevates plasma T levels. Under any of these photoperiodic conditions, circulating T levels can be increased in males by exposure to chemosignals from females, especially during the females' proestrus period. The neuroendocrine mechanisms mediating these stimulatory and inhibitory social effects are not fully understood but appear to involve both PRL and the endogenous opiates (Perret, 1992).

p0505 Circulating T concentrations in males are similarly influenced by social partners of both sexes in the squirrel monkey, a seasonally breeding New World primate that lives in large, multi-male, multi-female groups. In captivity, plasma T levels are higher in males housed with multiple females than in males housed with only a single female, and are higher in dominant males than in intermediate- and low-ranking males (Mendoza, Coe, Lowe, & Levine, 1979; Schiml, Mendoza, Saltzman, Lyons, & Mason, 1996). Nonetheless, seasonal changes in T, as well as in circulating cortisol levels and body mass, occur in all males, regardless of social rank or access to females (Schiml et al., 1996; Schiml, Mendoza, Saltzman, Lyons, & Mason, 1999). Importantly, inter-individual differences in T levels result from, rather than cause, differences in rank: male T levels prior to group formation do not predict subsequent attainment of social status, but increase in dominant males and decrease in subordinates following both formation of all-male groups and introduction of females (Mendoza et al., 1979).

9.2.2. Females s0205

p0510 Reproductive attempts are considerably more costly for female mammals than for males, as a consequence of the physical constraints and energetic demands imposed by pregnancy, lactation, and maternal behavior. Consequently, females are likely to undergo more intensive selection than males to initiate breeding attempts under auspicious environmental conditions, and hence to take advantage of environmental cues indicative of conditions favorable for infant survival, including cues arising from the social environment (Wasser & Barash, 1983). Not surprisingly, therefore, females across a wide range of primate taxa exhibit clear reproductive responses to social variables. As with males, social factors can modulate the timing and trajectory of reproductive maturation in young females, as well as reproductive physiology in fully mature adults.

9.2.2.1. Social influences on reproductive maturation in females s0210

p0515 In several primate species, interactions with or cues from unrelated adult males advance puberty in young females. Female Garnett's greater galagos and Senegal lesser bush babies (*Galago senegalensis*), e.g., undergo their first vaginal estrus significantly earlier if pair-housed with an adult male than with a peer male (Izard, 1990). Similarly,

cohabitation with a stepfather has been associated with earlier puberty in human girls (Ellis & Garber, 2000).

p0520 As in male primates, interactions with or cues from same-sex conspecifics tend to delay puberty in females. Among captive rhesus macaques, e.g., age at menarche is not associated with dominance status, but high- and middle-ranking females undergo their first ovulation at significantly younger ages than low-ranking females (Schwartz, Wilson, Walker, & Collins, 1985; Zehr, Van Meter, & Wallen, 2005). In free-ranging baboons (*P. cynocephalus)*, menarche occurs earlier in daughters of high-ranking females than in daughters of low-ranking females (Bercovitch & Strum, 1993; Wasser, Norton, Kleindorfer, & Rhine, 2004; Charpentier, Tung, Altmann, & Alberts, 2008). Earlier menarche in baboons is also associated with a number of additional social factors, including living in a group with more maternal half-sisters or fewer adult females, and a longer period of coresidency with the father during the daughter's juvenile period (Charpentier et al., 2008a; 2008b). The mechanisms underlying such social modulation of female reproductive maturation are not known but have been suggested to involve differences in nutritional status, body mass, or psychosocial stress (Bercovitch & Strum, 1993; Wallen & Zehr, 2004; Zehr et al., 2005).

s0215 #### 9.2.2.2. Social influences on reproduction in adult females

p0525 Social cues influence ovarian cycle dynamics in adult females of several primate species. In gray mouse lemurs, both tactile and distal cues from other females cause lengthening of the ovarian cycle, associated with an increase in luteal-phase length and a decrease in plasma P_4 concentrations (Perret, 1986). In women, axillary secretions both from other women and from men have been implicated in modulating the ovarian cycle. Axillary secretions taken from women in the late follicular phase increase LH pulse frequency, advance the timing of the preovulatory LH surge, and shorten ovarian cycle length in recipients, whereas axillary secretions collected from women during the ovulatory phase of the cycle produce the opposite effects (Stern & McClintock, 1998; Shinohara, Morofushi, Funabashi, & Kimura, 2001). Collectively, these effects might underlie the pattern of menstrual synchrony documented in many, but not all, studies of women roommates, friends, and coworkers (Weller & Weller, 1993). Luteinizing hormone pulse frequency is also increased in women exposed to axillary secretions from men (Preti, Wysocki, Barnhart, Sondheimer, & Leyden, 2003).

p0530 Perhaps the most dramatic example of social regulation of reproduction in female primates is reproductive suppression in the Callitrichidae (marmosets and tamarins). These small New World monkeys live in groups of approximately 4−15 individuals, which may include several adults of each sex as well as juveniles and infants. In most species of callitrichid, however, only a single, behaviorally dominant female breeds in each social group (Digby, Ferrari,& Saltzman, 2007). Subordinate females fail to breed, as a result of social suppression of ovulation and/or inhibition of sexual behavior, and instead serve as nonreproductive alloparents, helping to rear the infants of the dominant female. The mechanisms underlying this social control of fertility, or 'social contraception' (Abbott, 1984), differ among species (French, 1997) but have been studied most thoroughly in the common marmoset (reviewed by Abbott, Digby, & Saltzman, 2009; Saltzman, Digby, & Abbott, 2009). Most subordinate females in laboratory groups of common marmosets, and at least some in wild groups, fail to ovulate and exhibit impairments in ovarian steroidogenesis and follicular development. These deficiencies in ovarian function, which may last for periods of up to several years or more, are caused by suppressed pituitary secretion of CG, which is released by the anterior pituitary instead of LH in this species (see Section X). The AQ19 exact mechanism underlying CG inhibition is not yet known; however, it appears to be associated with enhanced negative-feedback sensitivity of the brain and/or pituitary to low levels of estrogen, blunted responsiveness to estrogen-positive feedback, and enhanced CG inhibition by AQ20 endogenous opioids. Surprisingly, however, CG suppression does not appear to be associated with altered hypothalamic secretion of GnRH and is not accompanied by manifestations of generalized stress (Abbott et al., 2009; Saltzman et al., 2009).

9.3. Energetics of Reproduction s0220

9.3.1. Introduction s0225

p0535 The mammalian reproductive system is adept at monitoring maternal condition and parsing the energy available for gamete production, fetal growth, and infant growth. The manner in which maternal energetic state is sensed and signals are processed to alter reproductive function has been a particularly active area of research for the past two decades. A good part of that research interest has been driven by the discoveries of a variety of endocrine and autocrine factors produced by adipose tissue, as well as identification of new hormones produced by the gastrointestinal tract, all offering a myriad of possible cues of metabolic state (Wade, Schneider, & Li, 1996; Baird, Cnattingius, Collins, & Evers, 2006; Tena-Sempere, 2007; Roa et al., 2008).

p0540 From the standpoint of tradeoffs, one would expect that early stages of reproduction, including ovulation, placentation, and fetal growth, might be more plastic in response to maternal energy stores than lactation because of the

extent of investment already made late in the reproductive event. The ability of the mother to 'cut bait' early in investment and save energy stores for future investment might offer more of a selective advantage the earlier in reproduction this event occurs. Later investment, including lactation, by which time the primate mother has already invested large amounts of energy and time in the infant, should be less responsive to changes in maternal energy stores, enhancing the likelihood that the mother's investment (i.e., the offspring) survives. Therefore, certain stages of placental, fetal, and infant development may be more affected by changes in maternal status than others, and the manner in which autocrine, paracrine, and hormonal factors convey information regarding maternal energy state differs among the following points at which a female mammal might adjust investment: ovarian folliculogenesis leading to ovulation; placental transfer of resources from mother to fetus; and mammary gland transfer of resources from mother to infant. What follows is a discussion of autocrine/endocrine signals that may act at different points in the primate reproductive cascade to signal energy excess or deficit.

s0230 ### 9.3.2. Energetics of hypothalamic-pituitary function

p0545 The cellular processes leading to maturation of gametes — both sperm and ova — are controlled by central nervous system mechanisms that respond to both negative feedback and positive feedforward from steroids and other hormones produced by the gonads. The basics of this HPG axis control system have been relatively well characterized for some time. More recent research has begun to better characterize those signals that may alter pituitary GTH release — through either altered hypothalamic GnRH pulse generation or direct effects on the pituitary — and thus alter the production and release of gametes. Recently identified signals that may indicate energetic state include leptin, produced in adipose tissue, and ghrelin, produced in the gastrointestinal tract.

p0550 As circulating leptin concentration is correlated with the amount of adipose tissue, leptin can function as a signal of stored energy availability. As such, the impact of leptin in the central nervous system is generally to reduce food intake and to enhance reproduction. Studies in rodents, monkeys, and humans reveal that leptin exposure stimulates pituitary LH release (Tena-Sempere, 2007). Normal pulsatile release of LH and FSH can be restored by leptin treatment in calorie-deprived women (Schurgin, Canavan, Koutkia, Depaoli, & Grinspoon, 2004). In rats, intrahypothalamic infusion of leptin alters GnRH pulse generation (Watanobe et al., 2005), but there is also evidence of direct effects of leptin upon pituitary gonadotropes. The interaction of leptin with GnRH neurons may be mediated by Kp (Tena-Sempere, 2007). While the overall picture of leptin as an energy signal is one in which leptin supports reproduction, leptin also has been found in some studies to perform actions that may impair GTH release (see also Section 9.3.3). In addition, studies of human obesity indicate that individuals with extremely high adiposity may become leptin-resistant. The full picture of the manner in which leptin, alone or in concert with other signals, alters HPG axis function remains, therefore, to be elucidated.

AQ21

p0555 As opposed to leptin, the peptide ghrelin, produced by the gastrointestinal tract, is a potent orexigenic stimulus in the hypothalamus and has been proposed as a signal of energy insufficiency. Ghrelin, like leptin, affects reproductive aspects of HPG axis function as well as t food intake. Administration of ghrelin inhibits LH pulsatility in rodents and monkeys (Vulliémoz et al., 2004). Recent studies suggest that this effect may be mediated by the HPA axis: ghrelin induces elevations in circulating glucocorticoid concentrations, and inhibition of this action abolishes ghrelin's ability to alter LH pulsatility (Vulliémoz, Xiao, Xia-Zhang, Rivier, & Ferin, 2008).

AQ22

9.3.3. Energetics of gonadal function

s0235

p0560 The actions of the HPG axis on folliculogenesis and ovulation are mediated by a large number of peptide signals, many of which are produced in the ovary. Some of these signaling systems are reasonable prospects as possible metabolic cues. A primary example is the IGF system. Insulin-like growth factor-1 and IGF-2 are present in follicular fluid, as are five of the six IGF-binding proteins that control cellular access to IGFs. Locally produced IGF and local control of IGF-binding proteins are proposed to regulate the development and/or atresia of antral follicles (Giudice, 2001). However, because circulating IGF is controlled by GH, a hormone that is sensitive to energy state, the IGF system that mediates folliculogenesis also may be affected by energy state.

p0565 In contrast to the hypothalamus and pituitary, where leptin and ghrelin have largely opposing effects, the direct effect of both of these peptides on the gonads is to inhibit production of steroids (T in the testis, E_2 in the ovary). In addition, expression and immunostaining studies indicate that ghrelin is produced by the gonads, as well as by the gastrointestinal tract (Tena-Sempere, 2007). The manner in which leptin and ghrelin exert local effects on primate gonads remains to be elucidated.

9.3.4. Energetics of pregnancy

s0240

p0570 Pregnancy represents a peculiar environment in which the short- and long-term reproductive interests of the mother are played out with — or against — the short-term interests of the fetus. Variation in placental structure and function

are mechanisms through which the mother may alter investment in the fetus, but they are also mechanisms through which the fetus may manipulate maternal investment (Haig, 1993; 1996; Crespi & Semeniuk, 2004). For example, increases in litter size in the common marmoset are accompanied by a dramatic expansion of the placental interface, which is the site of fetomaternal nutrient and hormonal exchange (Rutherford & Tardif, 2009). As the placenta has the same developmental legacy and genomic identity as the fetus, this functional plasticity has important implications for metabolic and hormonal signaling.

p0575 Placental growth is driven mostly by placentally derived growth factors, the most important being IGF-2, and mostly is inhibited by maternal factors (Lewis, Morlese, Sullivan, & Elder, 1993; Crossey, Pillai, & Miell, 2002). In nonprimates, deficiency of IGF-1 or IGF-2 results in a reduction in birth weight (Fowden, 2003; Gicquel & LeBouc, 2006). In cases of intrauterine growth restriction (IUGR), there is often a higher fetal : placental weight ratio, suggesting that the placenta may actually be more efficient in the transport of nutrients (Constância et al., 2002; Rutherford & Tardif, 2008), even though that increased efficiency is ultimately insufficient to sustain normal growth. Deficiency in IGF-2 leading to IUGR may be associated with upregulation of amino acid transport systems (Constância et al., 2002), indicating a specific role for placental hormonal signals in directing fetal metabolic pathways.

p0580 Two other placental hormones, GH and leptin, have been proposed to mediate a maternal insulin resistance and, therefore, a shift toward reliance on lipolysis for energy production. In humans, reduced placental GH and, therefore, reduced maternally produced IGF-1 is associated with IUGR (Lacroix, Guibourdenche, Frendo, Muller, & Evain-Brion, 2002). At the other end of the spectrum, gestational diabetes in humans is associated with markedly higher concentrations of placental leptin, and leptin pathways have been suggested as one of the possible mechanisms underlying diabetes-induced fetal macrosomia (i.e., birth weight ≥ 4000 g) (Hauguel-de Mouzon et al., 2006).

p0585 While numerous studies describe the relations among maternal condition and birth outcomes in primates, including humans (e.g., Lee, Majluf, & Gordon, 1991; Bowman & Lee, 1995; Fairbanks & McGuire, 1995; Bercovitch, Lebron, Martinez, & Kessler, 1998; Johnson, 2003), there are few primate studies in which maternal condition has been manipulated systematically. One such study was conducted in captive common marmoset monkeys exposed to a modest (25%) restriction of energy intake during either mid or late pregnancy. This restriction resulted in abortion of all mid-term pregnancies. Maternal urinary concentrations of CG, cortisol, and free E_2 were all lower in the restricted pregnancies, suggesting that the change in maternal energy availability resulted in impaired placental function. Restrictions in late pregnancy did not reliably induce pregnancy loss, though the number of preterm deliveries was higher than expected (Tardif, Power, Layne, Smucny, & Ziegler, 2004; Tardif, Ziegler, Power, & Layne, 2005). The extreme outcome in the face of a relatively modest restriction at midpregnancy suggests that placental formation and function in this very small primate is quite sensitive to maternal energy state. In contrast, a similar level of food restriction in captive baboons affected placental weight but not fetal growth (Schlabritz-Loutsevich et al., 2007), with fetal growth perhaps protected by decreased maternal activity and increased use of maternal stores.

9.3.5. Energetics of lactation

s0245

Given the time and energy investment represented by the primate neonate, one might propose that maternal postparturition investment would be somewhat less sensitive to maternal condition. Neville (2001) states that, 'unlike the nutrition received by the fetuses through the placenta, the nutrition received by breastfed infants is not dependent upon the status of maternal metabolism. For most milk components, the secretory mechanisms are insulated from the regulatory mechanisms that control nutrient flux in mothers, so sufficient milk of adequate composition is available to infants even during inadequate food intake by mothers.' Studies of primate milk are limited to a few species, with most studies being done in humans. While intra- and inter-species variation in relative fat content and, therefore, in energy density is a common finding (Power, Oftedal, & Tardif, 2002; Milligan et al., 2008), a complete failure of milk production is rare, supporting Neville's contention that milk production is more insulated from maternal insults. In lactating common marmosets that had either variable energy demand (e.g., nursing singletons vs. twins) or variable maternal energy availability (e.g., different maternal nutritive conditions or maternal energy restriction), the combination of high energy demand and low maternal stored energy availability resulted in slower growth of infants, but in no case did mothers cease investment (i.e., stop lactating) (Tardif, Power, Oftedal, Power, & Layne, 2001; Tardif & Ross, 2009).

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Perhaps the largest effects of maternal condition on lactation are noted in relation to the time to weaning. Lee et al. (1991) proposed that weaning in primates was related to attainment of critical weights, so that slower-growing infants (e.g., infants of mothers with lower milk energy) would be expected to be weaned at later ages. As the mother's milk production is driven by the relative amount of emptying of the alveolar lumen, the lactating mother and the nursing infant make up a complex, behaviorally driven feedback system.

s0250 10. CONCLUSIONS AND FUTURE DIRECTIONS

p0600 Primates are morphologically generalized mammals that are distinguished by their large brains, advanced cognitive abilities, flexible behavior, sophisticated social systems, and long lives (Hartwig, 2007; Zimmermann & Radespiel, 2007). Although primate species exhibit marked diversity in morphology, ecology, life-history parameters, and social organization, they share a reproductive profile characterized by low fecundity and extensive investment in each infant, associated with delayed reproductive maturation, long gestations, small litters, large neonates, long lactational periods, and slow postnatal growth (Zimmermann & Radespiel, 2007). These trends are especially pronounced in the anthropoids (monkeys, apes, and humans), which additionally exhibit hemochorial placentation, menstrual cycles in many species, and emancipation of sexual behavior from hormonal influences, particularly in females. The evolutionary basis of these reproductive patterns is not fully understood but is thought to be associated with development of primates' characteristic large brains and cognitive sophistication (Harvey, Martin, & Clutton-Brock, 1987; Leigh, 2004; Martin, 2007; Zimmermann & Radespiel, 2007).

p0605 As reviewed above, many aspects of reproduction have been studied intensively in a small number of primates. In contrast, for most of the 637 extant species and subspecies – of which one third to one half are currently threatened with extinction (Strier, 2007; Rylands, Williamson, Hoffmann, & Mittermeier, 2008) – little or no systematic information on reproductive physiology is available. In recent years, however, the development of noninvasive methods for monitoring reproductive hormones (e.g., fecal, urinary, and salivary assays) has begun to greatly expand our knowledge of reproductive function in a wide range of primates in both captive and wild settings (Lasley & Savage, 2007). A top priority for future research on primate reproduction should be to characterize basic reproductive parameters and processes in some of the less-studied taxa, such as the tarsiers, pitheciines (New World sakis, uakaris, and tit monkeys), colobines (Old World leaf-eating monkeys), and hylobatids (gibbons and siamangs). Further, in view of the ubiquity of environmental instability, in terms of anthropogenic habitat degradation, global climate change, and, potentially, exposure to endocrine-disrupting chemicals, it is vital to deepen our understanding of environmental influences on reproductive physiology and reproductive behavior in a variety of primate taxa. Ultimately, both broadening and deepening our understanding of primate reproductive function can provide new insights into human reproduction, will illuminate the evolution of primate life histories, and may make important contributions to captive management and conservation efforts.

AQ25

ABBREVIATIONS

AQ26

11β-HSD	11β–hydroxysteroid dehydrogenase
ACTH	Corticotropin
CG	Chorionic gonadotropin
CRF	Corticotropin-releasing factor
CRH	Corticotropin-releasing hormone
CS	Chorionic somatomammotropin
DDE	Dichlorodiphenyldichloroethylene
DDT	Dichlorodiphenyltrichloroethane
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulfate
DHT	Dihydrotestosterone
E_1	Estrone
E_2	Estradiol
ER	Estrogen receptor
FSH	Follicle-stimulating hormone
GABA	γ-aminobutyric acid
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
GPR54	G-protein receptor 54
GTH	Gonadotropin
HPA	Hypothalamus-pituitary-adrenal
HPG	Hypothalamic-pituitary-gonadal
IGF	Insulin-like growth factor
IL	Interleukin
IUGR	Intrauterine growth restriction
Kp	Kisspeptin
LH	Luteinizing hormone
MEL	Melatonin
NMDA	*N*-methyl-D-aspartate
NPY	Neuropeptide Y
OXY	Oxytocin
P_4	Progesterone
$P450_{scc}$	P450 cholesterol side-chain cleavage
PCB	Polycholorinated biphenyl
PCOS	Polycystic ovary syndrome
$PGF_{2\alpha}$	Prostaglandin $F_{2\alpha}$
PR	Progesterone receptor
PRL	Prolactin
T	Testosterone
T_3	Triiodothyronine
T_4	Thyroxine
TGFβ	Transforming growth factor-β
TSH	Thyrotropin

AQ27

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