

Developments in Primatology: Progress and Prospects

Series Editor: Louise Barrett

Kathryn B.H. Clancy

Katie Hinde

Julienne N. Rutherford *Editors*

Building Babies

Primate Development in Proximate
and Ultimate Perspective

 Springer

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Series Editor

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Editors

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and Ultimate Perspective



Springer

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*We dedicate this book to babies, and to those
who build them.*

Preface

The building of primate babies is a confluence of genes, ecology, nutrition, activity, health, and social dynamics experienced by both the parent and the offspring in time and space. To maximize lifetime reproductive success, parents must allocate finite resources to maintenance and reproduction, precipitating trade-offs among parental condition, current and future reproduction, and quality and quantity of offspring. Moreover, reproductive function and parental style themselves are shaped by early life and intergenerational factors. As a result, each individual's developmental trajectory varies as a function of parental investment and behavioral care. The developing primate, however, is not a passive recipient of parental investment, but can exploit physiological and behavioral mechanisms to extract parental resources to a greater extent than is in the parent's interest to provide. Consequently, development is perhaps an overly simplistic term for a process that is a dynamic relationship between progeny and parent.

Adult primates encounter complex social dynamics and diverse foraging tasks that directly influence survival and reproduction, the currency of natural selection. Yet the physical, physiological, cognitive, neurobiological, and behavioral capacity to confront these challenges reflects, in part, the unique ontogeny of each individual. For these reasons, investigations of developmental processes inform our understanding of what it means to be a primate. Primates are generally characterized by slow life histories, complex neurobiology and social dynamics, relatively large brains, and high parental investment in dependent offspring. Development is directly relevant to all these phenomena, as the chapters in this book demonstrate. Here we address ontogeny in a comparative framework, one that explicitly includes humans as primates, not just nonhuman primates, as model systems for human biology and evolution. In this way, we gain a deeper insight into the evolution, function, and causation of developmental trajectories in the order *Primates*.

Building Babies explores the dynamic multigenerational processes of development from many perspectives. The book is organized thematically along the developmental trajectory: conception, pregnancy, lactation, the mother–infant dyad, broader social relationships, and transitions to independence and adulthood. In this volume, we showcase the myriad approaches to understanding primate developmental trajectories

from both proximate and ultimate perspectives. These collected chapters provide insights from experimental manipulations in captive settings to long-term observations of wild-living populations, and consider levels of analysis from molecule to organism to social group to taxon. In addition, strepsirrhines, New World monkeys, Old World monkeys, apes, and humans are all well represented in this volume. Contributions by anthropologists, microbiologists, psychologists, population geneticists, and other experts passionate about primates provide *Building Babies* a uniquely diverse voice. We thank the authors for the care with which they put together their chapters from the outset and through the course of this book's development.

Each chapter in this book was reviewed by two or more of the editors in addition to being anonymously reviewed by two to four external referees. We are very appreciative of the numerous colleagues who peer reviewed chapter drafts and in so doing greatly enhanced the quality of this volume. We thank David Abbott, Michael Bailey, Jacinta Beehner, Alison Bell, Michelle Bezanson, Kristin Bonnie, Graham Burton, Katharine Campi, Isabella Capellini, David Coall, Herbert Covert, Jeremy De Silva, Amanda Dettmer, Leslie Digby, Christine Edwards, Peter Ellison, Melissa Emery Thompson, Paul Garber, Peter Gray, Robin Hudson, Laura Klein, Richard Lawler, Steve Leigh, Rebecca Lewis, Zarin Machanda, Dario Maestripieri, William Mason, Thom McDade, Talia Melber, Krista Milich, Carson Murray, Michael Nelson, Teague O'Mara, Ivy Pike, Meredith Reiches, Jeff Rogers, Michael Rudolph, Wendy Saltzman, Mar Sanchez, Karen Strier, Erin Sullivan, Elizabeth Sweet, Lin Tao, Zaneta Thayer, Jan Thornton, Wenda Trevathan, Claudia Valleggia, Eric Vallender, Derek Wildman, Jesse Young, and several anonymous others for their thoughtful comments.

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Lastly, we Lady Editors thank each other, having proved that the best starting point for an edited volume is finding co-editors with whom you agree unanimously on almost all editorial decisions and with whom you can really have an awesome time!

Cambridge, MA
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Part I
Conception and Pregnancy

Chapter 1

Inflammation, Reproduction, and the Goldilocks Principle

Kathryn B.H. Clancy

Keywords Inflammation • C-reactive protein • Ovarian function • Endometrial function • Pregnancy • Reproductive ecology • Human

1.1 Introduction

Great apes are a very low fertility clade among the already relatively low fertility primates. Giving birth largely to singletons, apes have interbirth intervals that range from 2 years to over 8 years (Furuichi et al. 1998; Galdikas and Wood 1990; Knott 2001; van Noordwijk and van Schaik 2005; Watts 1991; Wood 1994); confining human analyses to foragers ups the low end of the range to almost 4 years (Galdikas and Wood 1990; Lancaster et al. 2000). Apes undergo repeated, often very frequent copulations in the periovulatory period, and it still takes up to a year after lactational amenorrhea or anestrus has ceased for many to conceive (Watts 1991; Wood 1994).

Ultimate determinants of great ape low fertility include high parental investment and slow life histories (Kaplan 1996; Kaplan and Lancaster 2003; Walker et al. 2008). Because large-bodied hominoids, especially humans, rely on their parents and community for so long, a longer interbirth interval maximizes quality of each offspring, particularly as dependence of each offspring can overlap significantly. This longer interval also helps prevent maternal depletion, given the very high energetic costs of gestation and lactation, which then permits investment in future offspring.

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The study of proximate determinants of reproduction has largely fixated on energetics and ovarian suppression and to a lesser degree advancing age as it impacts chromosomal abnormalities and irregular cycles. Examining energetics and age reflects an attempt to understand the competing interests of current and future reproduction, growth and maintenance, and size, number, and sex of offspring because of the balance of weighing one's somatic investment with reproductive and sexual maturation when investing in offspring. This research has made it possible to understand how energy availability and energy balance impact reproductive cycles across multiple reproductive states and ages and is of enormous value to reproductive ecology and life history theory.

While energetic constraint is crucial to variation in ovarian hormones and reproductive cycles, other ecological stressors can also pull resource away from reproduction. Systemic inflammation offers a window into the ways in which ecological stressors increase somatic maintenance. Allocating energy towards maintenance demonstrates life history trade-offs in favor of survival over growth or reproduction, which may be necessary in marginal or otherwise constrained environments. Inflammatory processes are additionally important to attempts to implant an embryo and support a pregnancy. This means that determining whether inflammation is a cause or consequence of reproductive variation will be a continual challenge.

Inflammation is a biological response to trauma, from physical injuries to pathogens. Inflammation is a way the body tries to remove harmful stimuli and begin the healing process. And while acute stimulation of inflammatory processes is beneficial to the immune system, constant stimulation such that inflammation becomes chronic is correlated with several negative health outcomes. Prolonged inflammatory processes can lead to a constant cycle of cell destruction and healing. This may strain resources, shift the sensitivity of the immune system, or lead to amyloidosis, the depositing of excessive amyloid proteins in tissues of the body that is a precursor to diseases ranging from arthritis to Alzheimer's disease (Cunnane 2001; Merlini and Bellotti 2003).

Women's reproductive functioning involves significant tissue remodeling, the cycle of growth and repair that leads to the selection of a dominant follicle, ovulation, implantation, placentation, pregnancy, parturition, and lactation. Tissue remodeling is not only a kind of maintenance effort but is itself an inflammatory process. So inflammation can be caused by ecological stressors or simply the benign, normal functioning of the body. It is possible that activation of inflammatory processes from ecological stressors could disrupt normal tissue remodeling in female reproductive physiology, as well as shunt resources towards immune rather than reproductive function. Thus, there are two avenues that could connect the relationship from ecological stress to inflammation to reproductive function, disruption of function or diverting of resources, and an avenue from reproduction back to inflammation via normal tissue remodeling.

The reproductive system's sensitivity to ecological stressors, not just the stressors themselves, may be important to understanding variability in reproductive outcomes. An array of molecularly focused, clinical data demonstrate how the inflammatory

environment impacts reproductive success: too high an inflammatory response, or too low, and fetal loss follows. The Goldilocks principle seems useful here: the mother wants the environment to be “just right” in order to be willing to sustain a fetus. The way in which one’s inflammatory milieu must be “just right” for a pregnancy to take hold reflects multiple maternal trade-offs: between immunocompetence and reproductive success, maternal and paternal strategies, and maternal and fetal strategies.

This means an inflammatory milieu supportive of implantation, but how do we know “just right” when we see it? Further, is “just right” population dependent, and what are the evolutionary implications for this? The study of the inflammatory milieu is an ideal place to expand our understanding of proximate and ultimate determinants of reproductive success, and the purpose of this chapter is to expose the intersection between the two.

Therefore, I will review the factors that produce variation in inflammatory processes, the evidence for sensitivity to attenuations in inflammatory processes for reproduction, and the broader implications of this work. These data show that building babies requires not only adequate energy but an adequate prediction of immunological and psychosocial investment to be successful.

1.2 What Modulates Inflammation?

The maternal environment is context dependent, and due to high physiological investment during pregnancy and lactation, fairly choosy around the circumstances under which conception, implantation, and gestation occur. This complicates achievement of a “just right” maternal inflammatory environment. Factors related to energetics, diet composition, immunological health, and psychosocial stress all impact systemic inflammation: the maternal environment is shaped by past and current variation in these factors, and they in part dictate the relative ability of a mother to support the fetus.

C-reactive protein (CRP), an acute phase protein largely produced in the liver, is the most frequently used biomarker for inflammation. CRP is easy to measure (McDade et al. 2007), covaries with IL-6, and is used clinically to predict cardiovascular disease (CVD) risk (Honda et al. 2006; Pradhan et al. 2001; Rutter et al. 2004; Williams et al. 2004). CRP is particularly responsive to acute phase stimuli, which allows for sensitive measurement of the severity of inflammation and a more nuanced understanding of different disease states, physical trauma, and autoimmune disease (Steel and Whitehead 1994). Therefore, while a better understanding of the maternal inflammatory environment should eventually include examination of several inflammatory factors, CRP will be the primary biomarker discussed in this chapter due to its much higher prevalence in the literature and responsiveness to current stimuli. This section directs the reader towards specific points of inquiry and unanswered questions about how or whether these factors specifically influence the maternal inflammatory environment.

1.2.1 *Energetics*

The best-studied factors that influence inflammatory processes are anthropometric determinants of fatness and weight, and several measures of adiposity correspond to elevated CRP concentrations. Increases in waist circumference and weight with age are positively correlated with CRP in samples of adults in the Philippines (McDade et al. 2009, 2010; Rutherford et al. 2009). CRP and BMI correlate in a number of studies (i.e., Guzelmeric et al. 2007; Oh et al. 2009), which often leads study authors to control for BMI when trying to estimate the effects or relationship of CRP to other variables. This has also led to the idea that excess weight produces inflammation, as a stressor on the body (Baynard et al. 2008; Guzelmeric et al. 2007; Williams et al. 2004).

Broadly speaking, increasing weight and sedentism are correlated with increased CRP concentrations. Physical activity itself produces a short-term acute-phase response, particularly after strenuous activity. However over time physical activity has an anti-inflammatory effect (Kasapis and Thompson 2005). While specific kinds of physical activity exert different degrees of inflammation suppression over time, these effects are inconsistent, while the inverse relationship between the amount of time spent on physical activity and CRP concentrations is consistent across many studies (Kasapis and Thompson 2005).

Recent evidence indicates that the relationship between physical activity and CRP in women may be cycle phase dependent. In a study of rural Polish women, strenuous activity was associated with CRP concentrations, but only in the luteal phase, or latter half of the cycle (Clancy et al. 2012). Further, when women were grouped by CRP concentrations, those with low CRP performed significantly more strenuous physical activity. CRP was also inversely correlated with luteal progesterone in this population (Clancy et al. 2012). CRP may help highlight the conflicting relationship between progesterone and physical activity: physical activity tends to suppress ovarian function and thus progesterone concentrations (Jasienska and Ellison 1998), yet progesterone has been found to increase activity in mouse models (Lightfoot 2008) and is itself anti-inflammatory (Finn 1998).

Reductions in calorie intake reduce CRP concentrations (Belalcazar et al. 2010; Heilbronn et al. 2001; Kasim-Karakas et al. 2006; Nicklas et al. 2004, 2005; Noakes et al. 2005). This may be because adipose tissue is an active endocrine organ in its own right and secretes CRP as well as tumor necrosis factor-alpha (TNF- α), leptin, and interleukin (IL)-6 (Forsythe et al. 2008; Yudkin et al. 1999). Independent of intake, diet composition has been found to impact CRP. Micronutrients can prevent lipid oxidation, and fiber, as a prebiotic, can support healthy gut flora; both reduce CRP (King et al. 2003; Koyanagi et al. 2004). The consumption of refined carbohydrates, sodium, and certain fats upregulate the innate immune system and increase CRP (Liu et al. 2002; Lopez-Garcia et al. 2004). Further, inflammation is higher in populations that eat a western-style diet high in simple carbohydrates and saturated fats, as opposed to a Mediterranean diet higher in fruits, vegetables, and unsaturated fats (Chrysoshoou et al. 2004; Lopez-Garcia et al. 2004). In a sample of rural Polish women, there were

trends to support negative relationships with fiber and monounsaturated fat intake ($p=0.08$ and 0.06 , respectively) (Clancy et al. 2011).

CRP is positively correlated with energy status, energy availability, and energy balance, and these relationships are population specific. Further, CRP correlates with markers of a poor quality diet, including sugars, fats, and refined carbohydrates. Therefore, CRP is not necessarily independent of energetic factors, and any desire to understand the impact of other ecological stressors on CRP needs to control for this. This provides support that CRP indicates resource allocation towards somatic maintenance.

1.2.2 *Psychosocial Stress*

Psychosocial stress, as in clinical depression, is associated with both CRP and IL-6 (Miller et al. 2002). In this study, neither smoking nor infection was found to explain the relationship, and adiposity only partly explained it. Clinical depression also attenuates the relationship between acute stressors and inflammation: in a study of 36 women with depression and an equal number of age- and ethnicity-matched controls, participants were subjected to a mock job interview acute stressor. While CRP increased after the stressor in both groups, clinically depressed participants were more sensitive to stress at the beginning of the study, but that sensitivity declined after the stressor; the inverse was true for the nondepressive participants (Miller et al. 2005). That is, when inflammatory processes initiate, depressed participants had an impaired capacity to halt these processes once the stressor was over (Miller et al. 2005). The study of inflammation and psychosocial stress, then, needs to take into account variable sensitivity to stress as well as the stress response and activation of inflammatory cytokines.

Adversity in early life, or stressors that impact the maternal environment, may profoundly and differentially impact adult stress sensitivity. In a community sample of older adults, childhood adversity was associated with serum IL-6 concentrations, even after controlling for factors such as age, BMI, and gender (Kiecolt-Glaser et al. 2011). Danese et al. (2009) performed a longitudinal study that assessed adversity at 3 years of age and then again at 32 years of age. Individuals with adverse psychological experiences at 3 years were more likely to have higher CRP at 3 and 32 (Danese et al. 2009). Finally, in an effort to parse relationships between early adversity, inflammation, and other familial factors, Rooks et al. (2012) examined adult male twins from the Vietnam Era Twin Registry. Early life trauma was positively associated with adult CRP concentrations, and the between-pair, not within-pair, effects were positively associated with early trauma. This suggests that familial factors linked to early life trauma help explain adult CRP concentrations.

CRP varies by sex and race within the US, where women and people of color have on average higher CRP (McDade et al. 2006; Nazmi and Victora 2007). These group differences have been further supported in other studies (Chenillot et al. 2000; Hutchinson et al. 2000) and in a meta-analysis that supported both nonwhite race

and poverty as risk factors for elevated CRP (Nazmi and Victora 2007). But more importantly, self-reported discrimination (Lewis et al. 2010), perceived discrimination (Flores et al. 2008; Guthrie et al. 2002; Pascoe and Smart Richman 2009), and other aspects of racial discrimination and identity (Mays et al. 2007; Paul et al. 2008; Slopen et al. 2010; Thurston and Kubzansky 2007) positively associate with CRP concentrations. Therefore, constitutional, systematic, and institutional stressors must be considered as factors that influence systemic inflammation and perhaps reproductive functioning.

1.2.3 Immune Stress, Maintenance and Development

Like intrapopulation variation, interpopulation variation in systemic inflammation may be due to reaction norms from developmental exposure to immune or other stress. Microbial exposure in infancy, measured by diarrheal episodes and animal fecal exposure, corresponds to lower CRP in a sample of Philippine adults (McDade et al. 2009a, b). In this same sample, CRP was elevated in adults with a lower birth weight (McDade et al. 2009a, b). It is interesting to note that these two states can often co-occur in individuals from certain populations, which indicates trade-offs between maintenance and growth. Priming via exposure may impact the sensitivity of the immune system and offset the elevated CRP from a lower birth weight. These results also lend support to the idea that microbial exposure in childhood was an important aspect of human evolution; this does not require symptomatic disease but simply exposure to the benign microbes that characterized our ancestral environment (Barnes et al. 1999; McDade et al. 2009a, b; Rook 2008, 2009). This means careful attention must be paid to the many factors that push and pull on CRP concentrations when making comparisons or links to reproductive functioning.

Slightly different results have been found in microbial exposure after infancy, where higher exposure to infectious agents predicted elevated CRP in a sample of Philippine women (McDade et al. 2008). Increasing measures of pathogen exposure is also associated with CRP concentrations in a sample of patients with coronary heart disease (Zhu et al. 2000). This relationship has also been found in Tsimané children between the ages of 2 and 15 (McDade et al. 2005). One meta-analysis of pathogen exposure, periodontal disease, and cardiovascular disease even considered elevated CRP a proxy for adult pathogen exposure (Mustapha et al. 2007).

CRP concentrations mean something very different in developed versus developing populations. Where CRP can predict CVD risk in developed countries like the USA (Aiello et al. 2009; McDade et al. 2006), it is not associated with CVD in a sample of lean horticulturalists (Gurven et al. 2009). Further, the relationship between adiposity and CRP, which has been confirmed in several studies of developed populations, is different in countries with different subsistence patterns and lifestyles. McDade et al. (2009, 2010) found that CRP concentrations were lower in a sample of Philippine subjects compared to US subjects with the same waist circumference. This is not unlike the finding that the relationship between weight and

energetic biomarkers varies by population: forager Ache subjects had similar leptin concentrations to US anorectics despite a much higher BMI (Bribiescas 2005), and HDL is lower in a sample of Cebu compared to US participants at a similar BMI (Rutherford et al. 2010).

Overall CRP decreases with energetic stress, increases with psychosocial stress, increases with adult immune stress and decreases with childhood immune stress. CRP reflects ecological stressors and maintenance effort. This means the body has to navigate many environmental factors in order to achieve a population-specific “just right” inflammatory milieu. Under ancestral conditions, where individuals were not presumably traveling great distances to environments with different pathogen exposures or greatly different energy availability, reaction norms that set adult systemic inflammation may be an adaptive trait that helps the body determine the appropriate allocation of effort towards maintenance, growth, and reproduction.

1.3 How Much Inflammation Is “Just Right?”

Maternal and fetal strategies are not always in alignment. The fetus should always want to secure more resources, while the mother wants to reserve enough for her own survival and future reproduction (Haig 1993; Sterner et al. 2012). Maternal–fetal conflict should produce variation in trophoblast invasion, as the degree of invasiveness should correspond to the degree of maternal and fetal control of maternal resources (Crespi and Semeniuk 2004). Developmental trajectories during the mother’s life may set the amount of resources available from the mother, which helps explain why the appropriate degree of inflammation for reproduction is context dependent. Inflammatory milieus are dependent on sex, race, and population, but the level of inflammation considered normal is dependent not only on those factors but on the desired reproductive state. For instance early pregnancy requires a slight inflammatory response; no response, or too much of a response, and fetal loss can result (Sacks et al. 2004). Thus, this section will identify the ways in which inflammation impacts certain reproductive pathways and states.

Previous research both on psychosocial stressors and inflammatory processes have found tenuous relationships with reproductive variables (Chisholm et al. 2005; Coussons-Read 2007; Dole et al. 2003; Ellis and Garber 2000; Ellison et al. 2007; Flinn and England 2003; Hogue et al. 2001; Nepomnaschy et al. 2006; Sanders and Bruce 1999; Wadhwa et al. 2001). In one study of normal women, there was a trend for psychosocial stress to associate positively with menstrual cycle length (Sanders and Bruce 1999); in another on newly incarcerated women, the authors found a significant positive relationship between stress and cycle length irregularity (Allsworth et al. 2007). The study of incarcerated women found not only a higher rate of oligomenorrhea and amenorrhea in this population than the general population, but having a parent with drug or alcohol problems, and having been a victim of childhood physical or sexual abuse, were all significant predictors of menstrual disturbances (Allsworth et al. 2007). Nepomnaschy et al. (2004) examined the effects

of daily stress on a sample of rural Mayan women. In the follicular phase, LH and FSH were positively correlated with cortisol, and cortisol was negatively correlated with progesterone when controlled for age. In the luteal phase cortisol was positively associated with FSH and positively associated with LH, estradiol, and progesterone at midcycle and near the menstrual phase (Nepomnaschy et al. 2004). This demonstrates a subtle, time-dependent interaction between stress and reproductive function (Nepomnaschy et al. 2004). Other studies have not shown a relationship between ovarian function and stress; for example, psychosocial stress did not impact ovarian hormones in a sample of college-aged American women studying for the MCAT (Ellison et al. 2007).

External factors that increase systemic inflammation, as well as immunological factors that produce an over- or under-expression of immune function, are some of the major culprits for reproductive pathologies. However, little is known about how to connect the mechanisms studied at the molecular level with lifestyle or population variation. As nice as it is to know what interleukins are in higher or lower concentrations for a particular reproductive pathology, what is stimulating that interleukin concentration variation in the first place? The following subsections of this chapter describe current knowledge about the relationship between inflammation and ovarian function, endometrial function and pregnancy. Pathological conditions help inform our understanding of what constitutes normal function. These subsections will be instrumental in building testable hypotheses to inform future areas for research in the final section of this chapter.

1.3.1 Ovarian Function

Ovulation occurs when the extracellular matrix (ECM) degrades at the follicular wall and the dominant follicle ruptures its surface. The corpus luteum, the site of follicular eruption on the ovary, is the most quickly vascularizing tissue in the body, and increases in size 20-fold over only a few days. Thus, the process of ovulation and ovarian maintenance of the endometrium and other reproductive processes rely on cyclical tissue remodeling, which itself relies on inflammatory processes (Smith et al. 2002).

While a vast literature exists to test relationships between multiple cytokines and inflammatory factors with reproduction, few are ever linked to reproductive outcomes or environmental determinants of stress. Ovarian remodeling is characterized by degradation and replacement of the ECM. The main players are cytokines—particularly IL-1, IL-6 and TNF- α —and matrix metalloproteinases (MMPs). However, CRP is also correlated to many of the above factors.

It was once thought that follicle recruitment occurs continuously (Baird 1987) or at only a single time during the menstrual cycle (Bakos et al. 1994; Gougeon 1979; Lenz 1985; O’Herlihy 1980; Pache et al. 1990; Queenan et al. 1980; Renaud et al. 1980). In fact, follicular recruitment occurs in waves as a normal feature of the menstrual cycle and healthy ovarian functioning. These follicular waves have been

documented during the human menstrual cycle, using histologic, endocrinologic and/or ultrasonographic techniques (Baerwald et al. 2003a, b; Block 1951; Dervain 1980; Hackeloer et al. 1979). This is important for understanding normal variation in human ovarian physiology and fertility (Fehring et al. 2006; Lipson and Ellison 1996; Noyes et al. 2001; Wilcox et al. 2000). While endocrine hormones regulate follicle wave dynamics (Baerwald et al. 2003a, b), the factors which determine the type and number of follicle waves in women are not fully known.

Variation in inflammation may help to explain why women experience different follicle wave dynamics. Clancy et al. (in revision) have found that women with three follicular waves had greater serum CRP concentrations than women with two waves. Furthermore, when more follicular waves emerged in the follicular phase and were spaced more closely together, greater CRP concentrations were detected (Clancy et al. in revision). And though CRP correlates with age and BMI in other samples (Guzelmeric et al. 2007; Hutchinson et al. 2000; McDade et al. 2008, 2009a, b), such relationships were weak or nonexistent in this dataset. These data suggest considerable variation in follicle wave dynamics even in normo-ovulatory women and a link to inflammation that has considerable clinical implications (Clancy et al. in revision).

Existing studies reveal significant differences in the relationships found between CRP and ovarian hormones. Jilma et al. (1997) found that CRP was significantly higher in single blood samples of women at midcycle and the midluteal phase compared to the follicular phase and that these increases were correlated with progesterone concentrations. Wander et al. (2008) found that CRP is positively associated with progesterone, but negatively with estradiol, in a sample of spontaneously cycling women. Conversely, Wunder et al. (2006) found no associations between CRP and menstrual cycle phase. However, methodological differences hamper adequate comparisons between these studies of women in industrialized populations, and none performed daily measures of reproductive hormones.

Recent work by Clancy et al. (in preparation) has found significant negative relationships between urinary CRP and both estradiol and progesterone in a sample of rural Polish women; further, women with high CRP had significantly lower progesterone through the luteal phase than those with low CRP (Fig. 1.1). The negative relationship between CRP and progesterone is counter to that found in spontaneous cycles in other samples. However, all other studies that have examined CRP through the menstrual cycle have been in industrialized populations, and the measure of CRP via urine may produce a value more averaged over time. This study is both the first to examine nonindustrialized menstrual cycle variation with CRP and to compare baseline CRP (not including CRP during ovulation or menstruation to avoid internal influences) to daily salivary hormones throughout the entire cycle.

The physiology of individuals at the edges of normal, those labeled pathological, can be instructive to our understanding of how and when the inflammatory milieu is disrupted. For instance, polycystic ovarian syndrome (PCOS) is a syndrome whose diagnostic criteria include elevated androgens, male pattern hair growth, cycle irregularities, a greater than normal number of immature follicles, and/or anovulation. Sonographic evidence supports the idea that women with PCOS have more than the

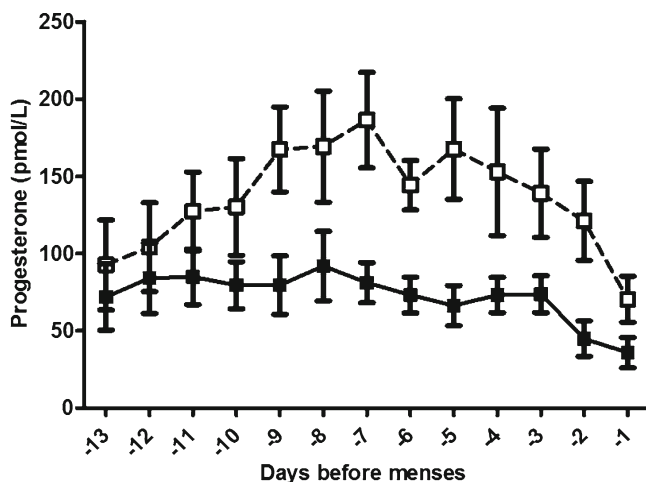


Fig. 1.1 Progesterone concentrations of individuals in high and low CRP tertiles (mean $\pm$ SEM). High CRP is represented by *black points* and a *solid line*, where low CRP is represented by *white points* and a *dotted line* (Clancy et al. [in prep](#))

normal number of follicular waves: one subject was measured to have six follicular waves before being diagnosed with PCOS and excluded from the normo-ovulatory sample (Baerwald, personal communication). The literature broadly supports a relationship between CRP and PCOS (Guzelmeric et al. [2007](#); Morin-Papunen et al. [2003](#); Oh et al. [2009](#)).

Endometriosis produces local inflammatory processes where the endometrial tissue external to the uterus is activated. When this tissue is on the ovary, it appears to increase risk of ovarian tumors (Brinton et al. [2004](#); Hoshiai [2000](#); Ness and Cotreau [1999](#); Nishida et al. [2000](#); Sainz de la Cuesta et al. [1996](#); Yoshikawa et al. [2000](#)). Pelvic inflammatory disease, an infection caused by sexual transmitted diseases like chlamydia and gonorrhea, is better known as a cause for cervical cancer but may increase risk of ovarian cancer as well (Risch and Howe [1995](#)). Therefore even those pathologies that we presume are genetic or energetic such as ovarian cancer may be additionally explained through inflammation.

1.3.2 Endometrial Function

The endometrium is composed of the functionalis and basalis layers; the functionalis comprises two thirds of the endometrium and is the part that proliferates and sheds each reproductive cycle. The basalis is adjacent to the myometrium and is the place from which the endometrium regenerates after menses. The proliferative (also known as follicular) phase is when estradiol promotes proliferation of endometrial tissue, whereas the secretory (also known as luteal) phase is characterized

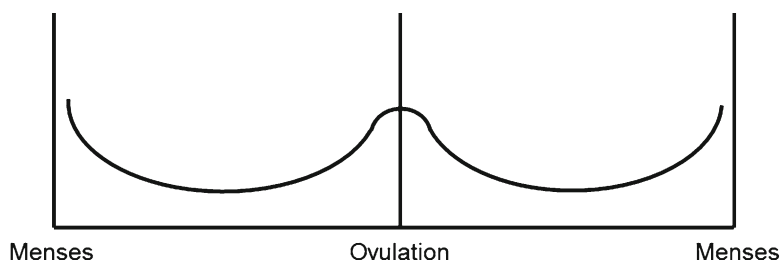


Fig. 1.2 Conceptual model for the increase in inflammatory processes at ovulation and menses during the ovulatory human menstrual cycle

by progesterone control of decidualization (the sum of the proliferation and secretion, as well as increase in vascularization of the endometrium) and menstruation. When endometrium proliferates, it often does so with narrow, straight glands and a thin surface epithelium, and angiogenesis continues as ovulation nears (King and Critchley 2010). After ovulation and during the secretory phase, the endometrium differentiates: endometrial glands become increasingly secretory, and by the late secretory phase spiral arterioles form. If implantation does not occur, the corpus luteum degrades, progesterone declines, and this triggers a cascade of events to produce menstruation: the state of the corpus luteum determines whether or not menstruation will occur.

Menstruation is a key inflammatory process of the endometrium when the functionalis is shed at the end of the human reproductive cycle. The basalis regenerates over the course of the next cycle. The demise of the corpus luteum and the associated withdrawal of progesterone precipitate inflammatory mediators that cause tissue degradation (Maybin et al. 2011). The withdrawal of progesterone is also associated with an increase in endometrial leukocytes and IL-8, which regulate the repair process (Maybin et al. 2011). At this time, other inflammatory factors promote MMP production to break down endometrial tissue (Maybin et al. 2011). Further, it is thought that progesterone withdrawal, not an increase in estradiol concentrations, leads to the repair of the endometrium so that it can resume activity for the next cycle (Maybin et al. 2011). Thus, variation in progesterone concentrations may lead to variation in inflammatory activity, degradation, repair, and cycling in the endometrium. Figure 1.2 demonstrates the likely timepoints along the reproductive cycle where inflammatory processes increase.

Another important component of menstruation is the control over vessel radius and blood flow. Prostaglandin $F_{2\alpha}$ and endothelin-1 cause vasoconstriction of the spiral arterioles to decrease blood flow in normal menstruation. Heavy menstrual bleeding, or menorrhagia, can be caused by unrestrained inflammation or impaired repair processes. Menorrhagia is alternately defined as menstrual bleeding in excess of 80 or 120 mL, where normal blood loss is around 30 mL. However, excessive prostaglandin concentrations and concurrently exaggerated inflammation, as well as immature spiral arterioles and lower concentrations of vasoconstrictor endothelin-1 are associated with heavy menstrual bleeding (Maybin et al. 2011). Women with

menstrual bleeding over 80 mL have reduced vascular endothelial growth factor (VEGF) mRNA expression (Maybin et al. 2011) and reduced VEGF-A, MMP-2, and MMP-9 concentrations in menstrual effluent (Malik et al. 2006).

Other endometrial pathologies appear to have inflammatory mechanisms or origins, particularly endometriosis, fibroids, endometritis, and endometrial cancer; understanding these pathologies may help us understand the extreme end of the range of endometrial functioning. Endometriosis affects about 10% of women in the USA and is caused by hormonally sensitive endometrial tissue that migrates out of the uterus found mostly on the ovaries, pelvic cavity, and peritoneum. Endometriosis is caused, in a sense, by retrograde menstruation, menses that flows back into the vagina and enters the abdominal and pelvic cavities. Epithelial to mesenchymal transitions (EMT), which is the loss of adhesion and increased cellular mobility in cellular remodeling, appear to play a role in the production of endometriotic lesions (Demir et al. 2005).

Like endometriosis, uterine fibroids can cause dysmenorrhea and infertility, depending on their placement. Fibroids, or leiomyomas, are benign tumors of myometrial origin that affect up to 70% of reproductively aged women. This pathology is controlled by ovarian steroids, but the mechanism of their production is mediated by inflammatory factors. And like menorrhagia, the cause of fibroids is suspected to relate to tissue repair dysfunction. Women with fibroids appear to have excessive inflammation of the endometrium, which may explain their increased risk for infertility. Women with fibroids have both higher TNF- α and endometrial macrophage infiltration (Agic et al. 2006; Miura et al. 2006).

Endometritis is an endometrial infection that tends to occur when debris is not fully cleared from the uterus after parturition but can also occur with bacterial and viral infections (Donofrio et al. 2010; LeBlanc 2010). IL-8, a cytokine scarcely present in healthy individuals, ratchets up in individuals with endometritis in a bovine model (Donofrio et al. 2010). IL-8 attracts granulocytes like macrophages and neutrophils to sites of infection.

Weight gain and obesity increase endometrial cancer risk in postmenopausal women, and it is generally assumed that estriol from fat cells is the cause (Barrett et al. 1995; Gull et al. 2001; Kaaks et al. 2002; Trentham-Dietz et al. 2006). Weight gain, overweight, and obesity are associated with CRP and thus systemic inflammation (Guzelmeric et al. 2007; McDade et al. 2006, 2008, 2009a, b; Rutherford et al. 2009; Williams et al. 2004); therefore, an inflammatory origin may augment the hormonal explanation for endometrial cancer, especially since inflammation can increase estrogen concentrations (Modugno et al. 2005). Chronic inflammation, such as that associated with the systemic inflammation caused by overweight, can induce rapid cell division, which increases the risk of mutations that can lead to cancer (Modugno et al. 2005).

From these pathologies, we can learn about the ways in which understanding hormones may be insufficient to understand endometrial functioning. While many of the mechanisms described above are hormonally mediated, it is unclear whether hormones always drive the variation that leads to pathology. Paracrine and perhaps even autocrine processes drive the basic endometrial cycle of proliferation, decidualization,

and degradation (Beier and Beier-Hellwig 1998; Bischof et al. 1998; Lessey 2003; Wu et al. 2009). Thus, measurements of local inflammatory factors are important to future work on variation in endometrial functioning.

1.3.3 *Pregnancy*

Like menstruation, implantation is an inflammatory process of the endometrium. In the proliferative phase, estrogen primes the endometrium and its receptors for progesterone secreted by the corpus luteum. The endometrium decidualizes, but chemokine and cytokine expression, and leukocytes also increase. Uterine natural killer cells (uNKs, a kind of leukocyte) are present in the implantation window and may aid in trophoblast invasion (King and Critchley 2010).

Implantation is a breach of the mucosal barrier of the endometrium, the first line of immune defense. Therefore, innate immune cells need to be activated in order to keep the site free of infection while not overexpressing to the point of attacking the trophoblast (King and Critchley 2010). The fact that the fetus is semiallogenic or partially unrelated to the mother means that the required immunological changes also need to be timed appropriately. The fetus is protected from maternal attack via embryologically derived trophoblast cells that then become the placenta (Rusterholz 2007). Further, the placenta itself secretes immunological and inflammatory factors that interplay with maternal factors: these factors may actually contribute to the regulation of local and systemic immunological changes needed for a successful pregnancy (Hauguel-de Mouzon and Guerre-Millo 2006; Rusterholz 2007). The placenta also expresses molecules that prevent destruction by NK cells and cytotoxic T lymphocytes (Rusterholz 2007). Further, the maternal immunological milieu is biased towards T-helper cell 2 (Th2) immunity during pregnancy, both at the intrauterine and systemic levels (Rusterholz 2007). This means that the humoral response is favored over the cell-mediated response, which is more likely to be destructive to a semiforeign body like a fetus (Rusterholz 2007).

Pregnancy itself is a state of mild inflammation, where the expression of several cytokines is increased compared to the nonpregnancy state (Rusterholz 2007). Maternal CRP concentrations are elevated as early as 4 weeks gestation, and remain elevated through pregnancy (Sacks et al. 2004). Related to this, supraphysiologic estradiol concentrations in women undergoing assisted reproductive technologies (ART) positively correlated with CRP (Almagor et al. 2004; Orvieto et al. 2004); however, normal concentrations were negatively correlated with CRP (Wander et al. 2008). A shift in the relationship between estradiol and CRP may occur at high concentrations of estradiol, from a negative to a positive correlation. The increment of increase in CRP has been further related to pregnancy outcome (Almagor et al. 2004; Orvieto et al. 2004); women with a serum CRP increase between oocyte retrieval day and 5–7 days posttransfer were more likely to have conceived. Other research has reported higher CRP in women with successful versus unsuccessful IVF outcomes (Sacks et al. 2004). Increased maternal CRP may

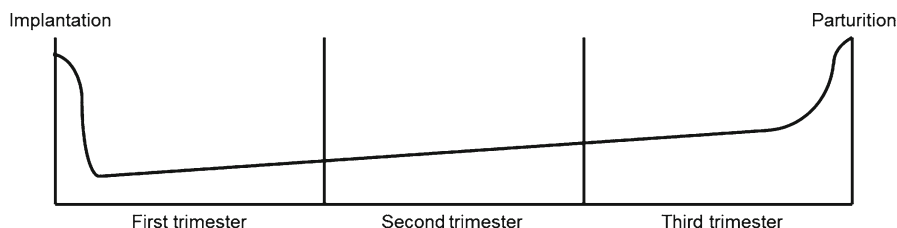


Fig. 1.3 Conceptual model for the changes in CRP from implantation to parturition in an uneventful pregnancy

be associated with protection from pregnancy loss, particularly in losses greater than 12 weeks gestation (Boggess et al. 2005), and that intentional local inflammation during blastocyst transfer improves IVF outcome (Gnainsky et al. 2010). Thus, an inflammatory response is thought to be a positive signal for implantation, but too much (or too little) inflammation could indicate pathology (Sacks et al. 2004). Figure 1.3 demonstrates a conceptual model of the behavior of CRP through pregnancy based on current evidence.

IL-6, strongly correlated with CRP, has also been studied in infertility patients. Demir et al. (2009) measured serum concentrations on day 3 of the menstrual cycle in infertility and fertility groups and found that IL-6 levels are higher in women diagnosed with unexplained infertility compared to controls. Bedaiwy et al. (2007) demonstrated that follicular fluid concentrations of IL-6 were higher in pregnant cycles compared to nonpregnant IVF cycles. However, Hammadeh et al. (2002) results in an IVF sample using the intracytoplasmic sperm injection (ICSI) method were not correlated with follicular fluid IL-6, nor was IL-6 correlated with peripheral blood measures of ovarian hormones. Other researchers have reported variation in follicular fluid IL-6 among different ovarian stimulation protocols (Ficicioglu et al. 2010).

The timing of parturition is one of the places that inflammatory factors can produce pathology. Normal parturition is associated with an increase in inflammatory factors, and these are necessary to activate the uterus and ripen the cervix. IL-1 and IL-8 can be measured in the cervicovaginal fluid and increases in these cytokines are strongly associated with the commencement of labor and the rupture of fetal membranes (Tanaka et al. 1998). Choriodecidual inflammation is a leading cause of late miscarriage and preterm birth and may be precipitated by NF- κ B cells (De Silva et al. 2010). NF- κ B, mentioned above, is inhibited by progesterone concentrations, but in its absence can stimulate IL-1 and IL-6 production (De Silva et al. 2010). Other inflammatory factors considered include MMPs, as tissue inhibitor of metalloproteinases (TIMPs), or molecules which inhibit MMPs, are reduced in women with a history of pregnancy loss (Anumba et al. 2010; Shibahara et al. 2005). Insulin resistance is also a concern, as insulin resistance beyond the normal range of maternal insulin resistance found in pregnancy may impact endometrial receptivity and activity (Levens and Skarulis 2008). Obese pregnant women who

use IVF have higher rates of cycle cancellation and miscarriage (Dokras et al. 2006) and lower rates of pregnancy (Maheshwari et al. 2007). The systemic inflammation associated with both extra weight and insulin resistance likely produce risk factors for recurrent pregnancy loss.

The mechanisms for inflammatory disruption of pregnancy can be an overly aggressive inflammatory response, or a too-weak response. These can, in turn, lead to trophoblast invasion, that is, too shallow, or too severe, resulting in preeclampsia/eclampsia and placenta previa, versus hydatidiform mole and choriocarcinoma. Preeclampsia is characterized by hypertension and generalized endothelium dysfunction, which in turn produces an exaggerated systemic inflammation response to pregnancy; this can lead to intrauterine growth restriction and seriously increases risks of maternal and infant morbidity and mortality. Preeclampsia occurs in higher frequencies in first pregnancies and in couples that have been together for a relatively short period of time; this may precipitate an overly aggressive immune response because the maternal body may be more likely to consider the fetus an invader (Robillard et al. 2008).

Several lines of evidence support the idea that the shallow invasion of preeclampsia relates to an aggressive immune system. Salafia et al. (1995) compared cases of preterm preeclampsia to spontaneous prematurity and found that those with preeclamptic pregnancies had a greater proportion of placental lesions related to chronic inflammation. Rusterholz (2007) described an inflammatory milieu very different in preeclamptic versus normal pregnancies, particularly regarding the distribution of NK cells and macrophages, and unopposed apoptosis and necrosis of trophoblast cells. And while there are conflicts in the literature, many inflammatory factors are markedly different in preeclamptic versus normal pregnancies, including TNF- α , IL-1 IL-6, IL-11 and others (Basar et al. 2010; Rusterholz 2007). Related to this, a study of too-deep invasion, from hydatidiform mole and choriocarcinoma cases, demonstrates that there needs to be a balance between T and NK cells in order to control trophoblast invasion (Knoeller et al. 2003).

These pathologies of too deep or shallow implantation leave room between for natural variation in trophoblast invasion based on populationally derived developmental trajectories and current ecological stressors. Therefore, future work should seek ways to measure local inflammation, invasion, and placental functioning.

1.4 The Moral of the Story: Implications for Biological Anthropology

Where does all this evidence leave poor Goldilocks, who just wants a warm meal and comfortable bed? The “just right” inflammatory milieu is dependent on reproductive state: inflammatory responses are necessary at menstruation, implantation, and parturition but may signal pathology at other times. Conversely, too little inflammation when it is needed may signal pathology, as with the correlation between low CRP and fetal loss in early pregnancy.

Methodological problems remain in elucidating relationships and directionality between inflammation and reproduction, in large part because each can influence the other. Elevated CRP is a bit of a noisy signal in that it can represent local increases in inflammatory factors as well as systemic increases tied to ecological stressors. To some extent, these problems can be mitigated by selecting collection days wisely: we can test relationships between CRP and reproductive variables at periods of expected high and low inflammation. Elevated CRP at periods of expected low inflammation may signal ecological stress. Other methodological issues include disentangling different types of ecological stressors and stress pathways; CRP is quickly becoming a catchall biomarker assumed to assess not only the temperature of the porridge but the softness of the bed. Complementing analysis of CRP with cortisol as an assessment of catabolic state, C-peptide for energy availability, and Epstein Barr antibodies for immune activation may help alleviate this issue in future work.

In addition to reproductive state, the “just right” inflammatory milieu is likely dependent on immunological and psychosocial developmental factors. Population, racial, and ethnic differences are also found not only in baseline concentrations of adult CRP but in several important reproductive dysfunctions such as preterm birth and low birth weight (Borders et al. 2007; Hvilsum et al. 2002). These differences are likely a result of several important factors: genetics, variation in early exposure to immune challenges, variation in adversity in early life, and variation in discrimination throughout one’s life history (Borders et al. 2010; Lewis et al. 2010, 2011; Picklesimer et al. 2008; Slopen et al. 2010). However, few studies have sought to link any of these sources of variation to reproductive physiology or outcomes. CRP is uniquely suited to studies of this kind, as it is correlated with the kinds of ecological stressors described, and with many aspects of reproduction. Therefore, future work should incorporate a broader understanding of psychosocial stress to include variation in adversity, discrimination, and racism, as well as in early life exposures to bacterial infections or other immune challenges, as a pathway to reproductive variation partially independent of the catabolic state reflected by HPA activity (Ellison et al. 2007). It is also possible that the mixed or negative results found in relationships between cortisol and reproductive hormones are due to largely homogenous sampling of industrialized and privileged populations that have experienced little adversity.

Parsing out the bidirectionality of the relationship between inflammation and reproduction benefits human reproductive ecology, evolutionary medicine, and comparative primatology. One of the more interesting findings from these data is that a little inflammation can be a good thing; this can help inform reproductive health practices as well as a better understanding of sex differences in autoimmune disease. Further, aspects of reproduction seemingly unaffected by energetic stress may be strongly impacted by stressors that increase inflammation. Developing an understanding of the context-dependent nature of normal inflammatory processes will help inform testable hypotheses across varying subsistence ecologies and field sites.

Finally, these data on humans may help us develop testable hypotheses about the context-dependent nature of normal inflammatory processes across other primate taxa. Different primate lineages have different models of maternal investment and

life history trade-offs around quantity and quality of offspring that are in part reflected by variation in placentation and trophoblast invasion. For instance, primate species with comparatively low trophoblast invasion may have a normal inflammatory milieu that appears reduced at implantation compared to humans. Thus evolutionary history and different investment strategies could be correlated to different inflammatory profiles across the primates.

Ultimately, the semiallogenic fetus represents an immune problem that females need to resolve within nearly all mammals. Implantation requires activation of innate immunity to avoid infection, while also allowing the fetus to breach the mucosal barrier of the endometrium and development of a placenta that then protects the fetus from future immunological insult. Thus, finding that balance of inflammation is a major mechanistic link between ecology and reproductive success.

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Chapter 2

The Primate Placenta as an Agent of Developmental and Health Trajectories Across the Life Course

Julienne N. Rutherford

Keywords Placenta • Developmental programming • Intrauterine environment • Nutrient transfer • Disparities

2.1 Introduction

The watery world in which a fetus develops has a temporal signature that extends beyond gestation and even beyond the immediate postnatal period and infancy. The developmental programming paradigm [known variously as fetal programming, developmental programming, the developmental origins of health and disease, and the Barker hypothesis (Barker et al. 1990; Gluckman et al. 2005; Godfrey 2002)] classically frames the “intrauterine environment” as a time and place during which insults are experienced and responses are launched by the fetus, events which change the developmental trajectory in such a way that trades off pre- and perinatal survival with some loss of function and health experienced throughout the life course. In more recent incarnations of the developmental programming paradigm, the intrauterine environment is held to “predict” the external world the developing fetus is likely to experience (Gluckman and Hanson 2006; Kuzawa 2005); a “mismatch” occurs when the environment actually experienced is far different than that experience in utero, as in the classic example of nutrient-restricted fetuses cast out into a calorically dense world.

This perspective has led to birth weight, as a reflection of prenatal investment and growth, to be utilized as an important predictor of later health. Groundbreaking

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epidemiological studies conducted by David Barker and colleagues in the 1980s in a population of adult males from Hertfordshire, UK demonstrated that the risk of mortality due to cardiovascular disease was increased in those individuals born at low birth weights, even when adult weight was accounted for (Barker 1995). Repeated studies in humans and other placental mammals like rats, guinea pigs, and sheep (Armitage et al. 2004) have shown that low birth weight predicts obesity, insulin resistance, inflammation, hypertension, and other diseases historically viewed as degenerative diseases of adulthood, especially in industrialized human populations. Because a fetus generally calibrates its growth to the availability of maternal nutrients (Jansson and Powell 2006), small body size at birth suggests an overall decrease in the nutritional milieu, especially glucose and amino acids, the primary fetal growth substrates (Cetin 2001a; Owens 1991). Small body size is also indicative of impaired or slowed organogenesis. For example, low birth weight fetuses have reduced numbers of nephrons (Mackenzie and Brenner 1995), the functional unit of the kidney that regulates blood filtration and pressure, thus potentially contributing to the increased risk of hypertension and chronic kidney disease in adults who were born at low birth weight (Bagby 2009). It is clear that the fetus is not totally buffered from the vagaries and even treacheries of the intrauterine environment, and that the adult that fetus becomes may never shake off the vestiges of its early environment.

These associations leave many questions unanswered. At a basic level, what is meant by the “intrauterine environment”? The term itself has been in use since the early twentieth century (Ballantyne 1902), but until relatively recently was something of a black box in models of developmental programming. In an attempt to more clearly operationalize this environment, Rutherford (2009) defined “maternal ecology” as “the nexus of nutritional, metabolic, endocrinological, infectious, genetic, epigenetic, and sociobehavioral inputs that coalesce into a particular pregnancy” (Rutherford 2009, p. 746; Fig. 2.1). Maternal ecology both generates and interacts with the growth dynamics of the fetus and is also shaped to some degree by conflict and cooperation with the paternal genome (Haig 1996; Sterner et al. 2012). Situating the intrauterine environment in an ecological framework is a useful heuristic as it reinforces the observation that birth weight is an outcome, not a process (Sibley et al. 2005). The focus on birth weight in studies of fetal programming is understandable: it is noninvasively attained, easy to measure, and readily available in animal colony demographic records and studbooks and in human medical records and self-reported data. However, birth weight is a limited proxy of the quality of the intrauterine environment and the fetal response to environmental variability. Further, a public health emphasis on reducing low birth weight ignores the fact that developmental programming effects operate across the range of birth weights (Burton et al. 2011b).

An ecological framework itself is not a tangible or discrete unit of analysis. In contrast, the placenta is the direct interlocutor between the external world experienced and transmitted by the mother and the growth, development, and long-term functioning of the resultant fetus/neonate/juvenile/adult. Alterations in placental structure and function—the “placental phenotype”—may be a better marker of the

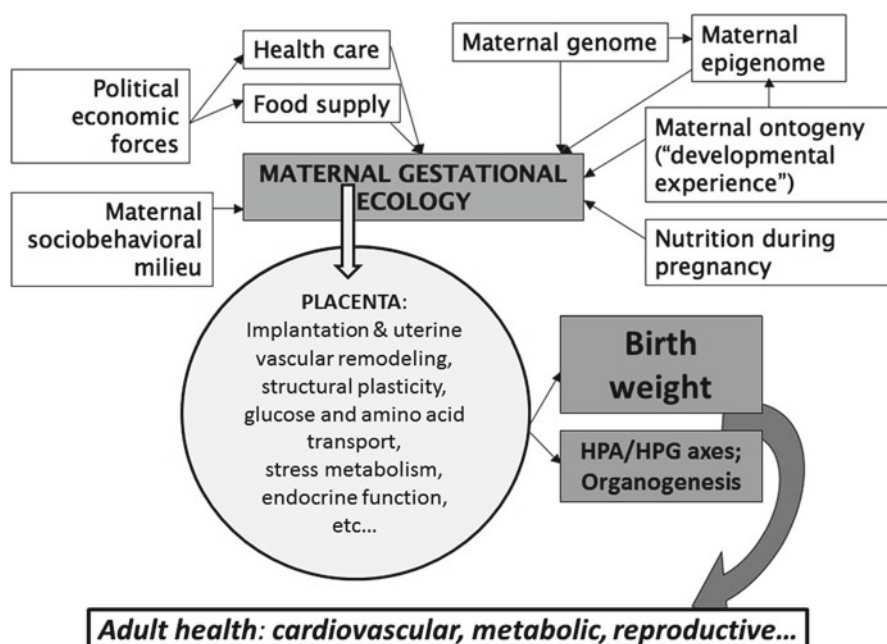


Fig. 2.1 Maternal gestational ecology impacts placental function and life course health outcomes. In humans, the impact of political economy on the availability of health care and food and on the perpetuation of institutional limitations and prejudices experienced during gestation is an important variable to consider in the developmental programming of social and health disparities (modified from Rutherford 2009)

quality of the intrauterine environment than birth weight alone, especially when birth weight falls within normal ranges (Jansson and Powell 2007; Sibley et al. 2005). While the placenta is widely appreciated as the necessary life raft for the fetus to navigate gestation successfully, the growing realization that prenatal development has lifelong consequences casts the placenta in new perspective (see recent reviews: Burton et al. 2011a; Fowden et al. 2006; Jansson and Powell 2007; Longtine and Nelson 2011; Myatt 2006). The developmental programming field is sufficiently well established so as to be beyond the “emergent” stage, but a more explicit exposition of the “intrauterine environment” is required to move research and intervention in innovative directions.

From an ethnographic standpoint, the placenta has long been appreciated as anchoring the living back to the womb, the geographical place of birth, and previous generations throughout the life span (Buckley 2006; Demetrio 1969; Schneiderman 1998). Likewise, from a scientific standpoint, the placenta is viewed as the direct physical interface between two individuals—and between multiple generations. It performs an astonishing array of functions during normal gestation and expresses enormous plasticity in the course of development in response to environmental variation. Framing the placenta as a sensor and transmitter of nutritional

and endocrine signals and thus consequently of maternal stressors within the programming paradigm is key to understanding how the developing individual responds and adjusts to its world, to both its detriment and advantage depending on the context (Rutherford 2009).

Most work investigating the role of the placenta in directing birth outcomes and long-term health sequelae come from non-primate animal models (e.g., mice and sheep) and human clinical research; little is known about these processes specifically in nonhuman primates. Indeed, in a recent analysis of animal model studies of intrauterine growth restriction (IUGR), the cornerstone of much of the developmental programming paradigm, only 2% of over 1,500 studies were based on nonhuman primates (Vuguin 2007). The goal of this chapter is to introduce the reader to the placenta as an extrasomatic organ of both fetal and maternal composition that interacts directly with maternal ecology, describe some of the mechanisms that underlie fetal development, explore the morphological and functional plasticity of the placenta in relation to fetal growth variation particularly in humans, and relate these observations to programming of adult function. Finally, I argue that including the placenta in primate research will lead to important evolutionary and clinically relevant discoveries.

2.2 Defining the Placenta

The placenta is the most unusual of mammalian organs. It is the only organ that is composed of tissue belonging to at least two genetically distinct individuals: mother and fetus.¹ During its short but critical life span from conception to parturition, the placenta allows the developing fetus to take up residence inside its mother's body by integrating metabolic functions of the two organisms. No other mammalian organ is designed to perform so many physiological tasks; during its brief life, it acts as lung (gas transfer), kidney (excretory function and water balance), gut (catabolism and resorption), bone marrow (hematopoiesis), liver (various metabolic and secretory functions), and even hypothalamus and pituitary (Petraglia et al. 2005). In fact, with the exception of some central nervous system and musculoskeletal activities, the placenta accomplishes all functions beyond the capability of the fetus throughout gestation (Benirschke and Kaufmann 2000).

The Greek root of *placenta* is *plakous*, meaning “flat cake” (Kelly 1992; Tycko and Efstratiadis 2002). This speaks not only to the placenta's disc-like configuration in humans and nonhuman primates but also to its nutritive function, which has been appreciated by many students of anatomy and natural history. Aristotle noted in his *Historia Animalium* that animals could be divided into those nourished by yolk and those nourished directly by the placenta (cited in Crespi and Semeniuk 2004).

¹ In the case of the litter-bearing callitrichine primates, all fetuses contribute to the genetic composition of the placenta.

Erasmus Darwin devoted an entire section of his masterpiece *Zoonomia* to the placenta, wherein he also expounded on the placenta as a respiratory organ that functions as a fetal lung while the fetus lives out its aquatic days (Darwin 1796; Dunn 2003). In 1876, what was known about placental function was summarized by Turner: “The foetal placenta possesses an absorbing surface and the maternal placenta (i.e., *deciduous tissue of the uterus*) a secreting surface. The foetus is a parasite which is nourished by the juices of the mother...” (Turner 1876). Since then, many scholars have detailed the incredible variation in placental anatomy both in comparative and clinical contexts (Benirschke 2002; Benirschke and Driscoll 1967; Benirschke and Miller 1982; Carter and Enders 2004a; Mossman 1937, 1987). The anatomical variation of the primate placenta specifically has been the subject of much research (Benirschke and Miller 1982; Carter and Enders 2004b; Carter and Pijnenborg 2011; Luckett 1974, 1976; Mess and Carter 2007; Wislocki 1929).

The shape the placenta takes at the gross level varies tremendously across mammalian taxa, ranging from the diffuse placenta of the pig to the discoid placenta of the primates. The extent of the variation is so great that it led Mossman (1937) to conclude that no other mammalian organ was more variable across taxa. Variation at the microscopic level is also extensive (Grosser 1909, 1927; Mossman 1937, 1987; Wooding and Burton 2008; see also Sterner et al. 2012). All of the anthropoid primates have a hemochorial placenta (Mossman 1987), meaning that fetal and maternal blood are separated by a very thin membrane comprising the fetal capillary endothelium, a small amount of fetal mesodermal connective tissue, and a highly attenuated epithelial tissue called syncytiotrophoblast. The syncytiotrophoblast is essentially a multinucleated cell that derives from fusion of an underlying layer of cytotrophoblasts (Fig. 2.2a). Reduction of cytotrophoblast due to this fusion, leading to a thinning of the transport membrane between maternal and fetal circulations, is a feature of placental maturation. Later in gestation, especially near term, this interface may be further attenuated by the reduction of the mesoderm separating fetal capillaries from the basement membrane of the syncytiotrophoblast. It is this continuous layer that forms the boundary of the placental membrane barrier between mother and fetus, and it plays a critical role in placental and fetal metabolism.

2.3 How the Placenta Builds Babies

The tissue that will give rise to the placental cells, the trophectoderm, derives from the outer cell mass of the blastocyst (Fig. 2.3). Early in human gestation, as the placenta is forming, the maternal uterine arterioles are plugged by clumps of extravillous trophoblast cells (Burton et al. 1999; Hustin and Schaaps 1987), a population of trophoblast cells that develop an invasive phenotype that can remodel and commandeer maternal uterine vasculature (Harris 2010; Kliman 2000). This blockage prevents maternal blood from perfusing the early placenta. This has two interesting consequences: (1) the embryo is protected from high levels of oxygen and

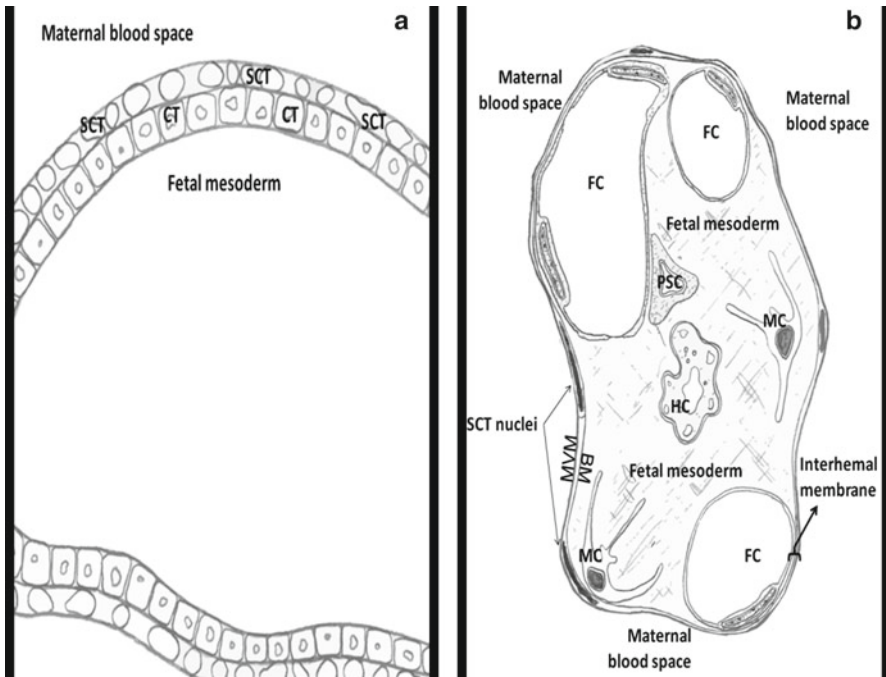


Fig. 2.2 The villus is the terminal structure of the hemochorial primate placenta that separates maternal circulation from fetal circulation. The distance between the two circulations is called the interhemal distance. The physiological membrane responsible for nutrient transport is the syncytiotrophoblast (SCT), a multinucleated tissue that forms via the fusion of individual cytotrophoblast (CT) cells. (a) is a schematic drawing of an immature villus demonstrating the relationship of CT to SCT, with the inside of the villus left blank for simplification. By term (b), most of the individual CTs have given way entirely to a thin highly attenuated interhemal membrane comprising primarily the SCT and the endothelium of the fetal capillaries. The surface of the SCT facing the capillary is referred to as the basal membrane (BM), and the surface facing the maternal circulation is the microvillus membrane (MVM). Active transport typically occurs on the MVM surface, whereas transporter-facilitated diffusion occurs along the BM surface. *FC* fetal capillary, *HC* Hofbauer cell (placental macrophage and antigen-presenting cell), *MC* mesenchymal fibroblast (cell that produces the connective tissue matrix of the villus), *PSC* placental stem cell

thus oxidative stress which can cause pregnancy loss (Jauniaux et al. 2003) and (2) early embryonic nutrition is not provided directly by maternal circulation but rather by endometrial glands (i.e., histiotrophy; Burton et al. 2002). As Burton et al. point out, “the development of the placenta is not autonomous, but is clearly heavily influenced by the uterine mucosa with which the trophoblast interacts” (Burton et al. 2011a, p. 2). This suggests that the development and maintenance of the endometrium prior to conception are critical but currently overlooked events in gestation and fetal development and certainly in fetal programming. Further, they are likely influenced by maternal energy status, inflammation, and psychosocial stress (Clancy 2009, 2012). Prospective studies of the energetic and sociobehavioral context of

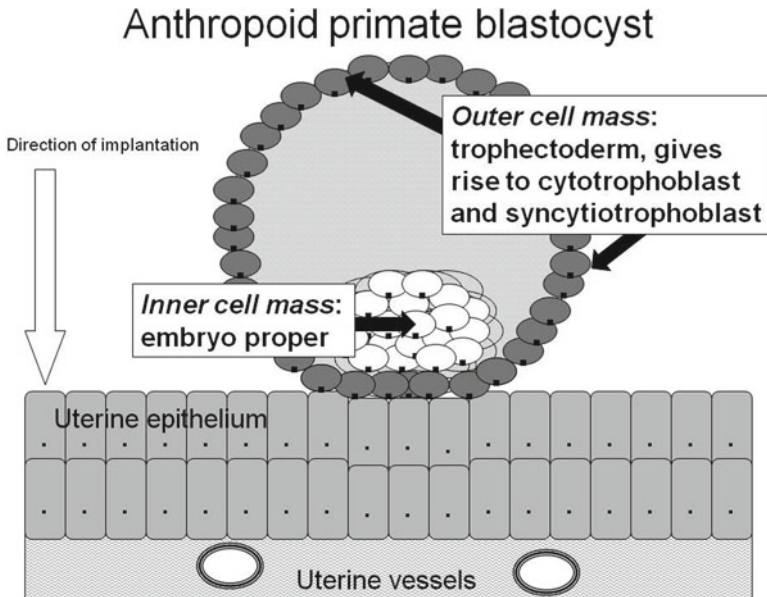


Fig. 2.3 The blastocyst is essentially a hollow ball. The inner cell mass is a cluster of cells that will ultimately give rise to the embryo, while the outer cell mass gives rise to the trophoblastic elements of the placenta. The mesenchymal elements of the placenta, i.e., stroma of the placental villi, come from a later migration of embryonic mesoderm (the middle of three germ layers formed during gastrulation)

endometrial development and receptivity followed by conception, implantation, placental function, and offspring pre- and postnatal growth in both humans and nonhuman primates will be incredibly valuable to the elucidation of the mechanisms and evolution of these processes.

Circulatory communication between the mother and placenta in the human pregnancy is established by approximately 10–12 weeks (Schaaps 1988). At this point, the primary substrates for embryonic and then fetal growth are glucose and amino acids. Diffusing capacity of the syncytiotrophoblast increases throughout pregnancy (Battaglia and Meschia 1986) even after overall placental growth has ceased (Kulhanek et al. 1974). The microscopic surface area of the maternal–fetal circulatory interface increases with gestational age, both absolutely and relative to the overall volume of the placenta (Benirschke and Kaufmann 2000; Rutherford and Tardif 2009). Further, it has been shown in the human placenta that while the diffusing capacity of the placenta increases over gestation, the relationship to fetal weight remains constant (Mayhew et al. 1993), suggesting a causal relationship consistent with the notion of the placenta as a nutrient sensor to which the fetus calibrates its growth (Jansson and Powell 2006). The hemochorial haplorhine primate (tarsiers, monkeys, apes, humans) placenta with its complex branched villous structure is considered to have the largest microscopic surface area relative to its volume when

compared to other mammalian placentas (Baur 1977). This enormous capacity for nutrient transport coupled with proposed evolutionary shifts in hominin diets and associated behavior may thus have played a central developmental role in the relatively extreme size of the human fetal brain (Abrams and Rutherford *in press*; Rutherford et al. 2012). Overall growth of the primate placenta slows in the last stage of gestation as fetal growth intensifies (humans—Benirschke and Kaufmann 2000; common marmoset monkeys—Chambers and Hearn 1985; vervet monkeys—Rutherford et al. 2010), suggesting that the increase in microscopic surface area and its associated transport function play critical roles in fetal somatic and brain growth near the end of primate gestation.

Metabolic and endocrine function of the placenta is myriad and complex (for reviews see Cetin 2001a, b; Mesiano and Jaffe 1997; Murphy et al. 2006; Pepe and Albrecht 1995; Stulc 1997). Gases, nutrients, and wastes are exchanged between mother and fetus through the placenta (Redmer et al. 2004) by passive diffusion, facilitated diffusion, active transport, endocytosis, and exocytosis (Murphy et al. 2006; Redmer et al. 2004). However, the placenta does not act merely as a conduit of maternal resources or as a simple filter; it also has its own metabolic needs to meet (Hay 1991a, b; Meschia et al. 1980). For example, the placenta consumes up to 70% of the glucose uptake by the uterus, significantly affecting the amount available for fetal growth (Hay 1991b). Glucose is the primary substrate for fetal metabolism and growth, particularly for fetal brain growth (Battaglia and Meschia 1986; Hahn et al. 1995; Murphy et al. 2006). The placenta is capable of modifying the balance of nutrient availability through endogenous metabolic processes such as glycolysis, oxidative phosphorylation, and amino acid interconversion, thus further altering the quantity and quality of fetal nutrition (Cetin 2001a, b; Hay 1991b). What follows is an intentionally brief primer on some of the substrates and transport mechanisms that underlie fetal growth.

2.3.1 Glucose Metabolism and Transport

As mentioned above, the placenta has an enormous appetite for glucose—meaning that some proportion of the glucose circulating in maternal blood does not reach the fetus directly. Transportation of glucose to the fetus is done so by facilitated diffusion along a concentration gradient, mediated by a family of glucose transporters located in the syncytiotrophoblast (Hahn et al. 1995). Glucose transporters are localized in the syncytiotrophoblast throughout pregnancy, with the strongest immunoreactivity found at term in the human placenta (Hahn et al. 1995), coinciding with the increase in fetal growth that characterizes the third trimester. Glucose transporter 1 (GLUT1) is found at the apical aspect of the syncytiotrophoblast which is in direct contact with maternal blood (Illsley 2000). Because it occurs at the front line of glucose transport, transporter density is a primary limiter of glucose metabolism (Illsley 2000). In humans, glucose transporter density is affected by maternal undernutrition and high-altitude hypoxia (Lesage et al. 2002; Zamudio et al. 2006).

In high-altitude human populations, low birth weights have been linked to increased hypoxia and reduced GLUT1 density (Zamudio et al. 2006). Thus, glucose delivery to the fetus is hierarchical, in the sense that maternal ecology (e.g., altitude and oxygen availability) affects the physiological capacity of the syncytiotrophoblast to transport glucose to the fetus and placental consumption further alters capacity. In this way, glucose delivery efficiency is one way a signal of the quality of the external environment can be conveyed to the developing fetus.

Glucose is a particularly critical growth substrate for the fetal brain. Even when uterine ligation causes placental insufficiency and dramatic IUGR in rodents, normal brain size is maintained, a phenomenon known as brain-sparing (Das et al. 1998). Rodent studies also suggest that in models of placental insufficiency, glucose transport is maintained at normal levels to the brain at the same time that it is diminished in other tissues such as lung (Simmons et al. 1992) and skeletal muscle (Sadiq et al. 1999). Glucose partitioning is likely to be particularly important in primate development and in particular human development, given the extreme size of the fetal brain and the complexity of cognition and behavior. Recent research suggests that baboon fetal brain growth is sensitive to relatively moderate restrictions in maternal global nutrient intake, with 30% maternal nutrient restriction during pregnancy yielding measurable differences in cerebral microscopic morphology and gene expression, even though body weight and gross brain size were not altered (Antonow-Schlorke et al. 2011). It has been suggested recently that the protection of brain growth in human fetuses may be associated with the intensively invasive form of human placentation and its attendant increases in microscopic surface area (Abrams and Rutherford *in press*; Rutherford et al. 2012), but much more research needs to be done to determine how this may occur.

2.3.2 *Amino Acid Metabolism and Transport*

Amino acid metabolism by the placenta is also critical for fetal growth, as amino acids are required for protein synthesis and accretion in the fetus (Regnault et al. 2002) and production of fetal insulin, a powerful growth-stimulating hormone (Hoffman et al. 1982). Individual amino acids are critical for adequate growth; for example, decreased taurine results in IUGR in animal models (Sturman 1988). Amino acids are transported from maternal to fetal circulations by active transport systems, yielding in many cases higher circulating fetal amino acid concentrations (Cetin 2001a, b; Jansson 2001), with essential amino acids such as leucine exhibiting higher transfer rates than nonessential amino acids. Amino acid transporters are localized in the syncytiotrophoblast (Jansson 2001), in both the microvillous plasma membrane (MVM) that faces the maternal circulation, the site of active transport, and the basal plasma membrane (BM) that faces the fetal capillaries, the site of transporter-facilitated diffusion (Jansson and Powell 2011; Fig. 2.2b). There are over 20 different amino acid transporters in the placenta, many with overlapping functions, increasing the redundancy of nutrient transport from maternal to fetal

circulation (Jansson 2001). One of the key amino acid transport systems is system A, a sodium-dependent transporter that mediates uptake of nonessential amino acids such as glycine, alanine, and serine into the cell (Johnson and Smith 1988). The placenta expresses all isoforms of system A (Desforges et al. 2006), and the activity of these transporters in the MVM is reduced in IUGR in humans (Dicke and Henderson 1988; Jansson et al. 2002; Mahendran et al. 1993).

The rate of amino acid transport from mother to fetus can be altered according to maternal ecology and has important implications for fetal growth. Amino acid transport function is reduced in hypoxia (Nelson et al. 2003) and maternal smoking (Sastry 1991) and increased in gestational diabetes, which is often associated with fetal macrosomia (overgrowth) (Jansson et al. 2006). Across placental mammals, maternal condition thus likely has an impact on fetal growth through disruption of transport function of the syncytiotrophoblast at the maternal–fetal interface. Placental size is often reduced in IUGR, raising the question of directionality: is the placenta small because the fetus is small or is the fetus small because the placenta is small? Jansson and Powell (2006) have suggested that the placenta is a nutrient sensor, conveying information about maternal ecology in the form of amino acid transport rates and quantities, and the fetus calibrates its growth accordingly. Thus, placental metabolic dysfunction in response to maternal condition may be the primary determinant, as opposed to being a consequence, of fetal growth disruption (Jansson and Powell 2006). Given that alterations to placental amino acid transport lead to reduced fetal growth, it is interesting to speculate—and currently uncharted territory—whether changes in gene expression relative to placental amino acid transport is responsible for the characteristically slower fetal growth rates in primates, and especially humans, when compared to similarly sized mammals (Dufour and Sauther 2002; Martin and MacLarnon 1990).

2.3.3 Fatty Acid Metabolism and Transport

Fatty acid transport in primate milk is an important consideration in postnatal brain growth (Milligan 2012). Similarly, lipid transport across the placenta plays a key role in fetal brain development (Cetin et al. 2009; Haggarty 2002). In particular, long-chain polyunsaturated fatty acids (LCPUFA) play a central role in fetal development (Herrera 2002). Docosahexaenoic acid (DHA) is one of the most important LCPUFAs for brain growth and function (Innis 2007). Umbilical cord blood LCPUFA concentrations are correlated with both body size and head circumference in human neonates (Leaf et al. 1992), suggesting a direct link between DHA availability and brain size. The placenta transports fatty acids in maternal circulation to the fetus (Cetin et al. 2009; Haggarty et al. 1999). While levels of other fatty acids that cross the placenta, linoleic acid and arachidonic acid, are lower in fetal than maternal circulation, DHA levels are twice as high in fetal compared to maternal circulation, indicating selective and active transport across the placenta and even potential enrichment (Haggarty 2002). The fatty acid concentration in placental

circulation is dependent on two main factors: the concentration of fatty acids in maternal circulation and the efficient transfer across the placenta (Cetin et al. 2009). Although LCPUFA transport across the placenta can occur passively across the maternal–fetal concentration gradient, recent research emphasizes the importance of plasma membrane-located transport/binding proteins (Duttaroy 2009; Hanebutt et al. 2008). The rates of both passive transport by diffusion and active transport via transport proteins are related to villous surface area.

Fetuses with IUGR, a condition often associated with impaired placental implantation and reduced villous surface area, have significantly lower circulating concentrations of DHA relative to maternal circulation than do appropriately sized fetuses, leading to postnatal fatty acid deficits and resulting in neural complications (Cetin et al. 2002). Further, a recent study demonstrated a significant association between maternal DHA supplementation during pregnancy and children's IQ at age four (Helland et al. 2003), and impaired brain DHA accumulation in rhesus monkeys was associated with higher frequencies of stereotypic behaviors and locomotor activity, evidence of behavioral reactivity (Reisbick et al. 1994). These findings indicate that maternal consumption of DHA and the efficient transport of DHA across the placenta combine to significantly impact the size of the neonatal brain as well as attendant behavioral and cognitive functions. Many scholars are actively exploring direct links between grade-level dietary adaptations (e.g., omnivory, frugivory, insectivory, etc.) and primate encephalization (Allen and Kay 2011; Navarrete et al. 2011; van Woerden et al. 2012). However, there is currently no research program investigating how these links map onto placental biology and intrauterine nutrient transport. This highly interdisciplinary approach is now possible given the richness of dietary data available from long-term field studies, tools for analyzing placental structure and function, and ultrasound imaging.

2.4 The Placenta in Fetal Growth Disorders: Intersections with Maternal Ecology

In normal pregnancy, the primate placenta grows in size but also in microscopic complexity such that the tree-like villi containing fetal capillaries become smaller in diameter and the lining epithelium—the syncytiotrophoblast—in contact with maternal blood becomes thinner. Beyond normal age-related changes in placental function and morphology, the placenta is capable of enormous plasticity in response to a changing or adverse intrauterine environment. This plasticity is exhibited both by morphological and functional changes. As a reflection of the many routes the placenta can take to nourish a fetus, this section summarizes some characteristic placental phenotypes associated with fetal growth disorders, emphasizing the effects of maternal nutrient restriction and psychosocial stress. Much of the work describing these patterns is from human epidemiological and clinical work, and similar patterns are much less studied in nonhuman primates. I focus predominantly on the placenta relative to birth weight as that is the most familiar tenet of developmental programming.

2.4.1 *The Placenta in IUGR Due to Maternal Nutrient Restriction*

The relationship of the placenta to the fetus is often termed “placental efficiency” and is calculated by dividing fetal or neonatal weight by placental weight. The placenta normally becomes more efficient in its support of fetal growth as pregnancy progresses (Myatt 2006); in humans, the fetal to placental weight ratio increases 40-fold from 6 weeks to term (Benirschke and Kaufmann 2000). Evidence from nonhuman primates suggests a similar, although less marked, pattern. In the vervet monkey (*Chlorocebus sabaeus*), placental efficiency increases nearly two and a half times from midgestation to the last 2 weeks of gestation (~150–165 days) (Rutherford et al. 2010). In the common marmoset, placental efficiency increases nearly five times from 30 days gestation to term (~143 days) (Chambers and Hearn 1985). In humans, increases in placental efficiency over the course of normal gestation are achieved by an increase in villous volume and an expansion of the trophoblast surface area (Benirschke and Kaufmann 2000); evidence from nonhuman primate placentas suggest a similar mechanism of increasing efficiency (Merker et al. 1988; Rutherford and Tardif 2009; Rutherford et al. 2010). Work by Coan et al. (2008) in a mouse model has shown that the lightest placentas in a litter increase efficiency via a morphological expansion of the nutrient transport area, a phenomenon that precedes a late-gestation functional shift involving upregulation of genes responsible for glucose and system A amino acid transfer—an example of function following form. It is clear that within the physiological range of normal development, the placenta is a highly sensitive and plastic system.

Placental growth also responds to fluctuations in maternal nutrition and lifestyle. There is evidence from experimental studies that the response of placental growth to maternal nutrient restriction is sensitive to the timing, duration, and severity of the restriction and that this variation in the placental growth response is reflected in changes in the fetal to placental weight ratio (Fowden et al. 2006; Myatt 2006). For example, neither placentas nor fetuses of ewes undergoing moderate dietary restriction around the time of conception exhibit any reduction in weight at birth; however, when restriction is extended to include the period of rapid placental growth during approximately the first half of gestation, placental weight is increased (Oliver et al. 2005). Placental overgrowth (a decrease in the fetal to placental weight ratio) stemming from early maternal nutritional restriction with subsequent restoration of normal energy intake has been demonstrated experimentally in pigs (Pond et al. 1991), rats (Doherty et al. 2003; Langley-Evans et al. 1996; Woodall et al. 1996), and sheep (Robinson et al. 1994). Conversely, when maternal nutritional restriction occurs during mid- or late gestation, after the placenta largely has achieved peak growth velocity, relative placental growth is reduced at term (Fowden et al. 2005). Restriction occurring throughout gestation leads to reductions in the weights of both fetus and placenta (rat—Woodall et al. 1996; sheep—Osgerby et al. 2002), but the fetal to placental weight ratios are increased, so that the result is a

relatively smaller placenta in the restricted pregnancies. Because these relatively undergrown placentas support higher per unit fetal growth, many researchers have argued that the response of the placenta to limits on physical growth is to increase metabolic efficiency (Fowden et al. 2009; Rutherford and Tardif 2008, 2009).

Similar findings have been demonstrated in humans in the context of the Dutch Hunger Winter of World War II (Lumey 1998; Smith 1947; Stein et al. 1995; Stein and Susser 1975). From October 1944 to May 1945, German occupation of the Dutch town of Rotterdam restricted food supplies, lowering daily intake from 1,600 kcal prior to occupation to 1,300 kcal afterwards. This was further restricted during the latter period of occupation to only 500–600 kcal per day. Once the German forces surrendered in May 1945, the famine ended abruptly with provisions from Allied forces. Demographic records of newborn and placental weights from births occurring during the famine period have allowed researchers to determine the effect of the timing, duration, and severity of maternal nutritional restriction on fetal and placental growth. Several models of developmental sensitivity to maternal restriction were evaluated: effects on the third trimester (occurring early during the famine period), second trimester (midway through the famine period), and the first trimester (end of the famine period) (Lumey 1998). Stein and Susser (1975) demonstrated that maternal restriction during the third trimester, but not during the first or second, led to significant reductions in placental weight. Lumey (1998) investigated the effect of restriction on the relation between placental and fetal growth. Famine-induced caloric restriction during the first trimester with subsequent restoration of energy balance yielded no reduction in fetal weight, but placental weight was increased. This decrease in the ratio of fetal to placental weight without attendant low birth weight suggests that the placenta is capable of responding to restriction of maternal resources during early gestation when placental growth and differentiation is approaching its peak velocity by engaging in compensatory growth pathways. The resultant large placenta is less efficient in its support of fetal growth, but in the case of early restriction followed by energy restoration, it succeeds in meeting fetal demands.

In contrast, restriction late in gestation appears to negatively impact the placenta and sometimes the fetus. In the Dutch Hunger Winter sample, third-trimester restriction yielded significant decreases in both fetal and placental weights, but depression of placental growth was even greater than that of the fetal pattern (Lumey 1998). This discrepancy revealed a relative undergrowth of the placenta and hence a high fetal to placental weight ratio. In a pattern reminiscent of the experimental literature, late-gestation restriction in this human population yielded a smaller but more efficient placenta, in terms of its ability to support fetal growth. More recent observations of a Saudi population found that while mean birth weights did not differ from European weights, placentas weighed much less and were therefore more efficient (Alwasel et al. 2010, 2011). Further, Saudi mothers who restricted food intake during Ramadan during their second and third trimesters gave birth to babies who were not different in birth weight than the babies of nonrestricted women, but their placentas were smaller and more efficient (Alwasel et al. 2010, 2011).

In addition to changes in placental efficiency, the microscopic structure of the placenta may be altered by nutrient restriction, particularly the architecture of the maternal–fetal interface. Many studies have demonstrated that alterations in maternal energy balance and health, as well as fetal growth and development, have a direct impact on microscopic placental structure (Mayhew and Jairam 2000; Mayhew et al. 2003; Roberts et al. 2001; Zamudio 2003). For example, maternal undernutrition before and throughout pregnancy leads to a reduction of the surface area of the labyrinth [the placental compartment in rodents that is homologous with the villous tree of the catarrhine primate (e.g., baboon, human) placenta and the trabeculae of the platyrrhine primate (e.g., marmoset) placenta] and increases the thickness of the exchange membrane at the maternal–fetal interface in the guinea pig placenta (Roberts et al. 2001). These changes in placental organization are associated with significantly lower birth weights and reduced absolute placental weights, but the reduction in placental weight is not proportional to the reduction in birth weight (Roberts et al. 2001), resulting in a placenta that per gram supports a higher level of fetal growth (i.e., increased placental efficiency). Coan et al. (2010) restricted maternal nutrient intake during gestation in a mouse model; resultant placental weights and placental expression of glucose were reduced by gestational day 16 (of an approximately 21 day gestation), though fetal weights were unaffected. However, by day 19, both placental and fetal weights were diminished, as well as the surface area of the labyrinth (Coan et al. 2010). Despite these morphological diminutions, the affected placentas demonstrated an increase in glucose and system A amino acid transporter expression to compensate for reductions in surface area. These elegant studies demonstrate that there is a tremendous amount of placental responsiveness to maternal ecology underlying the endpoint of a reduced fetal weight.

In humans, Mayhew et al. (2003) found that preeclampsia, a condition involving elevated maternal blood pressure usually due to improper remodeling of the uterine vessels perfusing the placenta, with or without IUGR, is associated with significant decreases in the intervillous space and total villous volume. Fetal capillary volume is also significantly decreased in placentas from growth-restricted pregnancies (Mayhew et al. 2003). Egbor et al. (2006) also found that placentas from human IUGR pregnancies exhibited significant reductions in villous volume and surface area. In baboons, maternal nutrient restriction leads to reductions in villous volume and surface area (Schlabritz-Loutsevitch et al. 2007). IUGR has been linked to placentas that not only differ in size from controls but also in constituency of microscopic vascular compartments (Krebs et al. 1996) and in hormone production (McMullen et al. 2004).

These and other studies suggest that conditions which potentially alter the availability of maternal resources to fetal and placental growth and development will yield measurable differences in the functional morphometrics of placental tissue components. In this way, a direct link between the quality of the intrauterine environment and placental structure is forged. Placental solutions to the problems of metabolic shortages may be adequate to support growth to a minimum threshold required for survival to term, a threshold that might not otherwise be met. Mechanisms

of growth at the microscopic level may critically increase the efficiency of the placenta in its support of fetal growth.

2.5 The Placenta in the Program: Linking Placental Growth and Function with Adult Health

Given that placental structure and function play such critical roles in determining fetal size and organogenesis, it is unsurprising that placental characteristics are strongly associated with adult health outcomes. Godfrey (2002) reviewed several studies (summarized in Table 2.1) that found associations between placental size and coronary disease (Forsen et al. 1997; Martyn et al. 1996), elevated blood pressure (Barker et al. 1990; Eriksson et al. 2000), and diabetes risk (Eriksson et al. 2000; Phipps et al. 1993). More recently, meetings in 2009 and 2011 at the Centre for Trophoblast Research at the University of Cambridge have generated anthologized discussions of the role of the placenta in human developmental programming (Burton et al. 2011b; Fowden et al. forthcoming). This is a growing area of investigation as it offers a clearer path to understanding the mechanisms of developmental programming than an emphasis on birth weight alone. Indeed, Godfrey (2002) suggests that “optimizing placental structure and function is likely to have lifelong health benefits for the offspring.”

Table 2.1 Relations between placental size and disease in adulthood

	Blood pressure	Heart disease	Glucose tolerance
High placental weight (absolute)	↑ Adult blood pressure ^a ↑ Childhood blood pressure ^b ↑ Childhood blood pressure (boys only) ^c		
Low placental weight (absolute)	↑ Adult blood pressure ^d ↑ Adult blood pressure with diabetes ^e	↑ Coronary heart disease (men) ^f	↑ Type 2 diabetes ^g
Low F/P weight ratio (low placental efficiency, relatively high placental weight)	↑ Adult blood pressure ^h	↑ Coronary heart disease (men and women) ⁱ	↑ Prevalence of impaired glucose tolerance ^j

Table modified from Godfrey 2002

^aBarker et al. (1990)
^bLaw et al. (1991) and Moore et al. (1996)
^cTaylor et al. (1997)
^dCampbell et al. (1996) and Thame et al. (2000)
^eEriksson et al. (2000)
^fForsen et al. (1997)
^gForsen et al. (2000)
^hBarker et al. (1992) and Moore et al. (1999)
ⁱMartyn et al. (1996)
^jPhipps et al. (1993)

2.5.1 Maternal Nutrition and Stress, the Placenta, and Offspring Health in Adulthood

Activation of the maternal hypothalamus–pituitary–adrenal (HPA) axis in response to a variety of stressors—nutritional, metabolic, inflammatory, and psychosocial—can lead to elevated maternal cortisol levels (Fowden and Forhead 2009; Gheorghe et al. 2010; Nyberg 2012; Seckl 2008). Maternal glucocorticoids are implicated in the placental programming of offspring hypertension and glucose intolerance (Vaughan et al. 2011). Exposure to endogenous maternal or exogenous administered glucocorticoids alters cardiovascular, endocrine, and metabolic function in the pre- and postnatal periods, as well as program hypertension and glucose intolerance into adulthood (Seckl 2008; Vaughan et al. 2011). Both mother and fetus produce glucocorticoids, but the concentration is higher in maternal circulation, so the predominant direction of transport is from mother to fetus, across the placental membrane. Glucocorticoid receptors are found in most placental cell types in human, rat, and sheep placentas (Vaughan et al. 2011). Fetal cortisol concentrations increase in concert with maternal elevations in cortisol as a result of transplacental transport but also independently as a result of fetal nutrient stress or hypoxia (Vaughan et al. 2011). The placenta produces the enzyme 11 β -hydroxysteroid dehydrogenase 2 (11 β -HSD2) which in primates converts maternal cortisol to inert cortisone (Pepe et al. 1999). When placental 11 β -HSD2 secretion is diminished, fetal cortisol levels can rise even when maternal or fetal HPA activity is unchanged. Interestingly, experimental nutrient restriction of pregnant female rats and sheep leads directly to downregulation of placental 11 β -HSD2, with or without increased maternal cortisol levels (Langley-Evans et al. 1996; McMullen et al. 2004). Thus, while elevated maternal serum cortisol represents a potential risk to fetal development and long-term sequelae, it may not fully reflect the degree of exposure to stress experienced by the fetus.

Dexamethasone is a synthetic glucocorticoid used therapeutically in humans as a treatment for asthma and also to prevent preterm labor (ACOG 2008; Clifton et al. 2006). There is a concern that while this may serve immediately desirable purposes, the long-term, life course consequences of dexamethasone administration are understudied. Not only does glucocorticoid exposure often lead to global fetal growth restriction, but there are heretofore poorly understood impacts on individual organ systems. For example, in the rhesus monkey, repeated prenatal treatments of dexamethasone yielded dose-dependent degeneration of hippocampal neurons and overall hippocampal volume, effects that lasted into early juvenility (Uno et al. 1990). In rats, glucocorticoid administration yields impaired function of adult cardiovascular and metabolic physiology (O'Regan et al. 2004). By an alteration in the placenta's ability to metabolize maternal stress hormones adequately, either by overproduction of glucocorticoids from the maternal side directly or by downregulation of 11 β -HSD2, offspring may experience lifelong health impairment. Of particular concern are human population differences in asthma, with resultant differential in utero exposures of dexamethasone. African-Americans and Hispanic-Americans

experience asthma at a much higher rate than do Americans of predominantly European descent in large part due to higher poverty levels (Bryant-Stephens 2009; McWhorter et al. 1989), and as a result, some populations of pregnant women may be prescribed dexamethasone at higher rates, indicating a potentially powerful entry point of medicalized perpetuation of health disparities in birth weights and health sequelae. It is unclear if there are population differences in placental 11 β -HSD2 production and if there are, whether they map onto differences in birth weight and adult hypertension and glucose intolerance; this is an area ripe for additional research in both humans and nonhuman primates.

Building on the initial observations that low birth weight was a predictor of hypertension risk in adults in humans, Barker and colleagues have considered the contribution of placental characteristics (Barker et al. 1990; Campbell et al. 1996; Forsen et al. 1997; Taylor et al. 1997), finding that both low and high placental weights predict hypertension. This U-shaped distribution suggests that there are other underlying factors or disparate mechanisms. One of those factors might be maternal nutritional status. Among individuals born to short mothers in the Helsinki Birth Cohort (HBC), the prevalence of hypertension in adults was negatively associated with their placental area (Barker et al. 2010). For adults born to tall mothers in the HBC, the distribution was U-shaped: both very small and very large placental areas were associated with hypertension prevalence, which is consistent with patterns found for fetal weights without considering placental architecture. Although genes certainly contribute to height, maternal stature is thought to be in part a signature of earlier-life growth and development—and the nutritional substrates or pathogenic insults underpinning that growth—while maternal BMI around the time of conception is a more targeted reflection of immediate nutritional status (Tanner 1989). If we assume that restricted growth across the life course of the mother increases the stress and inflammatory hormonal milieu during pregnancy (Clancy 2012; Nyberg 2012), then we can conceptualize a “womb-to-womb” framework of health phenotype transmission via placental function (Fig. 2.1).

2.6 Placental Developmental Plasticity and Reproductive Programming as Evolutionary Mechanisms

That the prenatal period has an impact on postnatal growth and development, and adult function has been convincingly demonstrated, particularly in the realm of cardiovascular and metabolic health. What remains less explored is how the intrauterine environment generally—and the placenta specifically—impact reproducing and rearing offspring in the next generation (i.e., fitness). This is an understudied area, but evidence has accumulated to suggest that the response of the fetus to its local environment during development may program reproductive effort in adulthood. In humans, Ibáñez and colleagues have shown that low birth weight predicts reduced ovarian function [reduced follicle stimulating hormone (FSH), reduced ovarian volume] and reduced uterine volume in adolescence, controlling for current BMI

(Ibañez et al. 2000, 2003). Certainly, there are links between a woman's birth weight and that of her offspring: a mother's own birth weight is often the strongest predictor of offspring birth weight (Ramakrishnan et al. 1999). Epidemiological work focusing on a transgenerational dataset from the State of Illinois demonstrated in an urban African-American population that a neonate's low birth weight is strongly predicted by its mother's birth weight (Coutinho et al. 1997) and its grandmother's socioeconomic status during the gestational period (Collins et al. 2009). The Dutch Hunger Winter demonstrated that women who themselves experienced intrauterine restriction due to the famine during fetal life produced lower birth weight infants (Lumey and Stein 1997). This suggests that the process by which they produced placentas during their pregnancies was impacted by their own fetal experience, a tantalizing but relatively unexplored area of inquiry.

Evidence is mounting that an individual's own fetal development dramatically impacts her fertility in adulthood. For example, a large-scale epidemiological study in Sweden demonstrated that low birth weight and prematurity in both men and women are associated with reduced probability of reproducing in adulthood (deKeyser et al. 2012). Recent work in the common marmoset monkey suggests that females who were born as triplets suffer over twice the rate of pregnancy loss as those born as twins, though there is no difference in total number of offspring produced (Rutherford et al. [under review](#)). Marmoset triplets exhibit many intra-uterine and postnatal features of a nutrient-restricted phenotype (Rutherford 2009, [in press](#)), including lower birth weights and elevated postnatal growth rates (Tardif and Bales 2004), higher perinatal mortality (Jaquish et al. 1991), and relatively small yet efficient placentas with expansions of the surface area for nutrient transport (Rutherford and Tardif 2008, 2009). This suggests that folliculogenesis, conception, implantation, and early placental function may not differ according to birth condition, but that a female's downstream ability to successfully gestate is impaired. Given the illuminating but somewhat limited research to date, prospective studies of human and nonhuman primate pregnancy and specifically of placental growth, morphology, and function during gestation are necessary for understanding the plasticity of specific mechanisms of placental nutrient transport and "stress transmission" in variable ecological contexts and their impact on reproductive system development and health in adulthood.

2.7 Conclusion

Many unanswered questions remain concerning the evolutionary implications of placental function (see Sterner et al. 2012 for more discussion). For example, do placental growth rates or shifts in metabolic function (e.g., glucose metabolism, fatty acid transport) correlate with brain growth in primates in a way that is informative about primate brain evolution and hominin encephalization (Abrams and Rutherford [in press](#); Clancy 2009; Rutherford et al. 2012)? Some evidence suggests that the villous hemochorial primate placenta has a greater surface area per gram of

fetal growth (Baur 1977). As a consequence, the surface area for nutrient transport is potentially increased, particularly later in gestation during the period of greatest fetal brain growth (Abrams and Rutherford [in press](#); Rutherford et al. 2012). This is an exciting and as yet largely unexplored area of research.

Studying primate placentas to expand this exploration is undoubtedly challenging. Nocturnal parturition and placentophagy are common among primates, making collection of the placenta difficult. Infant guarding behavior immediately postpartum and the importance of not interfering with bonding processes also complicates the researcher's quest for fresh tissue. However, the placenta plays such an important role in the developmental events underlying birth condition that the effort to collect placentas is worthwhile. In some lab-based cases timed c-sections or fetectomies are employed, and placental tissue can be collected and weighed easily, fixed quickly in formalin or flash-frozen, and archived or shared. There are also some noninvasive opportunities to include the placenta in research during gestation, including assays of placental hormones (e.g., chorionic gonadotrophin, c-reactive protein, corticotrophin releasing hormone, etc.) in maternal blood and urine (and potentially feces for field studies) and sonographic measures of placental size (Azpurua et al. 2010) and function (Tuuli and Odibo 2011). The payoff is the intersection of evolutionarily informed and biomedically salient studies of the placenta. A robust investigation across primates showing how a female's birth condition programs her ability to conceive, gestate, and raise offspring—and how the placenta translates maternal ecology into that birth condition in the first place—holds great potential to revolutionize not only the study and treatment of infertility and the biological transmission of health and social disparities but also our understanding about evolutionary developmental processes.

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Chapter 3

Placental Development, Evolution, and Epigenetics of Primate Pregnancies

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Keywords Placenta • Fetal–maternal conflict • Uterine environment • Imprinting • DNA • Symbiosis

3.1 Introduction

Understanding the **epigenetic** (bold terms defined in Glossary at end of chapter) regulation of pregnancy in primates requires the integration of many fields of scientific inquiry including primate phylogeny, the evolution of placental anatomy, comparative genomics, and epigenomics. Primate pregnancies vary enormously in terms of timing of embryo implantation, placental anatomy, uterine shape, rates of fetal growth and development, neonatal body mass, number of offspring per pregnancy, and gestation length (Martin and Martin 1990). Epigenetic mechanisms

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may play a role in regulating some if not all of these parameters in pregnancy, but current knowledge is limited. Moreover, in addition to normal variation, epigenetics may play a role in disorders in pregnancy. For example, fetal loss via spontaneous abortion is quite common in humans (Edmonds et al. 1982; Fox-Lee and Schust 2007; Wilcox et al. 1988). Other common human problems in pregnancy have been termed the great obstetrical syndromes, and they include multifactorial disorders such as preterm birth, preeclampsia, and intrauterine growth retardation (Brosens et al. 2010; Romero et al. 2006). The potential role of epigenetics in these obstetrical syndromes is becoming more appreciated (Tobi et al. 2011), and the fetal environment in which epigenetic programming takes place can have long-lasting consequences on adult health (Gluckman et al. 2011). Study of the natural and pathological anatomical, genetic, and epigenetic variation that characterizes primate pregnancies should shed light on the evolution and diversification of the primates and also provide insight into the evolution of health and disease.

In this chapter, we focus on epigenetics in primate pregnancies. Much theoretical work on genetics, epigenetics, and effects on interindividual interactions has been done (Burt and Trivers 2008; Haig 2002), and it is well established that epigenetics plays a role in mediating intrauterine growth rates (Wu et al. 2004). Growth rates have been described in light of maternal–fetal conflict (Haig 2002) and the developmental origins of adult health and disease (Gluckman et al. 2008). In this chapter, we attempt to weave many of these themes together, but we appreciate that much more work needs to be done before anatomical, genetic, developmental, and epigenetic variation in primate pregnancy can be fully understood. Toward this end, we review the immunological paradox that characterizes pregnancies in placental mammals, and we also review the types of interactions that can exist between mother and fetus. These interactions are mediated through the placenta, an organ that includes both fetal and maternal tissue and range from conflict to cooperation. In order to describe potential conflict resulting from fetal–maternal interactions, it is necessary to consider the evolution of primate variation at the maternal–fetal interfaces. We also describe epigenetic mechanisms that potentially play a role in the cooperation and conflict that characterize maternal–fetal interactions. We propose that the placenta plays a unique role in maternal–fetal interactions due to its short life span, and we describe how different forms of maternal–fetal interdigitation can potentially be involved in fetal growth and development. There was likely a selective advantage gained by altering fetal growth rate, neonatal size, gestation length, and reproductive anatomy. The role played by epigenetics in these processes requires further investigation.

3.2 The Immunological Paradox of Pregnancy

In eutherian mammals, the mother and her developing offspring are genetically distinct individuals whose cells, proteins, **DNA**, and other molecules come in contact with one another during gestation. This interaction between maternal and fetal

components led Sir Peter Medawar to define the fetus as a semiallograft similar to a transplanted organ (Medawar 1953). In this view, proteins encoded by paternal alleles could cause an alloantigenic reaction in which the mother's immune system attacks the fetally derived tissues such as the **fetal membranes** (i.e., **chorion, amnion**) and the **trophoblast** cells in the placenta. The ultimate result of such an attack would be the rejection of the fetus and the termination of the pregnancy. How the fetal tissues avoid maternal attack has been the subject of much discussion (Goodman 1963; Moffett and Loke 2004), although studies have yet to resolve this apparent immunological paradox in which genetically distinct organisms coexist without rejection. David Haig built upon the concept of the immunological paradox of pregnancy by theorizing that because the fetus and mother have differing needs, *conflict* between the two is not only possible but likely (Haig 2002). This concept of the maternal–fetal conflict has received wide attention and has been applied to obstetrical syndromes such as preeclampsia (Yuan et al. 2005). Despite the existence of conflict, *cooperation* between the fetus and mother is also necessary for successful pregnancy.

One way to think about maternal–fetal cooperation and conflict during gestation is to imagine pregnancy as a special type of symbiosis. Symbiosis (from the Greek *sym*=with, *biosis*=life) refers to two or more organisms, usually above the species level, living together (Gilbert and Epel 2008). There is a continuum of symbiotic relationships ranging from parasitism to commensalism to mutualism. Parasitism is when one symbiont actually harms the other symbiont. Commensalism refers to symbiotic relationships in which one symbiont benefits and the other symbiont is unaffected. Mutualism is the case in which both symbionts benefit from the relationship. Moreover, symbiosis is usually divided into endosymbiosis in which one of the symbionts lives within the other organism and ectosymbiosis in which a symbiont is attached externally to the other organism. Mutualistic symbiosis has been best studied in the context of plants and the species that pollinate them. Indeed, Darwin was fascinated by the fit between the morphology of orchids and their pollinators (Bascombe and Jordano 2007; Ehrlich and Raven 1964).

If we imagine the fetal/maternal relationship as a special case of endosymbiosis, our next task would be to define the type of endosymbiosis represented. From the perspective of Haig (Haig 2002), while he recognizes that cooperation between mother and fetus is also necessary for successful pregnancies, the maternal–fetal relationship leans more to the parasitic side of the symbiotic continuum in which each of the distinct organisms is acting to further their self-interest. In other words, it is on this end of the symbiotic continuum that conflict can most readily emerge. Other maternal–fetal interactions could be considered commensal in that neither conceptus nor mother benefits or is harmed by the interaction. Some maternal–fetal interactions may be beneficial to both mother and developing offspring as exists in mutualistic symbiotic relationships. Untangling which maternal–fetal interactions benefit the fetus at the expense of the mother from those that primarily benefit the mother, from all the other types of costs and benefits possible during pregnancy, is a major challenge in evolutionary biology. What is known, however, is that differing environments are likely to have effects on maternal–fetal

interactions and the development of offspring (Barker 1992; Gluckman et al. 2008). We could also consider that in many cases, pregnancy and motherhood have additional benefits, such as euphoric feelings that may enhance the mother–offspring bond, protection from certain infections, and increased family/social support (Marlin et al. 2011). Indeed, humans and other anthropoid primates are very social animals and one of the most effective means of building social bonds is through pregnancy. Of course, many pregnancies are difficult—and some instances of spontaneous abortion, preterm birth, and preeclampsia probably can be considered cases in which cooperation between genomes was not established or broken down (Romero 1996).

Epigenetic actions during pregnancy have been advanced as a key mechanism in which the fetus and mother can adjust to variation and flux in the environment encountered during pregnancy. The term epigenetics, originally coined by Waddington (1942), refers to how the environment acts upon genes during development. In order to study epigenetics in primate pregnancies, it is necessary to examine (1) variations in the intrauterine environment and (2) the range of epigenetic mechanisms that act at the molecular level.

3.3 Variation in the Intrauterine Environment Among Primates: Focus on the Placenta

Maternal diet, climate, altitude, and other factors are important constituents of the intrauterine environment (Clancy 2012; Rutherford 2012). Here, we focus on the anatomical environment in which primate fetuses develop. Uterine anatomy varies; anthropoids have simplex uteri, while tarsiers and strepsirrhines have bicornuate uteri. The point of contact between mother and developing offspring is the placenta. The placenta has been defined as the apposition (i.e., placing together) of maternally and fetally derived tissues (Mossman 1987). Placental anatomy and physiology varies within and among primate species as does type and depth of embryo implantation and placenta invasiveness. For example, haplorhines have placentas with a discoid shape while the entire gestational sack apposes maternal tissues in strepsirrhines resulting in a diffuse shape (Wildman et al. 2006).

Cooperation and conflict is most acute at the maternal–fetal interface. Maternal–fetal interfaces are loosely regarded as falling into one of three categories ranging from less to more intimate. These categories are termed epitheliochorial, endotheliochorial, and hemochorial. Strepsirrhines have epitheliochorial placentas meaning the uterine epithelial cell layer remains intact, while haplorhines have hemochorial interfaces in which fetally derived tissues come into direct contact with maternal leukocytes (Benirschke et al. 2006; Luckett and Kuhn 1974; Mossman 1987). There are no primate species characterized by the intermediate endotheliochorial placenta, although this form is seen in tupaiid treeshrews (Fig. 3.1). It is likely that the hemochorial placenta poses a greater challenge to the maternal immune system than the epitheliochorial placenta because fetal (and by extension, paternal) proteins come into direct contact with the maternal immune

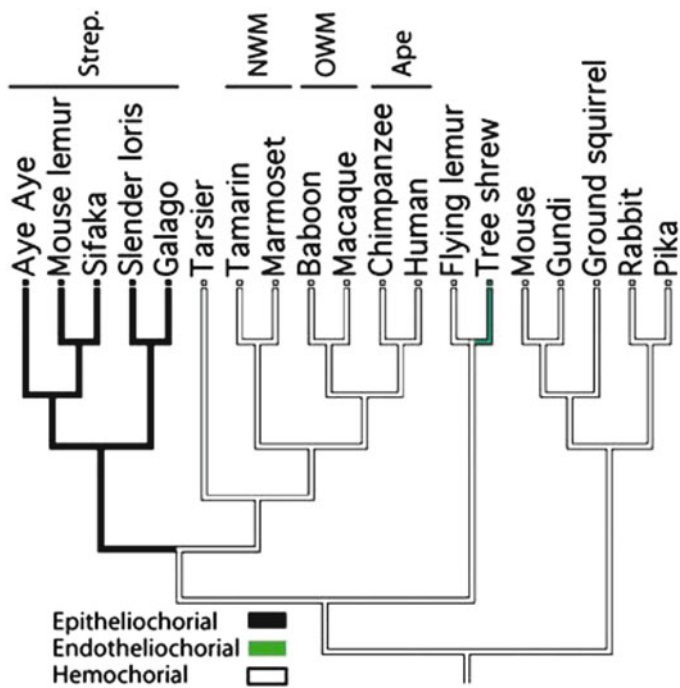


Fig. 3.1 The evolution of the placental interface in primates. Branch colors indicate the type of placental interface ranging from the least invasive, epitheliochorial, to the most invasive, hemochorial. The type of placental interface at internal nodes was determined using parsimony reconstructions (Figure from Wildman et al. 2006, with permission). *Strep* Strepsirrhine, *NWM* New World monkey, *OWM* Old World monkey

cells. This contact is greatly lessened in strepsirrhine maternal–fetal interfaces in which the uterine epithelial cell layer remains intact.

From an evolutionary perspective, it becomes necessary to examine whether the hemochorial or epitheliochorial placenta represents the ancestral state in primates. Previous work had assumed the less epitheliochorial form of placentation was the ancestral type (Luckett and Kuhn 1974); however, such studies were hampered because at the time there were no credible estimates of the phylogenetic relationships among the extant orders of eutherian mammals. Recent advances in molecular phylogenetics have resolved these relationships (Murphy et al. 2001; Wildman et al. 2007), leading to a series of studies that have traced the evolutionary history of the maternal–fetal interface as well as other features of placental anatomy (Carter and Mess 2007; Elliot and Crespi 2009; Mess and Carter 2006; Wildman et al. 2006). These studies have revealed that the last common ancestor of primates had a hemochorial placenta, that the epitheliochorial interface is a derived feature of strepsirrhines, and that the immunological paradox of pregnancy has been in place in human descent since the time of the last common ancestor of primates and has probably existed since the time of the last common ancestor of placental mammals. Figure 3.1 is a phylogenetic reconstruction of the evolution of the maternal–fetal interface in

Euarchontoglires (the clade that includes Primates, Dermoptera, Scandentia, Rodentia, and Lagomorpha). Implications of these findings require a reassessment of the evolution of maternal–fetal interactions in primates because the evolutionary events that resulted in the symbiosis between mother and developing offspring occurred quite anciently in our evolutionary past. In other words, it will be necessary to take a broad comparative perspective to understand the evolutionary and epigenetic adaptations and neutral events that led to human maternal–fetal interactions as well as such interactions in other lineages.

3.4 Epigenetics in Pregnancy

Waddington (1942) coined the term **epigenesis** to refer to the way in which developmental interactions produce adult phenotypes. As Gilbert and Epel (2008) have noted, this definition is equivalent to what today is considered developmental genetics. More recently, an alternative view of epigenetics, defined as heritable changes in **gene expression** not due to changes in DNA sequence, has emerged (Eccleston et al. 2007).

From a molecular perspective, there are many mechanisms in which epigenesis can occur. These mechanisms include **histone modification**, **DNA methylation**, and **gene imprinting**. Each of these mechanisms can promote or repress gene expression (i.e., activity) in different directions. Moreover, these mechanisms may result in contradictory patterns of expression across cell types, tissues, developmental stages, and species. What follows is a brief survey of the key mechanisms of epigenesis that can operate during pregnancy.

3.4.1 *Histone Modification and DNA Methylation*

Two common ways in which epigenetic modification to DNA and proteins occurs in the nucleus of the cell are histone modification and **CpG dinucleotide** DNA methylation (Fig. 3.2). In the nucleus of eukaryotic cells, DNA is wrapped around **histone** protein complexes, and this DNA/protein complex is referred to as a nucleosome. Nucleosomes and nonhistone proteins combine to form **chromatin**, which is the material that forms chromosomes. Histone proteins are key players in epigenesis because they either provide access to DNA or they prevent DNA from being accessed. If DNA is accessible to transcription factors and other molecules, the activity of genes can be regulated. Conversely, if DNA is not accessible to these molecules, it is likely that the encoded gene will be inactivated. Modification of histones is thus an important feature of gene regulation because the state of the histone around which a gene is wrapped partly determines the potential for that gene's activity. Histones can be epigenetically modified via a variety of chemical modifications involving the attachment of various chemical groups. Specifically,

mechanisms of histone modification include **methylation**, **phosphorylation**, **acetylation**, and **ubiquitination**. Histone modification results in more short-term and plastic silencing than processes with longer-term effects such as the inactivation of one of the X chromosomes in females and DNA methylation (Reik 2007). Indeed, we have suggested that histone modification may play a role in the differential timing of expression of genes in the beta-hemoglobin cluster (Johnson et al. 2006). In that study, we showed that the timing of gene expression of these important oxygen-transporting molecules is correlated with the physical distance (i.e., the number of base pairs) a gene is located from the locus control region. This distance may determine why catarrhines and platyrrhines have undergone different evolutionary trajectories in the fetal expression of hemoglobin genes. During pregnancy, different copies of the gamma-globin gene are fetally expressed in these clades, and this may affect oxygen transport from mother to fetus.

In contrast to the epigenetic effects of histone protein modification, DNA methylation occurs via a chemical modification of the DNA sequence itself. In comparison to histone modification, methylation results in more long-term silencing (Reik 2007). DNA methylation requires the addition of a methyl group to the 5' (i.e., upstream) carbon of a cytosine (i.e., the C nucleotide of the four DNA **nucleotides** A, G, T, C) to form methyl cytosine (Fig. 3.2). When cytosine precedes guanine (the G, in A, G, T, C) on a strand of DNA, the region is denoted as CpG, where the “p” stands for phosphate molecule that joins the two nucleotides to one another. The addition of a methyl group results in a “**hypermethylated**” state and the transcriptional repression (i.e., downregulating or silencing) of nearby genes. Once methylated, transcriptional repressors are recruited to the region and gene transcription is disrupted (Maccani and Marsit 2009). The term “**hypomethylated**” is used to describe a target for methylation that remains unmethylated. Genes whose promoters are hypomethylated DNA are typically more transcriptionally active than hypermethylated genes.

During organismal development, there are two main stages of epigenetic reprogramming and/or plasticity (Reik et al. 2001; Santos et al. 2002). Genome-wide DNA methylation patterns are erased in the embryo during **gametogenesis** and then again during early **embryogenesis**. During the first stage of reprogramming (gametogenesis), imprinted genes are reset. During the second stage of reprogramming (early embryogenesis), imprinted genes avoid this process of demethylation. At this point, the paternal DNA undergoes an active rapid loss of methylation, while maternal DNA undergoes a more passive loss of methylation. De novo methylation then reestablishes the developing fetus's methylation patterns in cell- or tissue-specific ways.

Methylation is an interesting phenomenon to consider from the perspective of evolution. For example, we have shown that methylation of CpG sites near a key neurotransmitter, solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (*SLC6A4*), modifies the effect of the number of traumatic events on risk for posttraumatic stress disorder (Koenen et al. 2011). Specifically, in a subset of Detroit residents, methylation of a particular *SLC6A4* promoter CpG site in the human genome, cg22584138, is associated with either risk for or protection from

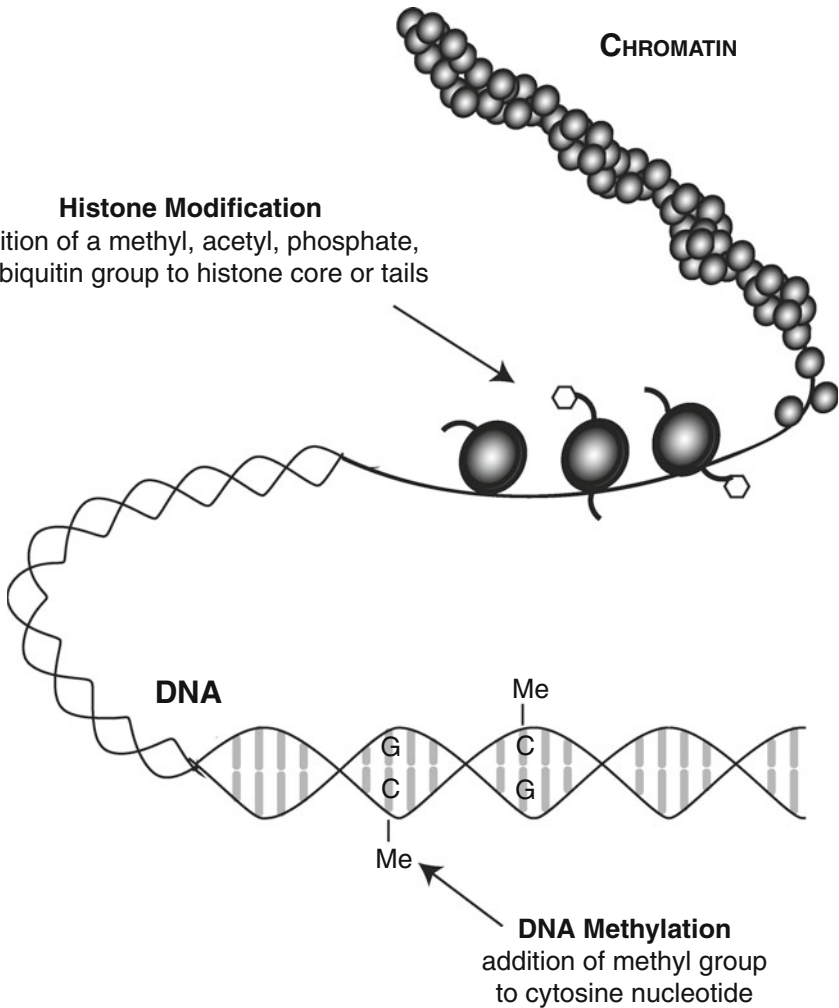


Fig. 3.2 Epigenetic modifications. Two common forms of epigenetic modification (modification to histone proteins and DNA methylation of CpG sites) are depicted on an unwound chromosome. See Glossary for definitions of terms

the development of PTSD depending on the number of traumatic events an individual has faced. This CpG site is located on human (hg18) chromosome 17, position 25,586,346. Examination of publically available primate genome sequences (<http://genome.ucsc.edu>) reveals that this particular CpG site is conserved in human, chimpanzee, orangutan, rhesus macaque, marmoset, tarsier, and mouse lemur. Conservation of this CpG site suggests epigenetic potential via methylation has existed throughout primate evolution. Interestingly, it has been shown that pre-natal exposure to maternal depressed mood affects *SLC6A4* methylation in infants

at birth (Devlin et al. 2010). *SLC6A4* encodes a serotonin transporter, and it has been shown that disinhibited behavior in infant rhesus macaques is associated by early life stress and predicted by *SLC6A4* gene expression levels (Kinnally et al. 2010; Kinnally 2012). Taken together, these findings point to the possibility of ancient epigenetic potential associated with the development of anxiety disorders in humans and other primates. Moreover, the emergence of anxiety disorders potentially can be linked to prenatal environment.

3.4.2 Gene Imprinting

In diploid cells, there are two copies of each gene. Both copies of each gene may not be equally expressed. Monoallelic expression is either random or dependent on the parent of origin. The latter phenomenon is referred to as gene imprinting and is mediated by epigenetic modification (e.g., DNA methylation) of parental alleles. Gene imprinting, also known as allele-specific gene expression, occurs when either the paternal or maternal copy of a gene is expressed exclusively (Reik and Walter 2001). Imprinted genes are not randomly distributed in the genome but rather cluster together and are controlled by an imprinting control region (Edwards and Ferguson-Smith 2007). Comparisons of imprinted and nonimprinted genes in human and mouse suggest differences in sequence conservation between maternally and paternally expressed genes (Hutter et al. 2010). That study demonstrated that paternally imprinted genes were more evolutionarily conserved at the DNA sequence level than were maternally imprinted genes.

Imprinting appears to be particularly important for placental and fetal development (Frost and Moore 2010). The expression of at least 50 imprinted genes has been described in the human placenta, and restricted fetal growth has been tied to aberrant expression of many of these genes (Nelissen et al. 2011). For example, *PHLDA2* (pleckstrin homology-like domain, family A, member 2) is maternally expressed in humans and is predominantly expressed in the placenta. Levels of *PHLDA2* expression at term are inversely correlated with fetal birth weight in humans (Apostolidou et al. 2007) and mice (Salas et al. 2004), and higher levels of *PHLDA2* in the placenta are associated with IUGR pregnancies (Diplas et al. 2009; McMinn et al. 2006). Moreover, transient neonatal diabetes has been associated with aberrations of gene imprinting at a cluster of genes on human chromosome 6p24 (Temple and Mackay 1993), and methylation analysis of this locus as well as the *IGF2R* and *H19* loci has shown that growth-restricted infants have different methylation patterns at these loci than seen in normal controls. Taken together, these findings point to a connection among gene imprinting, DNA methylation, and rates of fetal growth and development.

Gene imprinting is an attractive mechanistic candidate for mediating maternal–fetal interactions. The clearest examples of imprinted genes are those that lie on the X chromosome. In human females, only one copy of each X-chromosome gene is expressed. Imprinting is also known to occur at **autosomal** loci, and a number of

hypotheses have been proposed to explain the evolution of imprinting. The genetic conflict theory (Haig 2002; Haig and Graham 1991; Moore and Haig 1991) proposes that there is an inherent conflict between paternally and maternally derived alleles because paternal alleles have been selected to maximize fetal growth and nutrition while maternal alleles have been selected to balance the cost of an offspring with the projected cost needed for future offspring. As a result, paternally imprinted alleles are beneficial to the fetus while maternally imprinted alleles are beneficial to the mother. Imprinting should therefore be found in genes that influence placental growth and fetal growth and nutrient metabolism.

In instances when the maternal alleles are expressed and paternal alleles are silenced, imprinting may reflect coevolution between mother and fetus. Favoring maternal alleles protects the fetus by reducing the chance that foreign fetal proteins encoded by the paternal genome will be subject to dangerous attacks by the maternal immune system (Keverne 2009; Keverne and Curley 2008; Pijnenborg et al. 2008). In support of this hypothesis, maternal alleles are preferentially expressed in the mouse brain during embryonic and postnatal development, thereby preventing attack on the developing brain (Gregg et al. 2010a, b). To date, most work on imprinting has focused on maternal–fetal conflict, with an emphasis on how either mother or fetus benefits from imprinted loci. Returning to the concept of pregnancy as a special type of symbiosis, it becomes apparent that imprinting represents a relatively small proportion of the genetic and epigenetic actions that take place during pre- and postnatal life. Several recent studies have examined gene imprinting in mice using next-generation sequencing techniques (Gregg et al. 2010a, b; Wang et al. 2011). In the Gregg et al. studies, approximately 1,300 imprinted genes were identified in analyses of mouse brain tissue, or approximately 4–5% of all genes analyzed. The Wang et al. study identified or confirmed the imprinting status of about 40 genes expressed in the placenta as well as finding an additional 100 weakly imprinted genes. The vast majority of genes are not imprinted, and there is no reason to expect that these genes exhibit special maternal or fetal effects. Moreover, imprinted genes may not provide benefit to maternal or fetal units. Population genetics theory predicts that many imprinted genes will be homozygous, and therefore, the fetus or mother will be incapable of sensing the expressed allele's parent of origin. Thus, most genes cooperate during pregnancy. Mother and fetus must coexist for pregnancy to be successful, and while conflict undoubtedly plays a role, it is unclear how large this role actually is amongst all the players in pregnancy.

Detecting gene imprinting in nonhuman primates presents several methodological challenges. In mice, imprinting is typically shown via breeding experiments in which mutations can be traced across several generations in which crossing and backcrossing have occurred (DeChiara et al. 1991; Gregg et al. 2010a, b). Therefore, long-term pedigrees and associated DNA and RNA samples would be needed to assess imprinting in nonhuman primates because breeding experiments including backcrosses are costly and take a relatively long time in primates as opposed to mice. Imprinting in the human term placenta has been demonstrated in family studies focused on analysis of the genetics of human mother–father–offspring trios (Daelemans et al. 2010). Other than studies on stem cells (Fujimoto et al. 2006),

there is little published work on tissue-specific imprinting in nonhuman primates, but captive colonies would be a good place to start. Despite a general lack of knowledge regarding imprinting in nonhuman primates, it can be stated that natural selection does appear to act on imprinted genes, and one recent study has demonstrated that imprinted loci are constrained against gene duplication (O'Connell et al. 2010). In other words, imprinted loci, in contrast to most other genes, are constrained against duplication, a commonly described mechanism by which genes gain new functions or subdivide existing functions (Nei and Rooney 2005).

3.4.3 *Imprinting of IGF2 and H19 in Primates*

Individual gene-imprinting status is not conserved across mammals and may point to differences in maternal–fetal interactions between species (Monk et al. 2006). First identified in mice, insulin-like growth factor II (*Igf2*), its receptor *Igf2r*, and the long noncoding RNA *H19* are imprinted in many mammals and play an important role in fetal growth and development. Imprinting at the insulin growth factor II *IGF2* locus has been used as evidence for the genetic conflict hypothesis (Haig 2002). The *IGF2* gene is expressed in the placenta and is a major modulator of fetal growth (Constancia et al. 2002; Wilkins and Haig 2003). Imprinting of the *IGF2* gene and its receptor *IGF2R* evolved early in mammalian descent before the time of the last common ancestor of marsupial and placental mammals, but humans and possibly other primates have lost the ability for the *IGF2R* locus to be imprinted (Wilkins and Haig 2003). In mice, *Igf2* paternal allele is expressed while the *Igf2r* gene is expressed only by the maternal allele. This opposite pattern of expression suggests the conflict theory is appropriate in mice but may play less of a role in humans who do not imprint their *IGF2R* locus. Alternatively, imprinting can also reflect a more cooperative balance between parental alleles to unequal resource allocation. *H19* was initially found to be expressed in adult skeletal muscle, and from this observation, it earned the name *ASM*. The aberrant expression of this gene, which does not encode a protein, has been associated with **Beckwith–Wiedemann syndrome** and **Russell–Silver syndrome**, *Igf2* is expressed from the paternal allele, while *Igf2r* and *H19* are expressed from the maternal allele. Expression of the paternal *Igf2* promotes fetal growth, whereas expression of the maternal *Igf2r* and *H19* regulate this growth. In humans, *IGF2* and *H19* are part of a cluster of imprinted genes on human chromosome 11 (the 11p15.5 cluster) (Fig. 3.3). As noted above, human *IGF2* expression is similar to that observed in mouse, but humans have lost the ability to imprint *IGF2R* (Kalscheuer et al. 1993) and exhibit different patterns of *H19* methylation than observed in mice (Jinno et al. 1995). It is unclear when during primate evolution these changes occurred. Both maternal and paternal alleles of *H19* are expressed during the first 10 weeks of development, while maternal alleles are preferentially expressed in the placenta after 10 weeks (Jinno et al. 1995). The human *H19* promoter is hypomethylated during placental development while the 3' region of the locus has progressive

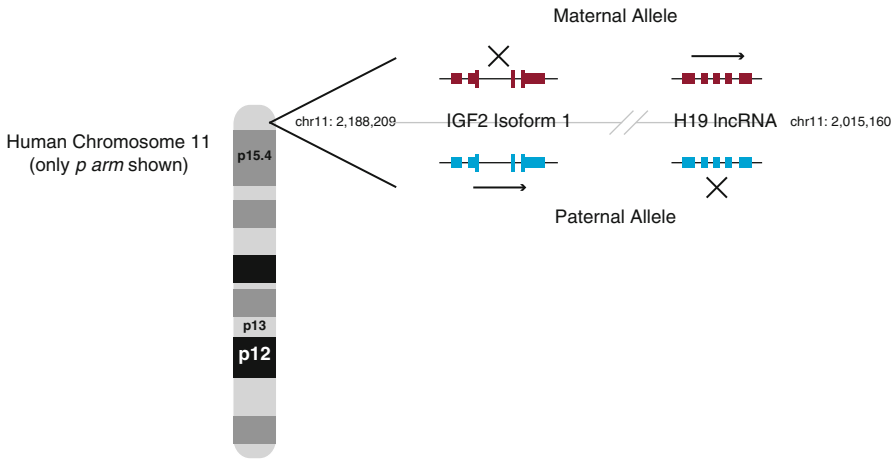


Fig. 3.3 Imprinting of *IGF2* and *H19* in primates. *IGF2* and *H19* are part of a cluster of imprinted genes on human chromosome 11 (11p15.5). Maternal alleles are shown in *red*. Paternal alleles are shown in *blue*. In humans, both genes are imprinted. Only the maternal allele of the long noncoding RNA *H19* and the paternal allele of *IGF2* are expressed

methylation of paternal allele with gestation (Jinno et al. 1995). The authors suggest this switch from biallelic to monoallelic expression may be regulated by *trans*- or *cis*-elements. Loss of imprinting of *H19* has been associated with fetal growth restriction (Ying et al. 2010).

3.4.4 ncRNAs and X-Chromosome Inactivation

Cellular RNAs that do not encode proteins are referred to as **noncoding RNAs** (ncRNAs). These ncRNAs are important regulators of gene expression and help silence gene expression by mediating DNA methylation and modification to chromatin structure (Zhou et al. 2010). The most widely studied example of ncRNA-mediated transcriptional silencing involves X-chromosome inactivation in mammals. The process of X-chromosome inactivation in female mammals ensures that males and females have similar dosage of X-linked genes. The first stage of X inactivation involves expression of *Xist* (X inactive-specific transcript; a long ncRNA (lncRNA) located on the X chromosome) from a randomly selected X chromosome (Brown et al. 1991, 1992). *Xist* RNA then coats the majority of the X chromosome selected for inactivation (Clemson et al. 1996). During early embryogenesis in the mouse, *Xist* is imprinted (the paternal allele is expressed while the maternal allele is repressed); however, both alleles are expressed in human and rabbit (Okamoto et al. 2011). During the final stage, there is extensive DNA methylation and histone modification to the inactivated chromosome that represses transcription (Chang et al. 2006). The inactivated chromosome is separated from the activated chromosome

and targeted to a distinct nuclear compartment during the cell cycle where these epigenetic modifications are maintained (Zhang et al. 2007). Additional ncRNAs have been shown to play a role in the transcriptional repression process that results in inactivation including *Tsix* (Cohen et al. 2007; Lee et al. 1999a, b; Ohhata et al. 2008; Sado et al. 2005; Xu et al. 2006), *Xite* (Ogawa and Lee 2003; Stavropoulos et al. 2005; Xu et al. 2006), and *DXPas34* (Cohen et al. 2007; Debrand et al. 1999; Stavropoulos et al. 2005; Vigneau et al. 2006).

3.4.5 Epigenetics of Fetal Development Is Influenced by the External Environment

There is growing evidence that many common adult diseases result from the interaction of genetic and environmental factors during development (Bookman et al. 2011). Ontogenetic epigenetic modifications can provide valuable insights into gene–environment interactions during these sensitive periods of growth and development. In addition, vulnerability to many adulthood conditions may originate from these epigenetic factors (Gluckman et al. 2008; Uddin et al. 2010a, b).

Information about the environment (e.g., nutritional quality and quantity) is passed from mother to fetus through the placenta (Gluckman et al. 2008; Rutherford 2009, 2012). For example, poor nutritional quality may reduce maternal body size and placental size, which in turn constrains or disrupts nutrient transfer to the developing fetus. The fetal epigenome is sensitive to environmental factors during early development, and a vulnerability to certain diseases (e.g., metabolic diseases) during adulthood may be traced to this sensitivity. Known as fetal programming, the concept was initially articulated by Barker as a result of epidemiologic studies that examined the relationship between the health of middle-aged individuals and their birth weight (Barker 1998; Nathanielsz 1999). The **fetal origins hypothesis** suggests fetal programming can play a significant role in the health of the individual throughout his or her life course. Intrauterine stresses include hypoxia, protein deficiency, and caloric excess (Gheorghe et al. 2010), and it has been proposed that there is a link between fetal growth and maternal nutrition (Barker et al. 1993). Nutritional imbalance during gestation can result in reduced or increased fetal growth and may be associated with metabolic disorders that develop later in life (Hillier et al. 2007). Such intrauterine stress can reprogram expression of metabolism-related genes by altering chromatin structure through epigenetic modifications (Gluckman et al. 2008). These developmental cues are passed from mother to child and may also be passed from grandmother to grandchild (Gluckman et al. 2008). While any correlation between fetal growth in mother and offspring must partly reflect shared genes (Hoche et al. 2000), there is evidence for an epigenetic contribution to these correlations. Women whose mothers experienced the Dutch Famine while pregnant gave birth to offspring (the grand-offspring of the famine-exposed pregnant women) who were smaller (Lumey 1992), while similar findings have been reported in rhesus macaques (Price and Coe 2000; Price et al. 1999) and experimentally in rodents (Drake et al. 2005; Hoet and Hanson 1999).

In addition to maternal effects, paternal factors may also play a role on fetal growth and development. Paternal fasting has been shown to influence glucose levels in offspring in rodents (Anderson et al. 2006; Ng et al. 2010) and humans (Kaati et al. 2002; Pembrey et al. 2006). In mice, paternal diet influenced the expression of lipid and cholesterol biosynthesis-related genes by altering DNA methylation (Carone et al. 2010). In that study, males fed a diet with low protein content produced offspring with increased hepatic expression of genes that play a role in fat and cholesterol biosynthesis, but a decrease in cholesterol esters, suggesting transgenerational paternal effects on growth regulation. Taken together, these data suggest that paternal cues may also be encoded in the sperm genome and epigenome and passed from father to offspring (Curley et al. 2011).

Variation in primate developmental processes such as pregnancy should influence phenotypic diversity. Compared to most other mammals, primates have long gestation lengths, low reproductive rates, slow postnatal development with longer juvenile periods, and long life spans (Table 3.1; Kappeler et al. 2003). Primates also tend to have larger and more precocial infants (Kappeler et al. 2003). Longer gestational lengths extend the period of maternal–fetal interactions and place added selective pressure on a system that needs to accommodate the needs of the mother and fetus. In addition, a longer juvenile period of development extends interactions between parent and offspring well into postnatal life.

The degree of maternal–fetal and parent–offspring interactions varies as the result of differences in life history and pregnancy-related traits. In order to understand the molecular mechanisms that underlie variation in primate pregnancies observed between species, we can examine primate genomes. Using comparative genomics, we have identified those lineage-specific gene families involved in processes such as pregnancy. For example, **galectins** are proteins expressed in the placenta (at the maternal–fetal interface) that play a role in immune tolerance. This gene family arose by at least 40 million years ago and has expanded and diversified in anthropoid primates (Than et al. 2009). It is possible that greater, or at least longer lasting, immune tolerance between maternal and fetal tissues would be required in anthropoid primates, which generally have longer gestation lengths, larger offspring, and more invasive placentas (Table 3.1; Than et al. 2009). That being said, Table 3.1 shows some interesting trends in primate evolution, trends that are likely subject to epigenetic factors.

For example, among primate genera, it is *Tarsius*, with a 6-month pregnancy, that possesses the longest gestation length relative to its adult body size. Next on the list of longest relative gestation length are the New World monkeys. Interestingly, both *Tarsius* and New World monkeys have **trabecular placental–uterine interdigitation**, while strepsirrhines and catarrhines have **villous interdigitations** (Benirschke et al. 2006; Luckett and Kuhn 1974) (Fig. 3.4). Figure 3.4 depicts some differences between villous and trabecular interdigitation in the cross-sectional plane as viewed with a microscope. These structures are difficult to interpret for those without experience in histology and cell biology, so some description is warranted. At the gross anatomical level in catarrhines, the villous trees of the placenta resemble heads of broccoli, and these become intertwined with maternal tissue in the maternal blood

Table 3.1 Variation in primate life histories and pregnancies

	Gestation length (days)	Litter size	Interbirth intervals (days)	Age at weaning (days)	Age at sexual maturity (days)	Age at first birth (days)	Longevity (years)	Adult body size (g)	Uterus type	Placenta type
Hominidae	230	1	1,257	834	3,686	3,935	55	32,911		
Cercopitheciidae	174	1	560	360	1,700	1,705	29	7,829		
Atelidae	203	1	771	543	1,871	1,949	26	7,127	Simplex	
Cebidae	148	2	344	190	1,094	1,058	27	810		Hemochorial
Pitheciidae	158	1	496	167	1,325	1,054	21	1,682		
Tarsiidae	162	1	251	76	627	881	25	140		
Lemuriformes	122	1	470	137	767	976	20	1,787	Bicornuate	
Lorisiformes	145	1	267	116	434	533	17	482		Epitheliochorial

Life history data used to generate this table are from the PanTHERIA database (PanTHERIA_1-0_WR93_Aug2008.txt; downloaded April 28, 2011) and represent averages across species available for clade of interest. For more information about this database, individual data points, and references, see Jones et al. (2009). Uterus type and placenta type data used to generate this table are from Mossman (1987) and Wildman et al. (2006)

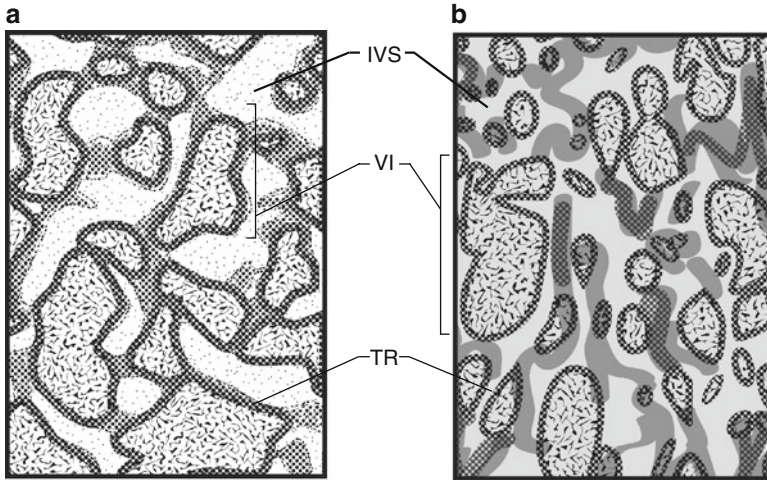


Fig. 3.4 Interdigitation of tissues at the maternal–fetal interface in primates. Cross-sectional view representing trabecular (a) and villous (b) placental interdigitation. Trabecular interdigitation, found in tarsiers and platyrrhines, is characterized by branching, globular folds eventually terminating into fingerlike villi. Villous interdigitation is present in strepsirrhines and catarrhines, provides increased surface area, and is characterized by a treelike branching pattern of the villi (Benirschke et al. 2006). TR indicates trophoblasts, VI indicates villi, and IVS indicates the intervillous blood space. Drawings were adapted from Hill (1932)

space. The trabecular form found in platyrrhines and tarsiers do not so much resemble heads of broccoli because the villi are more lobular (think Baobab tree). Thus, in cross section, the villi in villous interdigitation are more common. There are other forms of interdigitation in nonprimate mammals that point to the complexity of mammalian placentation in general. Recently, it has been suggested that the type of placental interdigitation predicts the length of gestation (Capellini et al. 2011; Wildman et al. 2006). Phylogenetic analyses are challenged by the distribution of these character states in primates (Wildman et al. 2006), and the ancestral character state for primates, haplorhines, and anthropoids is ambiguous. That tarsiers and New World monkeys share a trabecular interdigitation and relatively long gestations is intriguing from the standpoint of resource transfer during pregnancy.

In 2006, we proposed that mammalian species such as humans and cows that have a villous type of interdigitation (Fig. 3.4) tend to have absolutely long gestations (Wildman et al. 2006). Moreover, **placental lactogens**, key players in mediating rates of fetal growth and development, are highly expressed in the second half of pregnancy in species with villous placentas, but highly expressed throughout gestation in rodents (Robertson and Friesen 1981; Robertson et al. 1982), a group of species that have labyrinthine maternal–fetal interdigitation. Increasing concentration of placental lactogens in the maternal circulation results in the fetus being able to extract maternal resources more efficiently, and thus, placental lactogens can act as the substrate for maternal–fetal conflict and cooperation. Thus,

rodent fetuses with **labyrinthine** placentas extract resources at a greater rate than primates throughout gestation, resulting in shorter pregnancies in rodents relative to primates. We proposed that the villous form of placentation that convergently evolved in cetartiodactyls and primates represents an evolutionary compromise that enables the lengthening of gestation without depleting maternal resources excessively. Moreover, it has been shown recently that the type of maternal–fetal interdigitation is a key determinant of gestation length, with species possessing more interdigitated (i.e., labyrinthine) placentas having shorter gestations (Capellini et al. 2011). It is possible that the trabecular type represents a further compromise that enables relatively longer gestations in relation to body size; however, this remains to be tested. Placental lactogens are expressed in late pregnancy in New World monkeys (Papper et al. 2009). It is unclear whether tarsier placentas express genes orthologous to anthropoid lactogens.

Epigenetic modifications have also been shown to facilitate gene–environment interactions postnatally. Information about the postnatal environment may be observed by the infant directly and is also passed from mother to infant through lactation (Gluckman et al. 2008; Hinde 2012). Behavioral cues or cultural systems also serve as a mechanism for transmission of parental information (Jablonka and Lamb 2005). Both early life stress and genetic or epigenetic factors can play a role in the development of and vulnerability to mental health disorders as an adult (Cirulli et al. 2009; Kaufman et al. 2000). In particular, disruption of the mother–infant bond in rodents (Cirulli et al. 1994; Levine 1957; Sanders and Anticevic 2007; Weininger 1954) and primates (Harlow and Zimmermann 1959; Seay et al. 1962; Suomi 2006; Machado 2012) suggests there is a strong maternal effect during early postnatal development.

3.4.6 *Four Embryonic Lineages*

The tissues of a developing fetus arise from three distinct embryonic lineages: ectoderm, mesoderm, and endoderm, each of which are derived from the cells of the inner cell mass or embryoblast (Larsen 2001). Once differentiated, ectoderm, mesoderm, and endoderm are each subject to lineage-specific epigenetic modifications that account for their phenotypic differences (Chen et al. 2010). However, not all fetal tissues arise from these three lineages. Formation of the inner cell mass during this early stage of embryogenesis is accompanied by the formation of the outer cell mass or trophoblast (Fig. 3.5). During implantation, the trophoblast cells proliferate and begin evasation of the uterine lining, thus forming the placenta (Larsen 2001). Consequently, the placenta, as the first specialized tissue derived after fertilization, does indeed represent a fourth unique embryonic lineage. Although trophoblast-derived tissues and cells are often referred to as arising from a “trophectoderm” layer, it is merely due to their physical closeness to the embryonic ectoderm layer rather than a common origin of the two layers.

In light of the distinct origins described above, it is possible that the placenta undergoes epigenetic modifications different from those of the three other embryonic

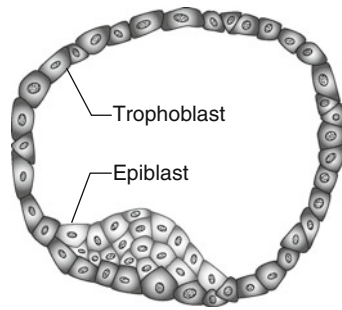


Fig. 3.5 Trophoblast and embryoblast differentiation in placental mammals. Early-stage (human pregnancy days 4–5) embryo depicting distinct trophoblast and embryoblast layers. The cells of the trophoblast or outer cell mass will proliferate and invade the uterine lining over the next several days, eventually giving rise to the placenta. The inner cell mass or embryoblast will differentiate during gastrulation to form the ectoderm, mesoderm, and endoderm of the embryo

lineages. Unlike most tissues whose development and lifespan are measured in years and decades, the placenta only needs to survive for a few months (Benirschke et al. 2006). Therefore, epigenetic modifications that would result in decreased lifespan in nonplacental tissues may be less harmful to the placenta. In other words, the placenta is potentially not as epigenetically constrained as other tissues and thus is free to take risks that to these other tissues would be disastrous. This may provide an explanatory mechanism for why the anatomy and physiology of the placenta varies so greatly among mammalian species (i.e., Fig. 3.4).

3.5 Summary

Pregnancy can be thought of as a special type of endosymbiosis. Some of the interactions between mother and developing offspring may result in conflict (e.g., gene imprinting), while other interactions necessitate cooperation (maternal immune tolerance of the semiallograft fetus). Many maternal–fetal interactions are mediated by the actions of genes and proteins in the placenta. The placental genes and proteins can be regulated epigenetically by mechanisms including histone modification and DNA methylation. Epigenetics during primate pregnancies is a difficult topic of study, but one likely to provide profound insight into the evolution of the order. This area of research requires integration of the factors that comprise the fields of comparative anatomy, life history studies, genomics, primate behavior, and environmental studies. Each of these factors can affect epigenesis at the level of DNA and protein. Unraveling the complex ways in which the environment, the genome, and phenotype interact with one another is further complicated in studies of pregnancy. This complication exists because the chemical signals are being produced by at least two separate and distinct genomes (i.e., mother and fetus). Moreover, the phenotype of the developing offspring and mother is plastic, and these phenotypes will differ

based on epigenetic responses to both the intrauterine and external environments. Despite these challenges, it is necessary to elucidate the role epigenetics during pregnancy has played in the diversification of primates and other mammals if we are to understand the evolutionary events that led to the emergence of the human species.

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Glossary

Amnion A protective membrane that surrounds an embryo; the amnion is in contact with the inner layer of the chorion

Autosome A chromosome that is not a sex chromosome (X or Y); humans have 22 pairs of autosomes (chromosomes 1–22) and 1 pair of sex chromosomes

Acetylation Posttranslational modification of histones that involves the addition of acetyl group; acetylation reduces binding affinity between histones and DNA which promotes transcription; deacetylation increases binding affinity which represses transcription

Beckwith–Wiedemann syndrome (BWS) A congenital growth disorder characterized by enlargement of body size, enlarged organs, hypoglycemia, and other symptoms. Many cases are associated with a defect in human chromosome 11

Chorion A membrane between the maternal tissue and the fetus; the chorion is divided into an outer layer formed by the trophoblast and an inner layer formed by the somatic mesoderm

Chromatin The materials that make up chromosomes; consists of histones, other proteins, and DNA; found in the nucleus

***cis*-regulatory element (*cis*-element)** DNA binding sites that regulates expression of neighboring genes; often located in the promoter of a gene; common *cis*-elements include transcription factor binding sites; e.g., hormone receptor proteins such as estrogen receptors bind DNA near “target genes” and alter their transcriptional activity

CpG dinucleotide (CpG sites) A region of DNA where a cytosine (C) precedes a guanine (G); the two nucleotides are linked to each other by a phosphate (p); in eutherian mammals, these sites can often be methylated

DNA Deoxyribonucleic acid; DNA consists of polymers made up of nucleotides that are organized sequentially along a “backbone” comprised of sugar and phosphate molecules; DNA encodes the genome

Embryogenesis The process by which an embryo is formed and develops

Epigenesis The development of an organism; the way in which developmental interactions produce adult phenotypes

Epigenetic Heritable changes in gene expression not due to changes in DNA sequence; examples of epigenetic change include DNA methylation, histone modification, and regulation by noncoding RNA

Fetal membranes Usually considered as the fetally derived amnion and chorion membranes that surround and protect the developing conceptus

Fetal origins hypothesis Fetal programming can play a significant role on the health of the individual throughout his or her life course

Galectins Proteins that regulate immune responses through the recognition of cell-surface glycans

Gametogenesis The process by which diploid or haploid precursor cells undergo division and differentiation to form mature haploid gametes; in animals, gametogenesis is the creation of sperm cells (spermatogenesis) in males and egg cells (oogenesis) in females

Gene expression The conversion of DNA to messenger RNA (mRNA) via the process of transcription

Gene imprinting Allele (e.g., maternally or paternally inherited form of a gene)-specific gene expression

H19 Imprinted, maternally expressed transcript; a long noncoding RNA (lncRNA) located in an imprinted region of human chromosome 11 near *IGF2*; plays an important role in regulating fetal growth and development through its interaction with *IGF2*

Histone Small, abundant proteins found in eukaryotic cell nuclei that package and arrange DNA into nucleosomes; histones act as spools around which DNA is wound and are important for gene regulation; histones include core and tail domains, and a nucleosome is an aggregation of eight histone proteins in complex with DNA; a histone core is a disc-shaped structure around which DNA is tightly wrapped, while a histone tail is a series of amino acids that extend outward from the core histone fold, and which can be covalently modified in ways that determine chromatin function and structure

Histone modification Posttranslational modifications (i.e., methylation, acetylation, ubiquitination, etc.) to the tails and cores of histone proteins; more tightly wound DNA is less accessible to regulatory proteins that can enable expression of a gene; more loosely wound DNA is more easily transcribed

Hypermethylated A target for methylation that is methylated

Hypomethylated A target for methylation that remains unmethylated

IGF2 Insulin-like growth factor II gene; located on human chromosome 11; imprinted, paternally expressed gene; this gene promotes growth and development

IGF2R Insulin-like growth factor II receptor gene; located on human chromosome 6; expression of this receptor regulates growth and development; imprinted in mice but both alleles are expressed in humans

Labyrinthine A type of maternal–fetal interdigitation in which maternal blood circulates through channels within the outermost fetal component of the placenta (i.e., the fetal syncytiotrophoblast)

Methylation (or DNA methylation) The addition of a methyl group to the 5' carbon of a cytosine nucleotide (that usually precedes a guanosine; denoted as CpG) to form methyl cytosine; the addition of a methyl group (hypermethylation) results in the transcriptional repression of nearby genes; demethylation refers to the removal of a methyl group

Noncoding RNAs (ncRNAs) Functional cellular RNAs that do not encode proteins; includes transfer RNA (tRNA), ribosomal RNA (rRNA), long noncoding RNA (lncRNA), small nucleolar RNA (snoRNA), microRNA (miRNA), small interfering RNA (siRNA), and piwi RNA (piRNA)

Nucleotides The structural unit of DNA and RNA; includes the nucleic acids adenine (A), guanine (G), thymine (T), cytosine (C), and uracil (U)

Placental lactogens Hormones expressed in the placenta that facilitate energy supply from mother to fetus; lactogenic activity is characterized by the ability of the proteins to bind to the prolactin receptors

PHLDA2 Pleckstrin homology-like domain, family A, member 2; located on human chromosome 11; imprinted, maternally expressed gene in the human placenta; plays a role in limiting fetal growth

Phosphorylation Posttranslational modification of histones (and other molecules) that involves the addition of a phosphate group; phosphorylation usually represses gene expression

RNA (or cellular RNA) Ribonucleic acid; made within a cell by RNA polymerases through the process of transcription or RNA replication; includes RNAs that encode proteins (messenger RNAs or mRNAs) and those that do not (see noncoding RNAs)

Russell–Silver syndrome A growth disorder characterized by low birth weight, short height, and lack of symmetry between both sides of the body. Approximately 35% of cases are associated with a defect in chromosome 11

SLC6A4 Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4; located on human chromosome 17; transports serotonin from synapse to presynaptic neurons

Trabecular placental–uterine interdigitation Type of maternal–fetal interdigitation of the placenta characterized by fetal tissue that both branch in villi and fuse

trans-regulatory element (trans-element) Proteins or other molecules that regulate gene expression by binding *cis*-elements

Trophoblast Specialized cells that form the outer layer of the blastocyst and develop into the placenta; trophoblasts play an important role in implantation of the embryo and transfer of nutrients to the embryo

Ubiquitination Posttranslational modification of histones that involves the addition of ubiquitin; ubiquitination is involved in both transcriptional silencing and repression

Villous interdigitation Type of maternal–fetal interdigitation of the placenta characterized by fetal tissue that branch in villi

Xist X inactive-specific transcript; a long noncoding RNA (lncRNA) located on the X chromosome; involved in X inactivation, a process by which one X chromosome is transcriptionally silenced in mammalian females

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Chapter 4

Nutritional Ecology and Reproductive Output in Female Chimpanzees (*Pan troglodytes*): Variation Among and Within Populations

Kevin B. Potts

Keywords Fallback foods • *Pan* • Population dynamics • Reproductive ecology • Reproductive success

4.1 Nutritional Ecology, Reproductive Output, and Demography in Primate Populations

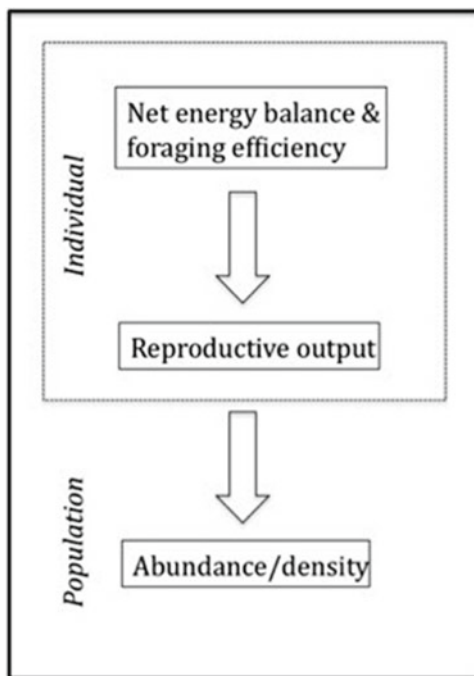
The efficiency with which animals procure calories and nutrients affects their growth, survival, and reproductive success (Bercovitch 1987; Altmann 1991, 1998; Koenig et al. 1997; Borries et al. 2001). In female primates, foraging efficiency may be a primary regulator of ovarian function, thus influencing the probability of conception and the duration of lactational amenorrhea (Knott 1998; Bentley 1999; Di Bitetti and Janson 2000; Brockman and van Schaik 2005). In particular, theoretical and empirical work has demonstrated that the quality and abundance of resources available and/or utilized during periods of relative food scarcity can have profound impacts on socioecology and population dynamics. Recently, attempts have been made to provide operational definitions of such resources (“fallback foods”; Lambert 2007; Marshall and Wrangham 2007; Marshall et al. 2009) and to generate testable hypotheses regarding their influence on primate ecology and evolution (see Potts et al. 2009; Harrison and Marshall 2011).

Despite somewhat inconsistent and informal usage of the term, a general consensus is emerging that fallback foods or, more generally, the “fallback strategies” employed by primates during periods in which preferred foods are generally scarce exert strong selection pressures on primate populations characterized by risk-averse

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Fig. 4.1 Ecological parameters vary among populations; therefore, the aggregate consequences of energy balance and reproductive output determine demographic differences among populations



life histories (i.e., long interbirth intervals coupled with low infant/juvenile mortality, e.g., *Hylobates albibarbis*, Marshall and Leighton 2006). Although data are scarce, which is largely a function of the relatively recent adoption of operational definitions of fallback foods, it is plausible that such foods engender reductions in foraging efficiency during times of food scarcity, thereby inhibiting female reproductive function (Koenig et al. 1997) and acting as a primary factor limiting lifetime reproductive outputs in species exhibiting risk-averse life histories. Because local demographic parameters are strongly influenced by intrinsic population growth rates (i.e., the net balance of reproductive output and mortality; Anholt 1997; Caswell 2001), the foraging efficiency of individual primates in these populations can profoundly impact local population densities. Intergroup variation in foraging efficiency, determined to a large extent by the spatiotemporal availability and quality of fallback resources, may thus act as a mechanism generating differences in local animal abundance and population dynamics across sites (Fig. 4.1). The goal of this chapter is to examine the potential role of site-specific fallback strategies (defined as dietary responses to periods of low overall food abundance) in influencing differences in reproductive output among sites in chimpanzees (*Pan troglodytes*). Chimpanzees represent an ideal taxon in which to investigate the influence of fallback strategies on female reproduction, as the quality and abundance of resources available during times of preferred food scarcity vary considerably among sites, as do population-level measures of reproductive output. Whenever it is available, ripe fruit dominates the diet of chimpanzees (approximately 60–85% of feeding

time; Wrangham et al. 1998; Potts et al. 2011). Fruiting cycles in chimpanzee habitats, however, are almost invariably seasonal and often unpredictable. Chimpanzees at most sites therefore face distinct periods of fruit scarcity.

Behavioral and dietary responses of chimpanzees to these fruit-poor periods vary across study sites since the nature of the habitat forces some populations to be more intensely obligated in their frugivory than others (Wrangham et al. 1996; Newton-Fisher 1999; Anderson et al. 2002; Mitani et al. 2002; N’Guessan et al. 2009; Potts et al. 2011). During periods of ripe fruit scarcity, chimpanzees frequently rely on leaves, pith of terrestrial herbs, unripe fruit, and bark (Wrangham et al. 1991, 1996), although some populations experience relatively less intense periods of ripe fruit shortages, and thus rely less on distinct dietary shifts as fallback strategies. Items consumed during periods in which ripe fruit is scarce contribute relatively little to the overall macronutrient content of the diet (Conklin-Brittain et al. 1998; Wrangham et al. 1998), can generally be considered fallback foods (as discussed by Marshall and Wrangham 2007), and are likely critical determinants of local population density in this species (Potts et al. 2009).

4.2 Energy Availability, Demographic Rates, and Reproductive Output in Chimpanzees

Analysis of the relative contributions of different demographic rates, including rates of individual survivorship, growth, and reproductive success, to variability in population growth rates within and among populations has received considerable recent attention (Pfister 1998; Hoekman et al. 2002; Coulson et al. 2005; Johnson et al. 2010; Lawler 2011). Investigations of the sensitivity of population growth rates to perturbations in survival and reproductive output suggest that fitness in primates is relatively buffered against temporal variability in demographic rates (Morris et al. 2011), largely due to relatively low variance in both adult and offspring survival compared to other mammals of similar size [e.g., black bears (*Ursus americanus*): Mitchell et al. 2009]. This suggests that birth rates may be the critical factor determining population dynamics and that many primates exhibit relatively risk-averse life history strategies. Chimpanzees, in particular, fit this risk-averse model, in that they have relatively low (but temporally invariant) annual reproductive rates, correspondingly low lifetime reproductive output, and generally high survivorship of infants, juveniles, and adults (Morris et al. 2011).

However, despite low temporal variability in reproduction, long-term monitoring of population dynamics of chimpanzee communities among and within populations has revealed substantial inter-site variation in reproductive output in this species (see recent summaries in Emery Thompson et al. 2007a; Stumpf 2007). This is likely a reflection of the potentially profound influence of small-scale ecological variability, especially in the availability and quality of putative fallback resources, on chimpanzee populations (Potts et al. 2009). More specifically, previous studies suggest that reproductive function in female chimpanzees is highly susceptible to relatively

minor changes in energetic status, often mediated by resource availability (Anderson et al. 2006; Emery Thompson et al. 2007b; Emery Thompson and Wrangham 2008; Jones et al. 2010), and that prolonged periods of non-fig fruit scarcity impose a particularly strong somatic burden on lactating females (Emery Thompson et al. 2010). However, although such periods are costly for female reproductive function (Wallis 1995), they do not appear, in most cases, to prevent successful conception and/or parturition (Emery Thompson and Wrangham 2008).

Female chimpanzees thus give birth during periods of both high and low food abundance (cf. Wallis 1995), and the low temporal variability in reproductive output characteristic of chimpanzees implies that females invest sufficient resources in each reproductive event to ensure that the offspring is successfully weaned. Successful weaning should be most easily achieved when the period of lactation, which is a time of particular energetic stress for mothers (Emery Thompson et al. 2010), occurs during periods of high food abundance than during periods of low food abundance. During times of high food abundance, mothers should be more capable of diverting energy away from their own somatic maintenance than during times of low food abundance, resulting in reduced periods of lactational amenorrhea, more rapid resumption of cycling, and thus potentially higher lifetime reproductive output. It therefore follows that females inhabiting sites with relatively infrequent periods of low food availability and/or with relatively high-quality fallback foods, which would reduce the somatic burden incurred during periods of low food abundance, should be capable of higher reproductive output than females inhabiting sites with frequent or prolonged periods of low food abundance and/or a lack of relatively high-quality fallback foods. In this way, the extent to which potential mothers must allocate resources to their own somatic maintenance, rather than to reproductive efforts during periods of low overall food abundance, may serve as a proximate mechanism linking local environmental conditions (and, thus, fallback strategies) to population-level reproductive success.

4.3 Fallback Strategies and Variability in Reproductive Output Among Chimpanzee Populations

Table 4.1 summarizes the available data on interbirth intervals across a range of sites of long-term research on chimpanzees and provides a brief synopsis of the fallback strategy utilized by females at each site. Below, I discuss potential ecological explanations for the observed patterns of reproductive output at each site, with particular attention given to the role of fallback strategies in influencing female reproductive ecology.

4.3.1 Gombe National Park, Tanzania

Recent analysis of long-term life history data from Gombe by Jones et al. (2010) suggested that the inclusion of an individual random effect, to index variation among individual females in “phenotypic quality,” in a model developed to explain birth interval

Table 4.1 Median interbirth intervals for seven long-term chimpanzee study sites

Site	Median IBI	Standard error	Number of complete intervals	References	Summary of fallback strategies (references included in text)
Gombe	67.4 58.5	4.0 N/A	74 77	Emery Thompson et al. (2007a) Jones et al. (2010)	High-ranking females monopolize high-quality feeding sites; low-ranking females chronically forage under conditions of scarcity
Mahale	71.9	2.0	116	Nishida et al. (2003) and Emery Thompson et al. (2007a)	Not well-known (see text)
<i>Kibale</i>					
Kanyawara	79.1	13.9	21	Emery Thompson et al. (2007a, b)	Forage on low-quality herbaceous vegetation (pith and stems) and relatively low-density figs (<i>Ficus</i> spp.)
Ngogo	63.0	8.3 ^a	20	Watts (2012)	Forage on relatively high-quality and high-density <i>Pterygota mildbraedii</i> fruit and leaves of common tree species
Tai	65.0	3.0	33	Boesch and Boesch-Achermann (2000)	Not well-known; period of low food availability roughly coincides with period of daily negative net energy balances in females
Bossou	63.9	2.7	21	Emery Thompson et al. (2007a) and Sugiyama (2004)	Forage on oil palm and raid crops during periods of low food availability provides high nutrient density during times of wild fruit scarcity
Budongo	62.7	3.0	13	Emery Thompson et al. (2007a)	May not experience extreme shortfalls of important resources; some of the most important foods are available year-round

Only complete intervals (i.e., intervals beginning with the birth of the first infant and ending with the birth of the second infant, or the end of the study or mother's death) and those in which the first infant did not die are included
^aStandard deviation

variation had a considerable impact on the model's fit (Jones et al. 2010). This suggests that individual heterogeneity plays a strong role in driving interbirth intervals at Gombe. This conforms well to previous research from this site suggesting that fitness indices differ substantially between females of high rank and those of low rank.

Pusey et al. (1997) found that daughters of low-ranking females produced their first anogenital swelling as much as 4 years later than daughters of high-ranking females, the offspring of high-ranking females were significantly more likely to survive to age 7 than those of low-ranking females, and high-ranking females tended to live longer than low- and mid-ranking females. More recently, Pusey et al. (2005) found that high-ranking females maintained higher body mass than did lower-ranking females, with an approximately 11% difference in mass between the highest- and lowest-ranked females. High rank appears to strongly influence female nutritional ecology at Gombe. High-ranking females tend to spend less time foraging and to forage on fewer and higher-quality items than females of low rank (Murray et al. 2006). Murray et al. (2006) suggest this situation results in low-ranking females chronically foraging under conditions of food scarcity, with probable reductions in foraging efficiency as a result.

Taken together, these data and those of Jones et al. (2010) suggest that high rank confers virtually year-round access to high-quality feeding ranges, thus conferring high body mass and likely contributing to enhanced reproductive output, whereas low rank engenders persistently low foraging efficiency, which likely inhibits reproductive output. Indeed, Pusey et al. (1997) found that rank alone explained 36% of the variance in annual production of offspring surviving to weaning age among 14 adult females, with nearly a threefold difference in annual production between the highest- and lowest-ranked female. It is therefore plausible to conclude that the relatively low median IBI exhibited at Gombe, particularly relative to the Mahale population, which is floristically comparable to Gombe (Goodall 1986; Collins and McGrew 1988; Nishida 1990), is primarily driven by unusually high reproductive rates among the highest-ranked females.

4.3.2 Mahale Mountains, Tanzania

Unfortunately, little systematically reported data are available from Mahale with which to assess the importance of resource seasonality and/or fallback foods in this population. However, given the floristic similarity between Gombe and Mahale noted above (although the forest in particular regions of Mahale is more continuous than at Gombe; Collins and McGrew 1988), it is plausible to suspect that Mahale chimpanzees contend with roughly similar ecological parameters as Gombe chimpanzees. Collins and McGrew (1988) suggest that seasonality, in general terms, is similar between two Mahale sites and Gombe, but further data are needed to quantify this. If it is, however, assumed that ecological pressures faced by Gombe females are similar to those faced by Mahale females, then the notably longer mean IBI of females at Mahale requires explanation.

It is possible that social and ecological factors interact to influence the difference in average interbirth interval between Gombe and Mahale females. Chimpanzees show a strong pattern of female dispersal (Pusey and Packer 1987), with the possible exception of Gombe females (Goodall 1986). Whereas all females at Mahale transfer from their natal group at puberty (Nishida 1990), females at Gombe often stay in their natal group all of their lives (Goodall 1986; Pusey et al. 1997) while “visiting” neighboring communities during estrous periods. Given the propensity of resident females to respond aggressively to new immigrant females (Pusey 1980; Kahlenberg et al. 2008), and for these immigrant females to subsequently be excluded from prime foraging areas (Williams et al. 2002; Murray et al. 2007) and to exhibit heightened levels of stress hormones (Kahlenberg et al. 2008), Gombe females remaining in their natal group rather than dispersing may avoid stress related to intragroup aggression and competition (although clearly dispersal options for females in the Kasakela community at Gombe are constrained by the fact that their community shares a border with only two other communities, both of which occupy habitat very close to the border of the national park; Pusey et al., 2007). Additionally, Gombe females frequently inherit prime foraging areas from their high-ranking mothers (Pusey et al. 1997), immigrant females are excluded from these areas (Murray et al. 2007), and the distinction between high- and low-quality feeding areas is most evident during times of overall food scarcity (ibid). Kahlenberg et al. (2008) and Emery Thompson et al. (2010) demonstrated the potential physiological impact of dispersal on female chimpanzees at Kanyawara, where immigrant females had significantly elevated cortisol levels relative to resident females. Given the propensity for Mahale females to disperse from their natal group and for Gombe females to frequently remain in their natal group (and foraging range), it is perhaps not surprising that the interbirth intervals of these females tend to be longer than those of the Gombe females.

4.3.3 *Taï Forest, Côte d’Ivoire*

Chimpanzees at Taï are subject to considerable seasonal fluctuation in fruit availability (Anderson et al. 2005), and periodic reductions in fruit availability appear to inhibit normal estrus cycling (Anderson et al. 2006). Furthermore, adult females at Taï routinely experience negative daily net energy balances (range: 31–56% of days; N’Guessan et al. 2009) during periods roughly coinciding with the period of low fruit availability (as determined by Anderson et al. 2005), and only rarely are net energy balances negative outside this period (9% of all days; N’Guessan et al. 2009).

4.3.4 *Bossou, Guinea*

Chimpanzees at Bossou face dramatic temporal fluctuations in the availability of their preferred resources (Yamakoshi 1998). However, during times of fruit scarcity,

the habitat at Bossou provides chimpanzees with an abundance of lipid-rich exotic species such as oil palm (*Elaeis guineensis*; Yamakoshi 1998). Additionally, chimpanzees at Bossou frequently raid crops growing in plots just outside their home range, a strategy that, while potentially dangerous, appears to provide chimpanzees with a nutrient rich “fallback” during times of wild fruit scarcity (up to approximately 25% of feeding time during periods of wild fruit scarcity; Hockings et al. 2009).

4.3.5 Budongo Forest Reserve, Uganda

During a study period spanning 16 months, Newton-Fisher (1999) found little evidence of periodic shortages of preferred foods among the Sonso chimpanzee community in Budongo Forest Reserve. Individuals in this community fed on figs (a resource commonly used during periods of drupaceous fruit scarcity in other communities) throughout the year and relied very little on herbaceous pith and stems. Subsequent work at Budongo (Tweheyo and Lye 2003, 2005), however, provided evidence of temporal drupaceous fruit scarcity, suggesting that chimpanzees there do face periodic shortfalls in their preferred resources. It is notable, though, that *Ficus sur*, which frequently produces figs throughout the year (Tweheyo and Babweteera 2007), was the most important fruit-providing species, in terms of percentage of time spent feeding by chimpanzees, in Newton-Fisher’s (1999) study.

The relative temporal stability of the resource base created by the ubiquitous availability of *F. sur* may therefore reduce the intensity of any nutritional deficiencies experienced during periods of general fruit scarcity. However, to the extent that figs are of generally inferior nutritional quality relative to drupaceous fruits (Wrangham et al. 1993), it is possible that Budongo chimpanzees nonetheless experience nutritional shortfalls to some extent when non-fig fruit is unavailable.

4.3.6 Kibale National Park, Uganda

The majority of information regarding the reproductive ecology of chimpanzees in Kibale comes from the Kanyawara community (Wrangham et al. 1996; Wrangham 2000; Emery Thompson et al. 2007a,b; Emery Thompson and Wrangham 2008). Recently, Emery Thompson et al. (2007b) documented a noteworthy variability among females inhabiting different zones within the larger Kanyawara home range: “central” females, occupying a core area of relatively high quality (in terms of resource availability), had average IBIs of 70.3 months (if the previous infant lived); “northern” females, occupying a relatively low-quality range, had average IBIs of 114.1 months (Emery Thompson et al. 2007b). This suggests a strong effect of resource abundance on the ability of females to successfully reproduce at Kanyawara. It is notable that the “northern” females in this study range within an area with relatively abundant terrestrial herbaceous vegetation but a relative

paucity of large trees providing fruit during periods of habitat-wide scarcity (see Potts et al. 2009). Terrestrial piths and stems provide low caloric and nutritional returns (Conklin-Brittain et al. 1998), and thus it is likely that the difference in fallback strategies available to the northern and the central females at Kanyawara influences the clear difference in reproductive output between these two groups.

More recent life history data from the nearby Ngogo site, which supports at least three times the number of chimpanzees at Kanyawara (see below), suggest that median interbirth intervals are considerably shorter there than at Kanyawara (Watts 2012; see Table 4.1) and that Ngogo females have among the shortest IBIs of females at any long-term study site. These data reflect a notable difference between Ngogo and Kanyawara females in reproductive output, despite the fact that these sites are merely 10 km apart in the same contiguous forest. Below, I further explore this difference in reproductive output, and the potential ecological factors underlying it, as an illustrative example of the potentially profound impact of small-scale environmental variation on female nutritional ecology and group-level demographics.

4.4 Influence of Small-Scale Ecological Variation on Female Nutritional Ecology and Chimpanzee Population Density: Case Study from Kibale National Park (KNP), Uganda

Kibale National Park (KNP) is located in southwestern Uganda near the foothills of the Rwenzori Mountains. It is classified as a moist evergreen or semi-deciduous forest transitional between lowland and montane forest (Struhsaker 1997). Distinct heterogeneity exists within KNP, however, with a varied mosaic of vegetation formations represented (Chapman et al. 1997; Potts et al. 2009). KNP is composed of approximately 58% mature forest, 15% grassland, 6% woodland, 2% lakes and wetlands, and 19% colonizing forest regenerating in areas used in the past for agriculture (Struhsaker 1997; Chapman and Lambert 2000). A north–south decrease in elevation leads to lower temperatures and higher rainfall in the north than the south (Struhsaker 1997). Also likely related to this elevational gradient are distinct differences in vegetation composition and seasonality between northern and southern sites (Chapman et al. 1997, 1999; Potts et al. 2009).

Kanyawara is in the northwestern sector of KNP, at an altitude of approximately 1,500 m, and is classified as a *Parinari* forest, as stems of *Parinari excelsa* (which is a species of relatively little importance for chimpanzees) dominate the canopy (Skorupa 1988; Chapman et al. 1999; Potts 2008). Beginning in 1966, areas within and adjacent to Kanyawara were designated as forestry compartments and subjected to varying intensities of mechanized logging on a polycyclic scale (Kasenene 1987; Skorupa 1988; Struhsaker 1997; Chapman and Lambert 2000; Potts 2011). In some compartments, the long-term impact of logging on the resource base of chimpanzees has been minimal (Potts 2011), whereas in others, the effect has been profound, such that these areas are now dominated by relatively low-quality terrestrial herbaceous vegetation interspersed with emergent canopy trees.

Ngogo is located approximately 12 km southeast of Kanyawara, at a slightly lower elevation of 1,350 m, in the same contiguous block of forest. Floristic composition there differs distinctly from that at Kanyawara (Chapman et al. 1997; Potts et al. 2009). The dominant species at Kanyawara (*P. excelsa*) is still found at Ngogo, but the forest is far more mixed, where no species is considered dominant. The forest at Ngogo has never been commercially logged (Struhsaker 1997), but the site has a history of human habitation perhaps as recently as the 1930s (Wing and Buss 1970; Lwanga 2006). As a result, Ngogo is currently composed of heterogeneous forest types, including large tracts of old growth stands adjacent to colonizing forests, swamp forest, and anthropogenic grasslands maintained by burning (Lwanga et al. 2000; Lwanga 2003).

Previous work at Ngogo and Kanyawara has shown that important fruit-providing species in the diet of chimpanzees more frequently produce large fruit crops at Ngogo than at Kanyawara, fruit abundance indices vary less over time (on the scale of months and years) at Ngogo, and species important in the diet of chimpanzees at both sites more frequently produce fruit crops at Ngogo than at Kanyawara (Potts 2008; also see Chapman et al. 1997). Additionally, among several classes of resources hypothesized to be most important in the nutritional ecology of chimpanzee and most likely to impose constraints on population growth, the one class, that is, found at a higher density in the Ngogo home range than in the Kanyawara home range is fruit-providing species that produce large fruit crops (through synchronous fruit production among individual stems) that are utilized during periods of low food abundance (“synchronous low food abundance,” or sLFA, resources; Potts et al. 2009). These resources are akin to fallback foods (cf. Marshall and Wrangham 2007; Lambert 2007; Marshall et al. 2009), in that they ensure an adequate nutrient supply during periods of preferred fruit scarcity.

Community size at Kanyawara has varied between 39 and 52 since the onset of habituation of individual animals in the late 1980s and early 1990s (Wrangham et al. 1991, 1996, 1998; Conklin-Brittain et al. 1998; Emery-Thompson et al. 2007b). The community had 11 adult males, 1 adolescent male, 15 adult females, 3 nulliparous females, 8 juveniles, and 13 infants during a 2005–2006 study period (Potts 2008, 2011; Potts et al. 2009, 2011), and the density of chimpanzees at Kanyawara was approximately 1.4 individuals/km².

The community at Ngogo has been continuously observed since the mid-1990s (Watts 1998; Mitani and Watts 1999, 2005; Watts and Mitani 2001; Watts et al. 2006). It is the largest ever observed, with over 155 members. During the same 2005–2006 study period described above (Potts 2008; Potts et al. 2011), 23–26 adult males, 15 adolescent males, at least 44 adult females, 15 adolescent females, 17 juveniles, and 34 infants resided within the community at a density of approximately 5.1 individuals/km².

During the 2005–2006 study period mentioned above, I observed the feeding ecology of chimpanzees at each site to determine both qualitative and quantitative differences in the foraging efficiency of individuals at the two sites. I predicted that, since sLFA resources were more abundant at Ngogo, and such high-quality fallback foods should have a positive influence on female reproductive capacity and habitat-specific carrying capacity (Marshall et al. 2009; Harrison and Marshall 2011),

females at Ngogo would exhibit higher measures of foraging efficiency than would Kanyawara females.

I qualitatively assessed foraging efficiency differences between chimpanzees at the two sites by comparing activity budgets and percentages of feeding time devoted to various food items (ripe fruit, in particular; see Potts et al. 2011). I quantitatively assessed foraging efficiency (FE) using the following equation:

$$FE = (R \times T \times E \times W) - (D \times C)$$

where R = intake rate (items/minute) during the feeding bout (see below), T = time (minutes) spent feeding in the patch, E = energetic content (kcal/g) of the item being eaten, W = weight of edible matter (g) per item, D = distance traveled between successive feeding patches, and C = energetic cost (kcal/m) of walking. I counted, ad libitum (whenever the animal was in clear view), the number of items ingested by the focal animal in 1-min observations during feeding bouts to calculate intake rates (R). Details of nutritional assays used to determine food energy content (E) and edible matter weight (W) are given in Potts (2008) and Hohmann et al. (2010). I collected and analyzed plant samples from Ngogo only (see Hohmann et al. 2010) using methods that were very similar to those used by Conklin-Brittain et al. (2006) to analyze the nutrient content of plants at Kanyawara. Thus, the Ngogo and Kanyawara data sets were derived from comparable methodologies. The energetic cost of walking was calculated separately for individuals of each age/sex class using a formula modified from Steudel (1994), which in turn was derived from that given in Taylor et al. (1982). The foraging efficiency equation above provided an index of “net caloric intake” (kilocalories ingested during feeding bouts minus kilocalories expended in movement between feeding patches). More details on these methods can be found in Potts (2008) and Potts et al. (2011, in preparation).

During the 2005–2006 study period, females at Ngogo that were either pregnant or lactating spent more time feeding and less time resting than did their counterparts at Kanyawara. Females at Ngogo also incorporated ripe drupaceous fruit in their diet at relatively high frequencies year-round, whereas Kanyawara females were seasonally limited to figs (*Ficus* spp.) and/or nonreproductive parts of terrestrial herbaceous growth forms (Potts et al. 2011). Evidence from Gombe suggests that persistent consumption of ripe fruit may correlate with consistently high body mass in female chimpanzees (Pusey et al. 2005), and thus the Kibale results suggest that females at Ngogo may be physiologically more capable of devoting energy to reproduction than are their counterparts at Kanyawara.

Notably, females at Ngogo that were pregnant or lactating achieved relatively high net caloric intake rates on food items that were either extremely rare at Kanyawara or were absent entirely (Table 4.2; *Chrysophyllum albidum* ripe fruit; *Warburgia ugandensis* ripe fruit; *Pterygota mildbraedii* unripe fruit and seeds). Items that were common to the diet of pregnant/lactating females at both sites provided higher net caloric intake rates for Ngogo females than for Kanyawara females (*Ficus brachylepis* ripe fruit: 61.0 kcal/min vs. 15.1 kcal/min; *Uvariopsis congensis* ripe fruit: 23.9 kcal/min vs. 9.2 kcal/min). These differences in net caloric intake

Table 4.2 Net caloric intake rates (i.e., feeding efficiency) for pregnant and lactating female chimpanzees at Ngogo

Ngogo		Mean net kcal/min feeding	Abundance at Kanyawara
<i>Aningeria altissima</i>	RF	19.7	Present
<i>Uvariopsis congensis</i>	RF	23.9	Abundant
<i>Ficus mucoso</i>	RF	40.2	Rare
<i>Pterygota mildbraedii</i>	UF	48.2	Rare
<i>Warburgia ugandensis</i>	RF	50.5	Rare
<i>Ficus brachylepis</i>	RF	61.0	Abundant
<i>Chrysophyllum albidum</i>	RF	66.2	Rare
Kanyawara		Average net kcal/min feeding	Abundance at Ngogo
<i>Ficus exasperata</i>	RF	3.2	Abundant
<i>Ficus natalensis</i>	RF	4.0	Abundant
<i>F. exasperata</i>	YL	5.5	Abundant
<i>Ficus dawei</i>	RF	7.4	Present
<i>U. congensis</i>	RF	9.2	Abundant
<i>Celtis africana</i>	YL	12.0	Abundant
<i>F. brachylepis</i>	RF	15.1	Abundant
<i>Ficus capensis</i>	RF	16.3	Present

Site-specific lists include all items for which sufficient data were available. Data on species presence and abundance are from Potts et al. (2009)
RF ripe fruit, UF unripe fruit, YL young leaves

rate values from items common at both sites were apparently driven by significantly higher kcal/g among food items eaten by Ngogo females (Mann–Whitney U test; $N_{\text{Ngogo}}=33, N_{\text{Kanyawara}}=66, U=765.0, P=0.026$) and by significantly longer distances traveled between feeding patches by Kanyawara females ($N_{\text{Ngogo}}=33, N_{\text{Kanyawara}}=66, U=678.0, P=0.004$).

P. mildbraedii, in particular, may play a critical role in ensuring female chimpanzees at Ngogo remain capable of achieving high net caloric intake rates during periods of low habitat-wide food availability. Among species providing fruit mesocarp and/or seeds for chimpanzees at Ngogo during periods of low habitat-wide fruit availability, *P. mildbraedii* is found at the highest basal area at the site. *P. mildbraedii* is exceedingly rare at Kanyawara [it was absent from plots surveyed by Potts et al. (2009) and from transects surveyed by Chapman et al. (1997), at Kanyawara], which highlights the importance of small-scale differences in forest composition in influencing the nutritional ecology of even large-bodied and wide-ranging primates. Mature stems of *P. mildbraedii* are extremely large (mean DBH=77 cm) canopy-level trees that produce abundant crops of dehiscent capsulate fruits containing many wind-dispersed winged seeds protected by a thick, fibrous husk and dry mesocarp. These fruits can remain in the canopy of a tree for many months prior to dehiscing and releasing the seeds (Struhsaker 1997). Once the capsule has fully opened and the seeds are dispersed, the fruit appears to be unused by vertebrates, with the possible exception of

certain rodents (Struhsaker 1997). However, while the fruits are maturing, red colobus monkeys (*Procolobus rufomitratus*; Struhsaker 1997) and chimpanzees eat the seeds plus the seed wings and mesocarp.

Nutritional analysis of *P. mildbraedii* (Hohmann et al. 2010; KBP, unpublished data) revealed that the unripe seeds of this species are among the most protein- and lipid-rich items in the Ngogo chimpanzee diet and that they are capable of providing a net energy return (kilocalories per gram) matched by few other items commonly eaten by Ngogo chimpanzees. This species therefore provides an unusually abundant and concentrated source of calories and nutrients for chimpanzees during periods in which high-quality food sources are otherwise scarce. Such a calorie- and nutrient-rich resource is unavailable to chimpanzees at Kanyawara (see nutritional data provided by Conklin-Brittain et al. 2006), and it is likely that such a profound ecological difference between the two sites directly relates to differences between Ngogo and Kanyawara females in energy balance and reproductive output (see Potts 2008; Emery Thompson and Wrangham 2008).

4.5 Summary/Conclusion

Despite a diversity of data attesting to the importance of food limitation as a primary factor determining primate population densities (e.g., Coehlo et al. 1976; Cant 1980; Tutin et al. 1997; Chapman and Chapman 1999; Wasserman and Chapman 2003; Marshall and Leighton 2006), the precise mechanisms through which food limits demography in these populations are not always clear. Theory suggests that in species characterized by relatively long interbirth intervals, extensive maternal investment in offspring, and low infant mortality rates (i.e., risk-averse life histories), population growth rates should be intimately tied to the abundance and quality of fallback resources (Marshall et al. 2009). In chimpanzees, reproductive function of individual females is impacted by relatively minor shifts in energetic status, whether due to temporal fluctuations in net caloric intake and periodic reliance on low-quality fallback foods (e.g., Kanyawara) or to pervasive patterns of differential access to high-quality foods based to dominance rank (thus creating a situation in which low-ranking females must consistently forage in low-quality patches, e.g., Gombe, Kanyawara).

Similarly, inter-site variation in overall reproductive rates (as indexed by interbirth intervals) is largely predicted by the degree to which habitats provide relatively high-quality fallback foods and/or by the extent to which periods of high food abundance prevail. Consistent reliance on relatively low-quality fallback foods imposes energetic burdens on female chimpanzees which, while perhaps not sufficient to limit successful conception and parturition, nonetheless are likely to exert a strong influence on the ensuing length of lactational amenorrhea. Therefore, less frequent reliance on low-quality fallback foods should be associated with more frequent reproductive output at both the individual and the population (or community) level and, in turn, relatively rapid population growth. Chimpanzee communities characterized by

short interbirth intervals (e.g., Ngogo, Bossou) are those found in habitats providing an abundance of calorie-rich resources even during times of low overall fruit abundance (*P. mildbraedii* at Ngogo; oil palm and crops at Bossou). Conversely, communities in which average interbirth intervals are high (e.g., Kanyawara) are characterized by a relative lack of high-quality, nutrient-rich resources available during times of low overall fruit abundance.

4.6 Directions for Future Research

There is still much work to be done to fully substantiate the links between fallback strategies, individual- and community-level reproductive output, and population dynamics in chimpanzees. For example, more information is needed from certain long-term study sites, particularly Gombe, on the extent of seasonality experienced by pregnant/lactating females, as well as a more formal characterization of the fallback foods available and fallback strategies utilized at these sites. Such information will be critical for future investigations of the potential ecological underpinnings of the relatively short interbirth intervals of Gombe females (or, at least, high-ranking Gombe females; see above). Additionally, further investigation of quantitative measures of foraging efficiency (e.g., net caloric intake rates) across a range of sites will provide a useful index with which to systematically address the extent to which different fallback strategies and habitat-specific food availabilities impact the ability of females to acquire the excess calories necessary for reproduction.

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Part II
From Pre- to Post-natal Life

Chapter 5

Prenatal Androgens Affect Development and Behavior in Primates

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Keywords Prenatal exposure • Uterine environment • Testosterone • Sex differentiation • Infant outcomes

Abbreviations for Terminology

CAH	Congenital adrenal hyperplasia
CAIS	Complete androgen insensitivity syndromes
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulfate
DHT	Dihydrotestosterone
PAIS	Partial androgen insensitivity syndromes
PCOS	Polycystic ovary syndrome
TP	Testosterone propionate
ZFX	X-linked zinc finger protein gene
ZFY	Y-linked zinc finger protein gene

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5.1 Introduction

Maturation and differentiation persists throughout childhood, adolescence, and adult life into senescence; however, the foundation for normal postnatal development is established during fetal ontogeny. The organizational hypothesis proposes that nongenomic, environmental factors within the intrauterine environment attribute to prenatal programming (Phoenix et al. 1959). From the inception of this hypothesis over 50 years ago, researchers have documented the effects of exposure to prenatal steroid hormones, particularly androgens, on the behavior and growth of primate offspring. The effects of androgen within the intrauterine environment from maternal and exogenous sources can be observed in long-term changes to multiple developmental trajectories, including somatic growth, homeostatic functions of the body, and differentiation of sex-typical morphology, physiology, and behavior. Thus, the sensitivity and plasticity of the fetus during development toward androgens and other physiological cues from the mother and environment may underlie the development of diseases, a premise postulated by the Barker hypothesis (Barker 1998). In the current chapter, we discuss a number of prenatal and postnatal developmental outcomes associated with exposure to normal variations and excessive concentrations of androgens during prenatal life in human and nonhuman primates. In addition, it seems that the timing of androgen exposure during gestation and the sex of the fetus are two major factors that contribute to the concentration of androgens in the prenatal environment and the ultimate outcomes. Therefore, we also discuss the timing of androgen exposure during gestation and the sex of the fetus as modulating variables on the androgen-induced effects on development.

5.2 The Endogenous Origins of Androgens During Fetal Development

The preponderance of evidence outlines three periods in primate lifespan in which there are significant fluctuations in androgen production: intrauterine and infant development, adolescence and puberty, and senescence [e.g., human (*Homo sapiens sapiens*) (Forest 1983; Rabinovici and Jaffe 1990; Seidman 2003; Richmond and Rogol 2007; Seidman 2007), western lowland gorilla (*Gorilla gorilla gorilla*) (Stoinski et al. 2002), rhesus macaque (*Macaca mulatta*) (Resko and Roselli 1997; Mann et al. 1998), crab-eating macaque (*Macaca fascicularis*) (Steiner and Bremner 1981), chimpanzee (*Pan troglodytes*) (Marson et al. 1991; Martin et al. 1977), common marmoset (*Callithrix jacchus*) (Abbott and Hearn 1978b; Dixon 1986), Geoffroy's tufted-ear marmoset (*Callithrix geoffroyi*) (Birnie et al. 2011), cotton-top tamarin (*Saguinus oedipus*) (Ginther et al. 2002), gray mouse lemur (*Microcebus murinus*) (Aujard and Perret 1998)]. However, it is during fetal development that the organizational effects of androgens are most observed, e.g., affecting the onset of other critical periods such as puberty (Jones and Verkauf 1971; Goy et al. 1988b; Zehr et al. 2005; Herman et al. 2006) and androgen sensitivity

over the lifespan (Resko and Ellinwood 1984; Dumesic et al. 1997; Eisner et al. 2002; Abbott et al. 2008). The prenatal androgen milieu that primate fetuses are exposed to in the intrauterine environment originates from the fetus or mother, endogenously, or from environmental sources (see Svechnikov et al. 2010).

5.2.1 *Fetal Origins of Androgen*

The ontogenesis of fetally derived androgen in human and nonhuman primates is derived from the gonads or adrenal gland (d'Aux and Murphy 1974; Huhtaniemi 1994; Resko and Roselli 1997; Svechnikov and Söder 2008; Rouiller-Fabre et al. 2009). The primate fetal endocrine system develops early in gestation and results in androgen production within the first gestational trimester (Rabinovici and Jaffe 1990). In the presence of gene products from two loci—the *Sry* gene located on the Y chromosome and the *Sox9* gene on the X chromosome—the undifferentiated embryonic gonad develops into testes, occurring as soon as gestational week 8 in humans (Huhtaniemi 1994; Bendsen et al. 2003; O'Shaughnessy et al. 2007). The number of male human fetal Leydig cells increases substantially until peaking in week 19 of gestation, contemporaneously with a peak in the concentration of testosterone and dihydrotestosterone (DHT) in the blood and testicular tissue in the fetus (Tapanainen et al. 1981; Rabinovici and Jaffe 1990; Svechnikov and Söder 2008). Similar to human fetal development, male nonhuman primates begin to synthesize and secrete androgens shortly after the external genitalia and internal reproductive anatomy begin to virilize. For example, the external genitalia of rhesus monkey differentiate between gestational days 38 and 40 during the 168-day gestation (van Wagenen and Simpson 1965; Resko 1985), and fetal androgen production begins between gestational days 35 and 50 (Resko and Ellinwood 1981) and peaks around gestational days 40–75 (Resko 1985). Conventional wisdom suggests that, in contrast to male primate gonads, female fetal ovaries do not undergo significant steroidogenesis and the hypothalamic–pituitary–gonadal axis has been thought to remain quiescent prenatally (d'Aux and Murphy 1974; Ellinwood et al. 1982; Rabinovici and Jaffe 1990). However, recent evidence indicates that human fetal ovaries may express the androgen biosynthetic enzyme CYP17 and androgen receptors by midgestation (Cole et al. 2006; Fowler et al. 2011). Thus, primate fetal ovaries may not be as quiescent as traditionally viewed as the expression of such components suggests that ovaries have the capacity to produce androgens and be responsive to them.

In addition to the gonadal androgens, the primate adrenal cortex synthesizes and secretes androgens, mainly dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), in the fetal adrenocortical zone, an inner zone of the fetal adrenal gland present only in primates and some edentata (Conley et al. 2004; Pattison et al. 2005; Abbott and Bird 2009). The fetal zone is developed by midgestation and begins producing androgens, then regresses shortly after birth coinciding with a decrease in adrenal androgens in human and nonhuman primates (McNulty et al. 1981;

Mapes et al. 2002; Pattison et al. 2005, reviewed by Mesiano and Jaffe 1997). Unlike fetal gonadal androgen production that only occurs in males, the fetal zone in the adrenal cortex develops and secretes adrenal androgens in both sexes.

5.2.2 Maternal Origins of Androgen

Primate pregnancies are typified by a substantial increase in the production of progesterone and estrogen derived from ovarian and placental sources (Albrecht and Pepe 1990; Ojeda 2004). From conception, there is also a significant rise in maternal androgen in human and nonhuman primates [e.g., human (Rivarola et al. 1968; Bammann et al. 1980; Castracane and Asch 1995; Castracane et al. 1998), bonnet monkey (*Macaca radiata*) (Rao and Kotagi 1983), olive baboon (*Papio anubis*) (Castracane and Goldzieher 1983; Hodges et al. 1984), rhesus macaque (Challis et al. 1975; Ellinwood et al. 1989), marmoset (Chambers and Hearn 1979; Fite et al. 2005; French et al. 2010; Smith et al. 2010)]. While the total testosterone levels increase from conception, free testosterone levels remain similar to non-pregnancy levels until week 28 of gestation in humans. This suggests that much of the change in total testosterone is associated with an increase in bound testosterone. In fact, there is a significant increase in sex-hormone-binding globulin levels and a decrease in testosterone metabolism from the beginning of pregnancy (Saez et al. 1972; Bammann et al. 1980). In contrast, although maternal adrenal androgen production increases during pregnancies (Gant et al. 1971), there is a net decrease in circulating maternal adrenal androgen (Milewich et al. 1978), primarily due to the conversion of DHEAS into estrogen by the placenta (Siiteri and MacDonald 1963). While the primate placenta is critical in the production of gestational progesterones, estrogens, and peptide hormones such as chorionic gonadotrophin, corticotrophin-releasing hormone, and the insulin-like growth factors (reviewed by Pepe and Albrecht 1995; Murphy et al. 2006), it does not produce androgens (e.g., human: Licht et al. 1998; rhesus monkey: Ellinwood et al. 1989). Therefore, the rise in circulating androgens in pregnant women and other female primates originates from either the fetus or the mother.

Currently, there is some inconsistency in research that evaluates whether fetally derived androgens enter maternal circulation and consequently contribute to the elevated maternal androgens during gestations in primate species. In humans, fetal testosterone in both male and female fetuses is positively associated with maternal testosterone in mid- to late gestation, that is, 15–38 weeks gestational age (Gitau et al. 2005). While adult female adrenal glands and ovaries clearly produce androgens (Burger 2002; Stanczyk 2006), some studies have documented a significant increase in maternal androgens when carrying a male fetus as opposed to a female fetus in pregnant women (Nagamani et al. 1979; Meulenberg and Hofman 1991) and other female primates [yellow baboon (*Papio cynocephalus*) (Altmann et al. 2004), red-fronted lemur (*Eulemur fulvus rufus*) (Ostner et al. 2003)]. Antithetically, other studies do not report any effect of male fetuses on maternal serum androgens,

even when some of these studies report a clear increase in amniotic fluid and umbilical cord blood androgens when male fetuses are present (Rivarola et al. 1968; Glass and Klein 1981; Rodeck et al. 1985; Atkinson et al. 1996; Sir-Petermann et al. 2002; Steier et al. 2002; Troisi et al. 2003; van de Beek et al. 2004; French et al. 2010). Beyond fetal sex, it has been noted that androgens significantly increase in maternal circulation in human and nonhuman primates shortly after conception and before virilization of fetal gonads—a developmental step that precedes fetal gonadal steroidogenesis which occurs around week 8 in human gestation—or even the implantation and elaboration of the fetoplacental unit. In addition, subcutaneous injections of testosterone propionate (TP) into pregnant rhesus monkeys result in an increase in testosterone and androstenedione, but not estradiol or estrone, in maternal and fetal serum (Abbott et al. 2008). Therefore, while it is not clear if fetal androgens contribute to circulating androgens in the maternal system during mid- to late gestation, it is apparent that the initial rise in maternal androgens and, to some degree, later maternal androgens as well as fetal androgens can be attributed to the maternal endocrine system (Reyes et al. 1973).

5.3 Prenatal Androgens and Genital Differentiation

The dynamics of mammalian sexual differentiation is one of the best-understood ontogenetic processes in integrative biology. Several excellent recent reviews have encapsulated this process (Morris et al. 2004; Wallen 2005; Arnold 2009), and we briefly summarized this process above (see Sect. 5.2.1). With the caveat that there are important direct genetic effects on the differentiation of morphology, brain, and behavior (e.g., Arnold et al. 2004; Arnold 2009), the pattern described above—*gene action* → *gonadal differentiation* → *endocrine consequence* → *phenotypic divergence*—characterizes the common mammalian process of sexual differentiation.

5.3.1 Prenatal Androgen Excess on Human Genital Differentiation: Clinical Studies

There are three classic human disorders that lend credence to the genetic–gonadal–endocrine cascade hypothesis for the differentiation of genital morphology in humans. In congenital adrenal hyperplasia (CAH) and 46,XX male syndrome, chromosomal females (46,XX) have mutations in the genes that regulate steroidogenesis. In addition to other alterations in steroid biosynthesis pathways, androgen concentrations in fetal circulation increase [CAH (White and Speiser 2000; White and Speiser 2000), 46,XX male syndrome (Kousta et al. 2010)]. Female infants with salt-wasting CAH are born with completely fused labia and the clitoris hypertrophies into a phallus (Braga and Pippi Salle 2009; Nimkarn and New 2010). At birth, individuals with 46,XX male syndrome present with small testes, a masculinized

phallus and scrotum, and an absence of Mullerian tissue (Vorona et al. 2007), all of which are markers of a complete masculinization of genitalia in these chromosomal females via excess prenatal androgen exposure.

Finally, there are a variety of genetic variants that are associated with the lack of masculinization of external genitalia in otherwise normal 46,XY chromosomal males (Wisniewski and Mazur 2009). In one variant, males have dysfunctional intracellular androgen receptors, leading to either partial or complete androgen insensitivity syndromes (PAIS and CAIS) (Wisniewski and Mazur 2009; Philibert et al. 2010). Since the androgen receptors do not respond normally when bound with androgens, the effects of the androgen–receptor complex on nuclear DNA transcription are altered or eliminated (Ahmed et al. 2000). Individuals that present with PAIS have varying degrees of genital ambiguity, depending on the severity of the insensitivity, while individuals with CAIS present with a complete female phenotype, including labia, a blind vagina, female-typical fat distribution, and female breasts (Werner et al. 2010). Other 46,XY syndromes involve mutations that alter enzymatic function in steroidogenesis such as 5 α -reductase 2 deficiency—reducing testosterone conversion to DHT and feminizing external genitalia (Wilson et al. 1993)—and 17 β -hydroxysteroid dehydrogenase 3 deficiency—impairing androstenedione conversion to testosterone and feminizing internal sex ducts and external genitalia (Boehmer et al. 1999; Wisniewski and Mazur 2009; George et al. 2010). In conditions associated with disrupted androgen signaling or biosynthesis, the results emphasize the central importance of the choreography among genes, gonads, and androgen production and sensitivity in regulating the differentiation of external genitalia in human beings.

5.3.2 *Prenatal Androgen Excess on Nonhuman Primate Genital Differentiation: Two Models*

5.3.2.1 Manipulation of Prenatal Androgens on Genital Differentiation in Rhesus Macaques

Among nonhuman primates, the processes that underlie the differentiation of external genitalia have been most exquisitely outlined for the rhesus macaque in Prahalada et al. (1997), Thornton et al. (2009), and briefly above (see Sect. 5.2.1). Treatment of pregnant mothers with supplemental exogenous androgen, or disruption of androgen biosynthesis via exogenous treatment, has been extensively employed—being reported as early as Young et al. (1964)—to assess the mechanisms of endocrine effects on genital structure, and the timing of this differentiation. The degree of female fetal genital virilization depends on the timing and dose of supplemental androgen provided to the pregnant mother. Exposure to daily doses of 610–750-mg TP for 25–50 days starting on gestational day 39 (early androgenized females) completely masculinized the external genitalia of genetic females, including complete scrotal and penile development and a lack of a vaginal orifice (Young et al. 1964;

Eaton et al. 1973). These results have been replicated with significantly lower doses of daily injections of testosterone (15 mg/day) and also with DHT (Goy 1981; Goy and Robinson 1982; cf. Herman et al. 2000). However, female fetuses exposed to the same treatment regimen and dose from gestational days 115 to 139 (late androgenized females) showed no permanent masculinization of external genitalia and had normal vaginal openings (Goy et al. 1988a; Herman et al. 2000). It appears, therefore, that the critical period for genital masculinization is early in fetal development, and late androgen manipulations have minimal effects on genital structure in macaque monkeys.

An alternative approach for assessing the role of steroid exposure on the sexual differentiation of genital structure is to pharmacologically block the effects of androgens or alter steroid biosynthesis in developing male fetuses. Finasteride is a compound that inhibits the enzyme 5 α -reductase, which is critical for the bioconversion of testosterone to the potent androgen DHT. Male macaques whose mothers were treated with finasteride from days 20 to 100 of gestation displayed significantly smaller phalluses and small and poorly developed scrota, suggesting that DHT plays a role, along with testosterone, in masculinizing male genitalia (Prahalada et al. 1997). In a similar vein, Herman et al. (2000) treated pregnant mothers carrying male fetuses with the potent androgen receptor blocker flutamide either early in gestation (days 35–70) or late in gestation (days 115–155). There were again subtle but significant effects of flutamide treatment on some aspects of male genitalia. Males with either early or late treatment had significantly shorter phalluses, and their overall “masculinization” scores were lower than vehicle males, especially for the early gestational exposure males (Herman et al. 2000).

5.3.2.2 The Unique Intrauterine Environment of Marmoset Monkeys: Influences of Prenatal Androgen Exposure on Subsequent Genital Differentiation

Marmosets and tamarins constitute an interesting and important test case of sexual differentiation among primates. They are the only primates with obligate twinning, with dizygotic twin births constituting 70–90% of litters (Ross et al. 2007a). Unlike most twins, marmosets develop placental anastomoses between twins and share a common blood supply. This has important implications for genetic chimerism, as co-twins pass embryonic stem cells to each other and are genetic chimeras in multiple tissues, including germ line (Ross et al. 2007b). From the perspective of sexual differentiation, the intimate vascular connections between co-twins suggest the potential for interesting prenatal androgen effects on sexual differentiation, as males share a blood supply with their female co-twin. One might expect masculinization of female offspring in the case of male–female co-twins and the absence of masculinization in the case of female–female co-twins. As an evolutionary adaptation to prevent female masculinization, Abbott and Hearn suggested that the majority of sexual differentiation in marmosets may occur postnatally because of this shared fetal blood supply (Abbott and Hearn 1978a; Abbott 1984). This is supported by the

appearance of elevated testosterone levels in males from 15 to 100 days of age (Abbott and Hearn 1978a; Dixon 1986; Birnie et al. 2011). Postnatal testosterone treatment masculinized female marmoset genitalia, with hypertrophy of the clitoris and enlargement of the labia to resemble scrotal folds (Abbott and Hearn 1978b; Abbott 1984). Neonatal castration produced adult males with small genitalia, and testosterone treatment of these adults produced an increase in penile and scrotal size (Dixon 1993). Like other nonhuman primates (e.g., rhesus macaques, Brown et al. 1999), androgen exposure can further masculinize marmoset genitalia in the immediate postnatal period, but marmoset genitalia are already differentiated at birth (Abbott and Hearn 1978b).

Several reports have appeared on the occurrence of “ambiguous genitalia” in female marmosets. Isachenko et al. (2002) reported on a high incidence of fused labia in common marmosets (~32%) at the German Primate Center. Normally, the vulval opening in female marmosets is 8–10 mm, but in the affected females, the labial fold was only an average of 2.1 mm in length. Surgical separation of the fused labia revealed a normal vagina and cervix, and ultrasound confirmed the presence of a uterus and ovaries. In a case study, a female common marmoset that had ambiguous, masculinized genitalia also expressed the testis-determining *Sry* gene and the Y-linked zinc finger protein gene (ZFY) as measured in DNA analysis of hair bulb tissue (Sanchez-Morgado et al. 2003). A similar example of an XX/XY female lion tamarin (*Leontopithecus chrysomelas*) displaying masculinized external genitalia was recently reported (Goldschmidt et al. 2005). At the Callitrichid Research Center, we have recently genotyped two male and two female Wied’s black-tufted-ear marmosets (*Callithrix kuhlii*) for X-linked zinc finger protein (ZFX) and ZFY (see Fig. 5.1). In the gels, both males clearly expressed ZFY. In contrast, the female with a female co-twin expressed only ZFX, while the female with a male co-twin expressed ZFY. The ZFY female also had ambiguous genitalia at birth that became more feminized at 6 months.

Clearly, unusual features are associated with the development of genital structures in marmosets and tamarins, and we hope to determine if some of these phenomena interact with prenatal and immediate postnatal steroids of maternal origin. Given that postnatal androgen can masculinize female genitalia (Abbott and Hearn 1978b), it appears that some of the variation in genitalia may be caused by androgen exposure, but the presence of Y chromosome and its genes in some females suggests a more complicated scenario. This phenomenon is similar to freemartinism in cattle and other species (Lillie 1917; Capel and Coveney 2004), with the important exception that XX/XY marmosets are not sterile. Future work in our lab will address the extent to which ambiguous female genitalia are systematically associated with the presence of Y chromosomes, and whether more subtle aspects of female reproduction (e.g., age at puberty, age at first litter, offspring survivability) are associated with having a male co-twin. However, without more invasive manipulations, such as administering androgen receptor blockers to female fetuses with male co-twins or selectively knocking down Y chromosome activity, it will be difficult to disentangle genetic from endocrine influences on the development of female genitalia.

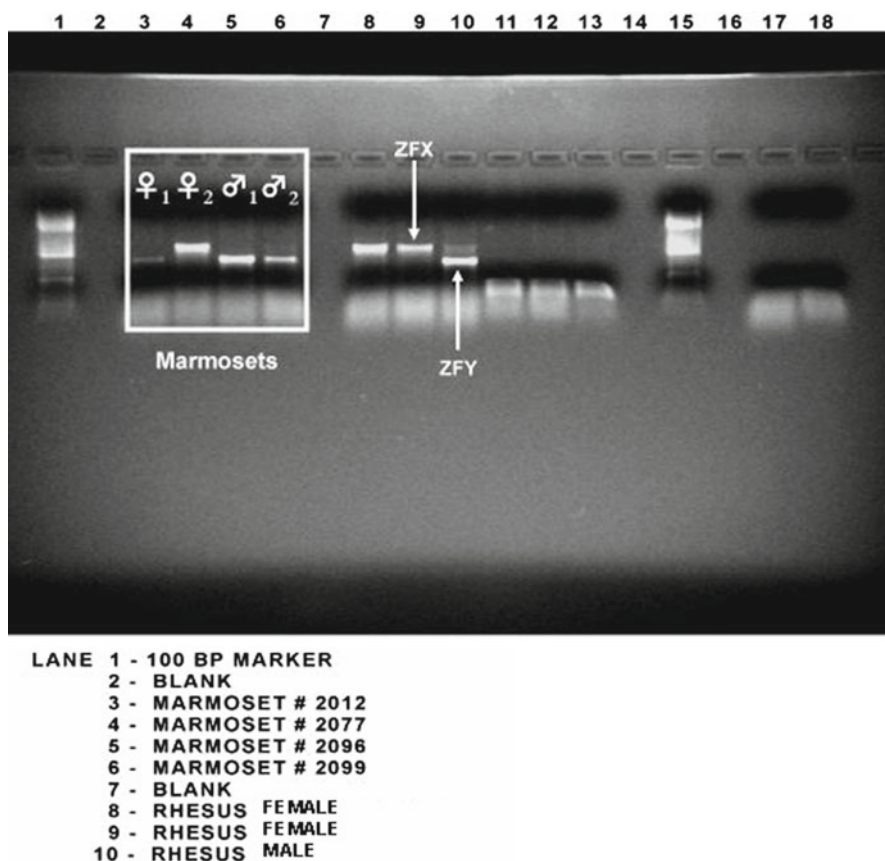


Fig. 5.1 Genotyping of marmosets for Y-chromosome and X-chromosome zinc finger protein (ZFY and ZFX, respectively). *Lanes 8 and 9* of the gel contain DNA from female rhesus macaques, while *lane 10* contains DNA from a male rhesus, revealing the sex-chromosome-specific patterns of zinc finger proteins. *Lanes 5 and 6* contain DNA from two male marmosets, and clear ZFY signals are evident. *Lane 4* contains DNA from a female marmoset that had shared the uterus with a female co-twin, and expresses ZFX. *Lane 3* contains DNA from a female marmoset that had shared the uterine environment with a male co-twin. She expresses ZFY, demonstrating that she maintains viable cells acquired early in embryonic development from her male co-twin

5.4 Prenatal Androgens and Fetal and Postnatal Growth

Androgens can also have organizational and activational effects on physical growth that manifest throughout the lifespan in primates. Androgens are potent anabolic hormones and, working in concert with growth hormones, can affect body growth. In pubertal development, testosterone can promote the growth of muscle mass and strength, increase bone density, and alter body composition,

specifically regional fat distribution (reviewed by Hiort 2002; Randall et al. 2002). In prenatal development, evidence of androgen-induced alteration of fetal growth and postnatal development can be observed in normal variation in maternal androgens and clinical cases of hyperandrogenism in pregnant women as well as primate models.

In normal pregnancies, maternal androgen production surges beginning at conception until about midgestation when levels are comparable to male conspecifics (see Sect. 5.2.2). In addition, there is normal variation in total androgen production that occurs between pregnancies in humans and nonhuman primates [e.g., human (Castracane et al. 1998); marmoset (Smith et al. 2010)]. This provides a source of androgen that fetuses may be exposed to in the intrauterine environment that would vary between pregnancies and, that is, more accessible to researchers than fetal or umbilical cord blood or amniotic fluid. From this research, it seems that the concentration of androgen present in maternal circulation may influence fetal growth. For example, early second trimester (gestation week 17) maternal testosterone was negatively correlated with birth weight and length in full-term human infants (Carlsen et al. 2006). Birth weight was 160 g lower in babies born to mothers with testosterone levels in the 75th percentile compared to those born to mothers with testosterone levels in the 25th percentile, a weight difference similar to the impact from fetal sex. In Geoffroy's tufted-ear marmoset monkeys, we have recently noted that male and female neonates born to mothers with high first trimester androgen levels had a smaller gross birth size (e.g., weighed less, were shorter, and had less upper-body girth) compared to marmosets born to mothers with low first trimester androgens (Smith et al. 2010). In addition, offspring from mothers with high first trimester androgens had depressed early infancy weight and girth gains and increased late infancy and juvenile growth rates in body girth. Further, maternal androgen levels in this species are not influenced by fetal sex ratio (French et al. 2010). Thus, maternally derived androgens early in gestation may alter normal fetal and subsequent prepubescent postnatal growth in primates.

The effects on physical growth do not seem to hold with late gestational androgens. Birth weight and length as well as first year gains are not associated with total or free androstenedione, testosterone, or DHT in maternal or umbilical cord blood collected at birth in full-term babies in humans (Gemer et al. 1997; Troisi et al. 2003; Whitehouse et al. 2010). Notably, Carlsen et al. (2006) also measured testosterone in maternal blood during gestation week 33 and found a negative correlation between third trimester maternal testosterone and birth weight and length of newborns. However, as gestational week 17 and 33 testosterone were highly correlated (Pearson's $r=0.75$) in that study, the association between late gestation androgens and birth size may be an artifact of the association between testosterone throughout gestation. In our research with marmoset monkeys, maternal androgens in the second or third trimester were not associated with prenatal and postnatal growth in offspring (Smith et al. 2010). Additional work is required to substantiate these findings. However, these data support the contention that subtle changes in the early, rather than

late, gestational androgenic environment can influence fetal development and subsequent postnatal growth in primates.

5.4.1 Prenatal Androgen Excess on Human Growth: Clinical Studies

There are several conditions that lead to a hyperandrogenic state in women, but the effects of hyperandrogenism associated with polycystic ovary syndrome (PCOS) on fetal development have been the most extensively and systematically studied. Women with PCOS have higher total and free androgens during early gestation (Sir-Petermann et al. 2002; reviewed in Abbott et al. 2005; Ehrmann 2005; Xita and Tsatsoulis 2006). Interestingly, several studies have noted that fetal growth may be reduced if the mother has PCOS. For example, Sir-Petermann et al. (2005) noted that women with PCOS give birth to small-for-gestational-age newborns (12.8%) at a higher prevalence compared to the general population (2.8%) with no difference in the rate of large-for-gestational-age newborns. In a meta-analysis that included 12 studies evaluating the birth weight in infants born to women with or without PCOS, women with PCOS gave birth to newborns with lower birth weights compared to controls, though this was not replicated in a subset of the studies analyzed (Boomsma et al. 2006). However, this effect should not be overstated as other studies have failed to replicate these results (e.g., Anderson et al. 2010). It is not clear why some studies report an effect on fetal growth while others lack support. Interestingly, while hyperandrogenism is used as a diagnostic criteria for women with PCOS, fetuses from women with PCOS may not always be exposed to intra-uterine androgen excess during development. This is evident when comparing results from two recent studies in which one reported hyperandrogenism in the umbilical cord blood during pregnancies in women with PCOS (Barry et al. 2010) but another did not (Anderson et al. 2010). If hyperandrogenism in the intrauterine environment is required to alter fetal growth, this may be one reason why only subsets of women with PCOS give birth to small-for-gestational-age newborns, and some studies do not report a difference in the birth size of babies born to women with PCOS compared to the general population.

Exposure to androgen excess during gestation can cause an increase in weight gain in adolescence and adulthood, particularly in adipose tissue, and lead to an increased incidence of obesity. In this regard, approximately 63% of adolescent girls with PCOS were considered obese compared to 32% of normal girls of similar age and ethnic background in a United States population (Coviello et al. 2006). In addition, girls that present with precocious pubarche with functional ovarian hyperandrogenism are more commonly born with small-for-gestational-age birth weights compared to girls with precocious pubarche without functional ovarian hyperandrogenism (Ibanez et al. 1998). Thus, exposure to androgen excess via maternal or fetal hyperandrogenism seems to alter fetal programming resulting in an abnormal growth trajectory that persists into adulthood.

5.4.2 *Prenatal Androgen Excess on Nonhuman Primate Growth: The Rhesus Model*

Rhesus monkeys have been used to develop a nonhuman primate model of PCOS. In the Wisconsin National Primate Research Center, a population of adult female rhesus monkeys receive androgen treatments during pregnancies (for additional general methods, see Sect. 5.3.2.1, Abbott et al. 2005) that results in a significant elevation of androgens in fetal circulation (Resko et al. 1987; Abbott et al. 2008). From this research program, it has been documented that early prenatal androgens may affect male fetal growth but not female fetal growth (Herman et al. 2000; Abbott et al. 2008), although recent evidence indicates a modest increase in head circumference in female fetuses (Abbott et al. 2010). However, early gestational exposure to androgen excess seems to pronouncedly affect postnatal growth in female rhesus monkeys. Female infants exposed to early testosterone treatment exhibit a heavier body weight (~10%) at 2 months of age compared to controls (Abbott et al. 2009, 2010). Prenatal testosterone treatment did not alter body weight or girth in male neonates during the first week of life (Bruns et al. 2004). However, this null effect in males may be a function of the low sample size or not treating during a critical period in fetal development as testosterone treatments were administered at early, mid-, or late gestation for different subjects. In addition, female rhesus monkeys exposed to testosterone excess early in gestation have increased body weight at menarche (Goy and Robinson 1982) and total body mass (Kemnitz et al. 1988), abdominal skinfold thickness (Abbott et al. 1998), and total abdominal and intra-abdominal fat depots that are independent of total body adiposity (Eisner et al. 2003) in adulthood compared to controls. Thus, exposure to androgen excess early in gestation can result in changes to postnatal growth and ultimately adult body composition in rhesus monkeys. These postnatal effects mirror the phenotype in offspring of women with PCOS. It is worth noting that the primate liver and placenta have an incredible capacity to inactivate or aromatize androgens and conjugate estrogenic products compared to other species, and prenatal estrogens can influence fetal programming altering physical growth (e.g., Linn et al. 1988). Therefore, it could be argued that these effects on growth are due to estrogenic, not androgenic, action. However, testosterone treatment during a rhesus pregnancy results in a significant increase of circulating androgens but not estrogens in maternal and fetal blood (Abbott et al. 2008). This suggests that many of the symptoms of abnormal growth and obesity in adulthood are attributable to excess androgenic actions in the early intrauterine environment.

5.4.3 *Prenatal Androgens and Growth: Metabolic Dysfunction and Other Potential Mechanisms*

While several symptoms associated with PCOS—heavier maternal body weight and a higher occurrence of gestational diabetes (Sir-Petermann et al. 2002; Ehrmann et al. 2006; Vanky et al. 2010)—would be expected to increase the birth weight of

newborns, fetal growth is unaltered or even restricted, as evident by low birth weight in newborn with mothers with PCOS (Sir-Petermann et al. 2005). Women with PCOS and their offspring also incur metabolic dysfunction such as hyperinsulinemia and insulin resistance more often (Dunaif et al. 1987), which increases the risk of type 2 diabetes (DeFronzo 1992). As obesity, upper-body adiposity, and muscle mass can contribute to insulin resistance (Yki-Järvinen and Koivisto 1983; Bogardus et al. 1985; Caro et al. 1989; Wagenknecht et al. 2003) and women with PCOS have increased rates of obesity (Goldzieher and Green 1962; Dunaif 1992) and adiposity (Kissebah and Peiris 1989), these parameters should be normalized to understand the effects of hyperandrogenism on insulin resistance. When body composition (via a precise method such as hydrostatic weighing) and waist to hip girth ratios are similar between women with and without hyperandrogenism, there is a significant decrease in insulin-mediated glucose disposal in women with PCOS (Dunaif et al. 1992; Morales et al. 1996). This indicates that insulin resistance may be a function of hyperandrogenism rather than other confounding parameters. However, it is important to note that the onset of hyperinsulinemia in daughters of women with PCOS often precedes androgen excess, and therefore, metabolic dysregulation may actually promote the ontogeny of hyperandrogenism rather than the reciprocal relationship (Sir-Petermann et al. 2009).

Studies in prenatally androgenized female rhesus monkeys provide insight into the consequences of prenatal androgen excess on normal fetal growth and metabolism and mechanisms that can cause reprogramming of these affected tissues throughout the primate lifespan. Androgenized female rhesus monkeys early in gestation exhibit impaired pancreatic β -cell function, abnormal insulin secretion and action, hyperlipidemia, and increased abdominal fat (Abbott et al. 1998, 2005; Eisner et al. 2000, 2003). The primate pancreas expresses androgen receptors (Winborn et al. 1987), so early gestational exposure to androgen excess that coincides with pancreatic organogenesis may alter pancreatic development leading to prolonged pancreatic β -cell dysfunction (Hoar and Monie 1981). In addition, prolonged prenatal androgen exposure may be deleterious to normal placental function (de Vries et al. 1998), since placental androgen receptors are responsive to androgen action and these actions mediate changes to factors such as fibroblast growth factor 2 and folic acid that regulate fetal and placental growth (Cloke et al. 2008; Sivakumaran et al. 2010; Uzelac et al. 2010). These insults to fetal metabolism could lead to malnutrition in the fetus, independent of maternal diet and nutrition, and subsequent fetal growth restriction and adult metabolic syndrome. Although male rhesus monkeys exposed to testosterone excess during gestation do not demonstrate altered androgen production in adulthood, there is a substantial decline in insulin sensitivity and impaired pancreatic β -cell function (Bruns et al. 2004). This further supports the notion that prenatal androgens can alter programming of key metabolic tissues.

As exposure to elevated or excessive androgen levels during gestation can stifle metabolic function and alter prenatal and postnatal growth and development, it is interesting that maternal androgen levels increase during the onset of pregnancies (see Sect. 5.2.2). While these androgenic effects seem harmful to offspring

development, maternal androgen levels may reflect a fundamental trade-off in metabolic effort by pregnant females. As described in life history theory (Stearns 1992; Kaplan and Gangestad 2005), there is a trade-off for a fully developed adult to allocate metabolic efforts among one's own maintenance and reproductive efforts. Thus, changes in maternal androgens may be one mechanism through which pregnant females regulate the amount of energetic resources that would be allotted to developing fetuses. Interestingly, there are examples in primate species in which androgen production varies as a function of social instability (e.g., Batty et al. 1986; Ross et al. 2004), periods that may pose increased metabolic challenges via active territoriality and aggression. Therefore, the surge in androgens during early gestation may function to alter the metabolic demands of developing fetuses and reflect an early conflict of mothers to metabolically invest in fetal development.

5.5 Prenatal Androgens and Juvenile Behavior and Beyond

Like other mammals, sexual differentiation in the primate brain is influenced by gonadal hormones, particularly androgens, during fetal development (Goy and McEwen 1980; Ehrhardt and Meyer-Bahlburg 1981; McEwen 1981; Pardridge et al. 1982; Bao and Swaab 2010). Normal variation in or manipulation of prenatal androgen can alter the development of sexually dimorphic brain regions and sex-typical behavior that manifest throughout the lifetime in multiple primate species (Goy and McEwen 1980; Hines 2004; Cohen-Bendahan et al. 2005). Many of the behaviors influenced by prenatal androgens begin to appear—or are at least more discernable—during the juvenile/adolescent period [great apes (Watts and Pusey 2002), humans (Power 2000), callitrichines (Yamamoto 1993)]. In primates, juvenility is extended relative to other mammals, making it a period of critical interest (Pereira and Fairbanks 2002).

Some recent research focuses on normative variation in gestational androgens and childhood behavior in humans, with mixed results. These studies have evaluated gender-related play behavior and habits of boys and girls of toddler, preschool, or elementary age as a function of testosterone exposure in early midgestation. Some of these studies use the Pre-School Activities Inventory—a parent-reported assessment of sex-typical behavior in children—to measure sex-typical play behavior. From these studies, male-typical play behavior has been positively correlated with higher prenatal testosterone levels sampled from either amniotic fluid between gestational weeks 11 and 21 (Auyeung et al. 2009) or maternal serum between gestational weeks 5 and 36 (Hines et al. 2002) or masculine second to fourth digit ratio (2D:4D), the latter being indicative of high androgen exposure throughout gestation (Hönekopp and Thierfelder 2009). With substantially smaller sample sizes, Knickmeyer et al. (2005) did not find an association between prenatal testosterone in amniotic fluid collected at similar gestational ages and gender-typical play behavior in children in the same age group, nor did van de Beek et al. (2009) in 13-month-old toddlers. Thus, the effect size of this relationship may be such that measures that

are more sensitive or larger sample populations may be required. It is speculated that the period of sexual differentiation of the brain and gonads coincide (Finegan et al. 1989). As there is a significance rise in fetal androgens from gestational weeks 8 to 24 with a peak at week 19 (Tapanainen et al. 1981; Rabinovici and Jaffe 1990; Svechnikov and Söder 2008), it is during this period that androgens may have the greatest effects on brain development in androgen-sensitive regions and behavior facilitated by these regions. Hines et al. (2002) noted that there is a relatively high degree of heritability in androgen production rates; thus, mothers with high androgen levels have daughters that produce high levels of androgen. Therefore, these findings do not allow us to separate the organizational effects of prenatal androgens from the effects of circulating androgens during childhood on influencing these behaviors.

The influence of normal variation in prenatal androgens on juvenile behavior in nonhuman primates has recently been investigated in the Geoffroy's tufted-ear marmoset. In this work, normative levels of urinary testosterone, but not androstenedione, collected from mid- to late gestation in marmoset mothers are associated with social rough-and-tumble play patterns in juvenile offspring (Birnie et al. *in press*). Interestingly, in our study, high levels of maternal testosterone during mid- to late gestation were related to decreased rates of both receiving play and overall play (the sum of play initiations and play receptions) with siblings, but not play initiations with siblings. When we examined this same relationship with male siblings only, we found that high levels of gestational testosterone were associated with lower rates of play initiations and somewhat lower rates of overall play with male siblings, but no relationship was found for receiving play from male siblings. No relationship between maternal androgens early in gestation and offspring play behaviors was observed. Our findings stand in contrast to the results from many experimental studies conducted in rhesus monkeys, which have consistently found that experimental exposure to androgen during gestation increases rough-and-tumble play initiations with peers in genetic female rhesus macaques (see Sect. 5.5.2). However, while rhesus macaques show a sexually dimorphic pattern in juvenile rough-and-tumble play and body size (Caine and Mitchell 1979; Andrade et al. 2004), callitrichine primates exhibit few sexual dimorphism in either (Stevenson and Poole 1982; Ford 1994; Guard et al. 2002; Birnie et al. *in press*). In addition, maternal gestational androgens are not differentially related to the play behavior of male and female marmosets (Birnie et al. *in press*). Such differences in social structure and sexual dimorphism may therefore signify different developmental responses to early-life androgen exposure in primate groups.

5.5.1 Prenatal Androgen Excess on Human Juvenile Behavior and Beyond: Clinical Studies

Much of what we know about the effects of prenatal androgens on postnatal gender-typical behavior in humans comes from studying women with CAH, an autosomal disorder that causes a deficiency for 21-hydroxylase and subsequent

decreases in cortisol and increases in androgens in fetal circulation (reviewed in Merke and Bornstein 2005; White and Speiser 2000). Girls with CAH typically show a masculinized behavioral phenotype, while boys with CAH typically show few behavioral differences compared to developmentally normal boys. For instance, girls with CAH show a preference for male social play partners and male-typical toys, activities, careers, and gender identity, while boys with CAH are comparable in their toy preferences to normal boys (Berenbaum and Hines 1992; Hines and Kaufman 1994; Berenbaum 1999; Berenbaum and Bailey 2003; Pasterski et al. 2005). Interestingly, there are forms of CAH that result in variations in the severity of androgen exposure, providing a natural analog to a dose response study. Nordenström et al. (2002) noted that male-typical toy preference varied in a dose-dependent manner among girls with various types of CAH: girls with the most severe form of CAH (and therefore, the girls exposed to the highest levels of prenatal androgen) preferred male-typical toys compared to girls with more mild forms of the disorder.

A criticism of such work on early human experience is that socialization may also be shaping behavior. For instance, it is possible that girls with CAH act more like boys in their behavioral tendencies because they look more like boys and are thus treated like boys. However, in general, parents encourage gender-typical play in children both with and without CAH, but this does not attenuate the preference for male-typical toys and play activities in girls with CAH (Pasterski et al. 2005). Furthermore, 3–8-month-old infants show a sex-based difference in visual attention to gender-typical toys that mirrors patterns in toy preferences of older children (Alexander et al. 2009). If gender biases in toy preference were due solely to socialization and independent of prenatal influences, then we would expect to see no difference in visual attention paid to gender-type toys in infants who are less socialized than older children and presumably unaware of their gender identity. In addition, nonhuman primates who are not socialized in toy preferences have shown similar patterns in that male nonhuman primates prefer to play with male-type toys and females with female-type toys [vervet monkeys (*Cercopithecus aethiops sabaeus*) (Alexander and Hines 2002), rhesus macaques (Hassett et al. 2008)]. These results suggest that prenatal androgens have an organizational effect on androgen-sensitive brain regions that control these behaviors.

5.5.2 Prenatal Androgen Excess on Nonhuman Primate Juvenile Behavior and Beyond: The Rhesus Model

Much of the experimental research evaluating prenatal androgens and juvenile behavior in primates has been done in macaques. Androgens can influence the development of cortical function in rhesus monkeys. For example, the difference in direct androgen binding, testosterone aromatization, and 5 α -reduction between male and female rhesus monkeys can affect the sequence of brain development (Clark et al. 1988; Clark and Goldman-Rakic 1989). Normal juvenile male

macaques initiate more play bouts (Goy and Resko 1972; Caine and Mitchell 1979), exhibit more mounting and less grooming (Goy and Resko 1972; Goy 1996), and show less interest in infants (Lovejoy and Wallen 1988) compared to normal females. Goy (1996) found that administration of TP to rhesus macaque mothers carrying female fetuses resulted in both masculinized genitalia and behavior, including increased rough-and-tumble play initiations, decreased maternal grooming, and increased mounting. Thus, androgen excess during gestation seems to promote male-typical behavior in female rhesus monkeys, potentially by altering the perception and, therefore, meaning of social cues during interactions. However, these prenatally androgenized females may have behaved differently as a result of responses from social group members to their virilized genitalia. In another study, TP treatment administered early in gestation (days 40–64) masculinized female genitalia but not juvenile play behavior (with the exception of mounting behaviors), while TP administration late in gestation (days 115–139) masculinized female play and mounting behaviors but not their genitalia or male-typical grooming behavior (Goy et al. 1988a). In follow-up research, neither blocking nor enhancing prenatal androgens at different time points throughout fetal development affected interest in infants in male and female juveniles (Gibber and Goy 1985; Kasckow et al. 2003). Thus, the masculinizing actions of androgens during gestation on behavioral development seem to be behavior-dependent, occur mainly but not exclusively later in gestation, and may be independent from androgenic effects on genital morphology. Furthermore, females exposed to lower doses of testosterone during fetal development displayed similar rough-and-tumble play compared to normal females (Eaton et al. 1990). Sexually dimorphic infant vocalizations (Tomaszycki et al. 2001) and mounting behavior (Eaton et al. 1990) were masculinized by the lower testosterone dose. Therefore, while lower prenatal testosterone doses are sufficient to affect some behaviors, the threshold for testosterone to influence play behavior is apparently higher (reviewed in Wallen and Hassett 2009).

Gestational androgen exposure has been reported to be a sufficient component in promoting male-typical copulatory behavior and diminishing female-typical sexual behavior. Sexually receptive female macaques typically solicit sexual interaction from intact males, but treatment with prenatal TP decreases this behavior (Thornton and Goy 1986). Also, pseudohermaphrodite females treated with TP during gestation and given another dose of TP prior to sexual behavior testing show higher rates of mounting a female than female controls, but not as high as intact, normal males (Pomerantz et al. 1986). Females exposed to lower doses of androgen prenatally have less masculinized genitalia but still mount females significantly more than normal females (Eaton et al. 1990). Treatment with TP or DHT propionate during gestation also decreases attractiveness and defeminizes female sexual behavior in rhesus monkeys by decreasing sexual receptivity in the presence of an intact male compared to control females (Pomerantz et al. 1985). Thus, it is likely that exposure to androgens during the prenatal and early postnatal periods accompanied by a surge in androgens during puberty is necessary to produce a masculinized sexual behavior repertoire in adulthood (Wallen 2005).

5.6 Conclusion

The organizational hypothesis proposes that nongenomic, intrauterine environmental factors such as fetal androgen can affect prenatal programming (Phoenix et al. 1959). Androgen within the intrauterine environment from maternal and exogenous sources can also cause long-term changes in multiple developmental trajectories of the fetus that can be adaptive or detrimental to postnatal survival. Thus, the plasticity of the developing fetus toward androgens and other physiological cues from the mother and environment may underlie the development of diseases, a premise postulated by the Barker hypothesis (Barker 1998). In the current chapter, we discussed a number of prenatal and postnatal developmental outcomes associated with exposure to normal variations and excessive concentrations of androgens during prenatal life in human and nonhuman primates (see Fig. 5.2). It seems that the timing of androgen exposure during gestation and the sex of the fetus are two major factors that contribute to the concentration of androgens in the prenatal environment and the ultimate outcomes. The timing of androgen exposure during gestation may influence what tissues are affected due to the variation of critical periods of develop-

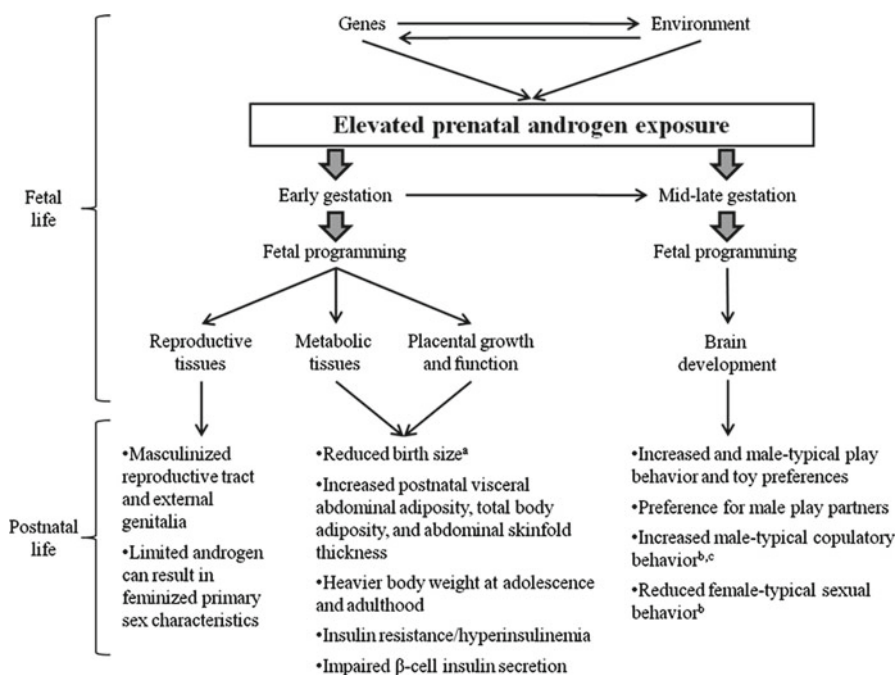


Fig. 5.2 Prenatal androgen exposure and subsequent fetal programming and postnatal outcomes. (a) Intrauterine growth restrictions are measureable in marmoset monkeys and a few but not all human populations and not in androgenized rhesus models. (b) This has only been noted in nonhuman primate species. (c) Androgen excess during early gestation can also promote male-typical mounting behaviors in female rhesus (Goy et al. 1988a)

ment and sensitivity for different tissue type. The sex of the offspring may dictate the influence of androgens via the sexual differences in the androgen system including androgen binding/levels, receptor distribution, and the activity of enzymes such as aromatase. The effects of normal and abnormal exposure to prenatal androgen are not limited to the sexual differentiation of the system in primates and warrant further investigation.

There are still a number of avenues that must be explored to better understand the proximate and ultimate functions of prenatal androgens on fetal programming. Such issues include specific timing and mechanisms through which prenatal androgens affect the growth and development of different tissue that are influenced by metabolic functions and prenatal testosterone, including the brain. In addition, since a number of developmental parameters are altered by prenatal testosterone such as growth, secondary sexual features, and behavior, it would be worth evaluating any mechanisms that would be developed by the offspring to compensate for insults that they would experience in their physical and social environment. This is particularly interesting as some androgenic effects seem harmful to offspring development, such as growth restrictions and metabolic dysfunction. By contrast, prenatal androgen exposure regulates normal sexual development and can promote behaviors that improve social rank, reproductive success, and allocation of territory and resources, such as social play, territoriality, and sexual behavior and receptivity. How these various altered characteristics interact to ultimately affect the life and reproductive success of an individual is a topic for further speculation and research. Not surprisingly, much more is known about physical and neuronal development in nonprimate species; however, there are ongoing research projects that focus on addressing the functions of different neurotransmitters and neural pathways associated with sexual differentiation in some nonhuman primate species. Despite the limitations in the current knowledge and technical logistics, nonhuman primates have and will continue to serve as paramount models to translate basic research findings into an understanding of normal and atypical development in humans.

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Chapter 6

Navigating Transitions in Hypothalamic–Pituitary–Adrenal Function from Pregnancy Through Lactation: Implications for Maternal Health and Infant Brain Development

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Keywords HPA axis • Maternal stress • Brain development • Developmental programming • Glucocorticoids

6.1 Introduction

Despite the tremendous interest in understanding the effects of prenatal stress on fetal health and the programming of adult disease risk, the adaptive functions of hypothalamic–pituitary–adrenal (HPA) axis activity in healthy pregnancies and during lactation have been less widely considered. Existing research has addressed the influence of glucocorticoids on altered patterns of fetal growth and development in humans (Kuzawa and Sweet 2009; Seckl and Holmes 2007; Sloboda et al. 2005; 2009a, b) and the effects of prenatal stress in animal models, particularly with respect to offspring birth weight and stress reactivity (Drake et al. 2005; Neumann 2001; Seckl and Meaney 2004). With several important exceptions, the majority of this research has invoked the concept of “maternal stress” to encapsulate the premise that maternal activation of the HPA axis is associated with adverse birth outcomes, without the simultaneous acknowledgment that progressive elevation of the maternal HPA activity across the course of pregnancy is part of an anthropoid-typical pattern of neuroendocrine activity (Bowman et al. 2001; Smith et al. 1999). Even less is known about the HPA dynamics of pregnancy in non-Western populations with distinct infectious disease ecologies and marginal energetic status (Nyberg 2012). Given the human reproductive strategy of giving birth to secondarily altricial infants (Martin 2007), basal glucocorticoids may play a pivotal role in facilitating parturition and accelerating fetal tissue maturation in coordination with the timing

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of birth (Power and Schulkin 2006; Pike 2005; Smith et al. 1999). These constraints on the duration of gestation may be imposed, in part, by the metabolic demands of pregnancy (Ellison 2001, 2010; Martin 1996) and are further impacted by the obstetrical dilemma, imposed by the “tight fit” between fetal head circumference and the maternal pelvis that occurred as a result of our hominin transition to obligate bipedalism (Rosenberg and Trevathan 2001). As a result, human birth is physiologically stressful, even by primate standards (Leigh 2004; Martin 1996; Rosenberg and Trevathan 2001).

Moreover, pregnancy, birth, and lactation are linked physiological events, and changes in HPA activity over the course of these transitions may reflect facultative shifts that prepare the mother and fetus for parturition, a major physiological stress reactivity event in its own right. Such dramatic shifts in neuroendocrine function require feedback mechanisms to restore maternal homeostasis postpartum, yet significant gaps remain in our understanding of the mechanisms and timing of HPA recovery. Too often, pregnancy and the postpartum context of HPA function are “separated at birth,” with each phase treated as a discrete unit, without consideration for the complexities and contingencies of the maternal–infant dyad (Linden et al. 1997; Bergant et al. 1998). Elucidating changes in measures of maternal HPA activity may thus hold clues for understanding maternal postpartum depression risk and behavior, which independently and synergistically hold important implications for infant brain development and priming of the neuroendocrine circuitry. Given the secondary altriciality of human infants (Martin 2007) and the context-dependent nature of postnatal brain development (Gunnar 1998; Lupien et al. 2009), the reciprocal interaction of mother and infant may provide mutual benefits, restoring the maternal HPA response following birth through lactation-induced suppression of stress hormones, while buffering the infant from excess glucocorticoids until its own diurnal rhythm and inhibitory feedback in the hippocampus have become established. The literature review provided in this chapter thus emphasizes the contingency and overlap of these transitions, conceptually depicted in Fig. 6.1, purposefully focusing on the breadth of the tandem shifts in maternal and fetal HPA activity across these temporal dimensions. Finally, this chapter will trace the proximate mechanisms linking differential patterns of HPA activity to maternal health and infant brain development, and consider the broader evolutionary context of the role of glucocorticoids in facilitating shifts in the timing of key life history periods of gestation, birth, and postnatal development unique to our species.

6.2 The HPA Reactive Scope

The HPA serves as a central anchor of the stress response and exhibits a strong diurnal rhythm, with peak activity occurring shortly after awakening and dipping to a nadir before sleep (Dallman et al. 1993; de Kloet and Sarabdjitsingh 2008; Kirschbaum and Hellhammer 1994). The response is hierarchically organized and is elicited in the brain upon the cognitive appraisal of a stressor, especially social or evaluative threat or in response to infection or other physiological stressors.

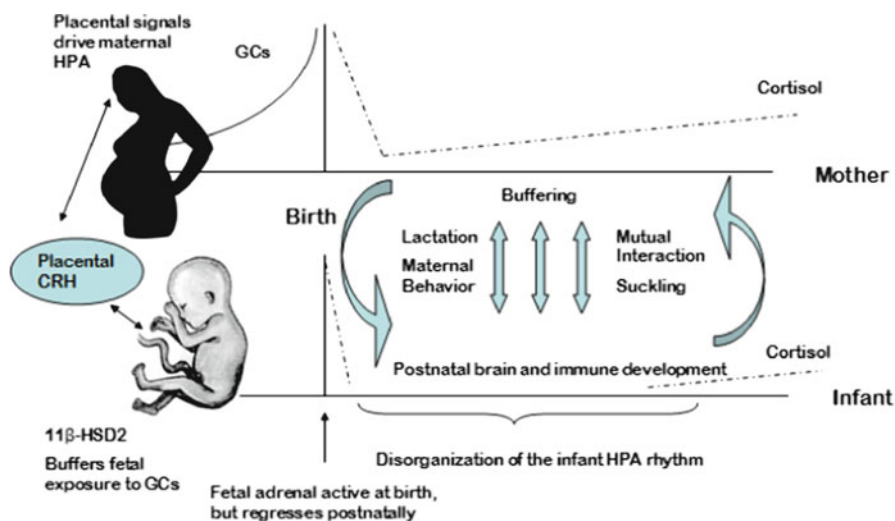


Fig. 6.1 Conceptual model of maternal–fetal HPA axis

The cascade of corticotropin-releasing hormone (CRH) from the paraventricular nucleus in the hypothalamus stimulates production of adrenocorticotrophic hormone (ACTH) from the anterior pituitary (Kirschbaum and Hellhammer 1994). Upon the arrival of the circulating ACTH signal to the adrenal cortex, cortisol is then released into the bloodstream. The HPA response is regulated primarily in the hippocampus via the high density of glucocorticoid receptors (GRs), which are the seat of the negative feedback circuitry, dampening cortisol levels postchallenge (Anacker et al. 2010; Galeeva et al. 2010; Young and Vasquez 1996).

In this chapter, the term “reactive scope” is used to encompass basal homeostatic functions, or daily housekeeping activities, as well as the capacity for reactivity, or adaptive shifts in response to stressors. Allostasis is another rubric offered to encompass the pleiotropic actions of the HPA axis, which emphasizes its ability to maintain the internal milieu through lability rather than through constancy (Cannon 1932; Romero et al. 2009; Schulkin et al. 2005; Sterling and Eyer 1988). By coordinating circadian metabolic functions and maintaining the capacity for stress reactivity, the HPA axis is situated at the dynamic interface mediating internal homeostasis, local ecology, and the broader psychosocial and sociocultural environment (Romero et al. 2009; McEwen and Wingfield 2003; Miller et al. 2009; Nyberg 2012; Schulkin 2003). By extension, the HPA axis also serves as a key mechanism of developmental plasticity (Del Giudice et al. 2011; Nyberg 2012) and modulates competing life history domains of growth (Nyberg 2009; Sloboda 2009), maintenance (i.e., immune function) (Cohen et al. 2007; Cole 2008), and reproduction (Clancy 2012; Nepomnaschy et al. 2006; Worthman and Kuzara 2005).

Amid the burgeoning field of research into the developmental origins of adult disease (DOHaD), there has been considerable interest in understanding the role of the maternal HPA axis in fetal programming and adult disease risk (Gluckman et al. 2010; Jones et al. 2006; Harris and Seckl 2010; Kajantie et al. 2002; Kapoor et al.

2006; Holmes et al. 2006). Studies have linked increased maternal stress to a variety of adverse health outcomes including preterm birth, low birth weight, reduced nephron proliferation in the kidneys, reduced head circumference, altered pancreatic function, elevated cardiovascular activity, and heightened stress reactivity later in life (Buske-Kirschbaum et al. 2007; Challis et al. 2001; Entringer et al. 2009; Kajantie et al. 2007; Kuzawa and Sweet 2009; Seckl 2004; Seckl and Holmes 2007; Sloboda et al. 2009a, b; Wadhwa 2005; Wust et al. 2005). Rather than revealing straightforward pathways linking maternal stress to pre-, peri-, and postnatal health, however, these studies have identified a multitude of mechanisms by which maternal prenatal and postpartum stress may contribute to HPA function in the offspring (Glover et al. 2010; Lupien et al. 2000 Wadhwa 2005), which include genetic, epigenetic, developmental, metabolic, and behavioral pathways.

Furthermore, while this research has provided unequivocal evidence of the importance of the HPA axis in mediating developmental conditions contributing to fetal and postnatal health (Giesbrecht et al. 2012), it has not fully integrated the perspective that HPA elevation throughout pregnancy is not simply a result of maternal stress and that a series of physiological mechanisms exist to buffer risk to fetal development. This contemporary debate surrounding maternal stress shows striking parallels to the historical dilemma over the stress concept. Despite making foundational contributions to the stress literature, Hans Selye's loose use of the term "stress" has left an indelible mark on the scientific literature, which often continues to conflate stress as a stressor, as the response, and as the consequence (Selye 1956). This tension is echoed in discussions of pregnancy—is pregnancy, birth, or the postpartum recovery period the stressor? Subsequently, how might psychosocial stress potentiate a physiological process that is inherently metabolically stressful? And, how are these transitions shaped by diverse ecologies characterized by infectious disease and nutritional stress?

An anthropological perspective, which combines a consideration of the ultimate evolutionary context, grants explicit attention to the range of natural variation in stress physiology and its proximate correlates, yet also recognizes that for humans, pregnancy and birth are mediated by a complex array of psychosocial, cultural, and socioeconomic factors may be uniquely poised to address this topic. To that end, a broader understanding of the range of variation in glucocorticoids during pregnancy and characterization of the "upstream" dimensions of this variation will yield much needed clarification of the thresholds at which buffering is exceeded and aid in identifying the "downstream" consequences for fetal health, which may in turn recalibrate disease risk across the lifespan (Belsky et al. 2010a, b; Chrousos 2000; Gluckman et al. 2010; McEwen and Wingfield 2003; Miller et al. 2002; Phillips 2007; Taylor 2011).

6.3 HPA Activity During Pregnancy

For many years, clinicians observed that women with rheumatoid arthritis who became pregnant experienced a dramatic reduction of arthritic symptoms, followed by progressive relief throughout the course of pregnancy (Crocker et al. 2002). At

the time, researchers did not know the nature of this substance “X” implicated in the anti-inflammatory, immunosuppressive state during pregnancy, although the substance had been recognized earlier in the syndrome described by Cushing (1932). After several decades of experimentation, Reichstein, Hench, and Kendall identified the hormones as originating from the adrenal glands (Hench et al. 1949a, b) and renamed substance “X” cortisone (the oxidized form of cortisol), a collaborative effort that led to the 1950 Nobel Prize in Medicine. During the 1970s, Mont Liggins’ studies of glucocorticoids in sheep and other animals revealed the role of stress hormones initiating parturition in some species and in promoting fetal lung maturation, underscoring the potential for developmental processes occurring in utero to influence postnatal offspring health (Liggins 1974; Liggins and Thorburn 1994).

More recently, studies examining the role of glucocorticoids in human and anthropoid primate pregnancies have verified the progressive upregulation of the maternal HPA axis throughout pregnancy (Alloio et al. 1990; Mastorakos and Ilias 2003; Kivlighan et al. 2008; Power and Schulkin 2006; Smith et al. 1999). Compelling primatological research has revealed that chimpanzees and gorillas also exhibit elevated cortisol profiles during pregnancy, although shifts in HPA function are less robust among gorillas compared to either chimpanzee or human-typical patterns (Smith et al. 1999). However, how these differential patterns relate to metabolic correlates, gestational timing, or brain development across primate species has yet to be explored.

Increased levels of cortisol are required for normal fetal organ growth and to coordinate fetal developmental maturation with the onset of parturition (Obel et al. 2005; Sloboda et al. 2005). In fact, by the final weeks of human pregnancies, these hormones may reach levels typically associated with Cushing’s disease, even among healthy women (Kammerer et al. 2006; Magiakou et al. 1997; Obel et al. 2005; Wadhwa et al. 2009). To identify the pathways by which adverse birth outcomes arise (Kramer et al. 2009), however, we must first establish a more comprehensive understanding of how the maternal HPA reactive scope navigates changing maternal and fetal metabolic demands throughout pregnancy, preparing the maternal–fetal dyad for the stress of birth. A thorough understanding of adaptive shifts in HPA activity across these transitions requires consideration of several linked changes in neuroendocrine function, topics that are elaborated upon in the following section. Briefly, diurnal cortisol rhythms are elevated across pregnancy but are accompanied by reduced maternal reactivity to stressors. The enhancement of buffering mechanisms underlies this dampened responsivity and shields fetal exposure to maternal glucocorticoids.

During pregnancy, the inhibitory feedback circuitry of the maternal HPA scope is disengaged, resulting in progressive upregulation of basal levels of stress hormones. Beyond the typical release of CRH from the pituitary as part of the maternal HPA axis cascade, the human placenta is also capable of producing CRH, which in turn can interact with the maternal HPA to release ACTH and cortisol, driving a feed-forward, positive cycle (Challis et al. 2001; Kramer et al. 2009; Mclean and Smith 2001). In response to this transient period of hypercortisolism, the maternal pituitary and adrenals exhibit a gradual increase

in size (Mastorakos and Ilias 2003). Placental CRH also stimulates the fetal adrenal to produce cortisol—both directly and via stimulation of the fetal pituitary—and appears to be a uniquely anthropoid feature (Bowman et al. 2001; Power and Schulkin 2006; Smith et al. 1999). It has been proposed that beyond playing an important role in the timing mechanism of parturition, the placenta subsumes functions similar to the central nervous system (CNS), hinting at its unique relationship to brain development in anthropoid primates (Schulkin et al. 2005; Smith and Nicholson 2007). CRH is therefore not just a simple correlate of the maternal HPA axis, but rather, a central regulator of maternal and placental–fetal physiology (Power and Schulkin 2006; Schulkin et al. 2005). An excellent detailed review of the role of placental mediation of the intrauterine and fetal environments is provided by Rutherford (2012).

Despite such marked increases in diurnal patterns of glucocorticoid release in pregnancy, however, the maternal capacity for stress reactivity is significantly dampened (Bergant et al. 1998; Brunton and Russell 2008; Mastorakos and Ilias 2003; Taylor 2011; Windle et al. 2011). Experimental studies have confirmed reduced responsiveness of pregnant women to physical stress (de Weerth et al. 2007), a CRH challenge (Schulte et al. 1990), the cold hand test (Kammerer et al. 2002), and in response to the Trier Social Stress Test (de Weerth and Buitelaar 2005a, b; Entringer et al. 2011). And, although studies have identified associations between maternal psychosocial distress and elevation cortisol (Giesbrecht et al. 2012), it is far from clear whether these signals are transduced via the placenta and the degree to which they impact fetal development (Wadhwa 2005).

Inhibition of maternal stress reactivity peaks late in pregnancy and is hypothesized to be a result of buffering mechanisms initiated by cortisol metabolites both in the placenta and in maternal blood supply (Challis et al. 2001; Kramer et al. 2009; O'Donnell et al. 2009). Of special significance is placental enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), which typically inactivates greater than 90% of maternal cortisol by oxidation to its inactive form, cortisone, thus mitigating fetal exposures to the adverse effects of circulating glucocorticoids (Benediktsson et al. 1997; Harris and Seckl 2010; Seckl and Holmes 2007; Sun et al. 1999). Notably, elevated concentrations of 11 β -HSD2 are also found in the fetal brain during gestation (Harris and Seckl 2010). Myriad other factors may influence the transplacental transfer of glucocorticoids, with maternal undernutrition and protein restriction serving as a major constraint to 11 β -HSD2 production, eroding the protective barrier against GCs (Harris and Seckl 2010; Vieau et al. 2007). Elevated levels of corticosteroid-binding globulin (CBG) also reduce the bioavailability of stress steroids, which demonstrate marked increases by the 28th week of gestation (Bowman et al. 2001; Mclean and Smith 2001). In addition, tissue receptor sensitivity may also be downregulated in response to the increased basal GCs, providing another salient pathway to reduced HPA reactivity (Entringer et al. 2011). The temporal dimensions of these changes, however, are not well elucidated, with studies identifying different critical periods of gestational stress depending on the type of stressor and the health outcome of interest (Entringer et al. 2011; O'Donnell et al. 2009).

6.4 Fetal Tissue Maturation

The involvement of the HPA axis in shifting the timing of developmental transitions across the lifespan has been documented across a wide range of taxa (Belsky et al. 2010a; b; Crespi and Denver 2005) but has typically focused on the life history staging of sexual maturation (Chisholm and Coall 2008; Power and Schulkin 2006). Mounting research has suggested that fetal stress response also plays a critical role in choreographing the advance toward parturition and in accelerating maturation of fetal tissues in preparation for birth (Kivlighan et al. 2008; Mclean and Smith 2001; Obel et al. 2005). Much of this research is informed by studies of infants at risk of preterm birth, prompting the administration of synthetic glucocorticoids to accelerate fetal lung development (Garbrecht et al. 2006; 2007). Similarly, in full-term pregnancies, metabolism of endogenous GCs promotes fetal lung maturation, enhances pulmonary surfactant, and signals maturation of fetal organs such as the pancreas and adrenals (Challis et al. 2001; Laatikainen et al. 1988; Roberts and Dalziel 2006a, b). During the third trimester, increasing levels of glucocorticoids, largely of placental origin, stimulate the proliferation of the fetal adrenal cortex. The fetal adrenal then increases in size and output, producing ACTH, ultimately triggering the release of cortisol (Freemark 1999). Beyond the ability of the fetal adrenal to secrete cortisol produced from placental progesterone, it also produces DHEAS, which is utilized to synthesize placental estrogens (Lockwood 2004; Mastorakos and Ilias 2003), thus signaling the onset of parturition. Fetal adrenal activity spikes during the birth event but subsequently undergoes a dramatic remodeling, regressing through cellular apoptosis during the first several months after birth (Levine et al. 1982; Mesiano and Jaffe 1997; Nguyen et al. 2008; Pepe and Albrecht 1990). In short, the form and function of the fetal adrenal are dramatically different compared to the neonatal and infant adrenal. Intriguingly, the timing of the adrenal regression coincides with a shift to a “hypo-responsive” period for the newborn’s HPA axis, during which stress reactivity is significantly dampened (Gunnar et al. 1996), a topic explored later in the discussion of the HPA axis and infant brain growth.

6.5 Lactation and Restoration of Maternal HPA Homeostasis

Given the dramatic elevations of maternal stress hormones during pregnancy, it is also critical to consider how the maternal HPA is able to reinvokethe negative feedback circuitry after birth, especially since the actions culminating in pregnancy involve suppression of the typical inhibitory feedback in the final weeks of pregnancy (Brunton and Russell 2008; Lightman et al. 2001). These massive shifts in maternal HPA activity over the course of pregnancy and parturition have important implications for post-partum depression, a condition affecting around 10–15% of women, with greater than 50% of women experiencing the subclinical condition of maternity blues (Brummelte and Galea 2010; Groer et al. 2002; Reck et al. 2004; Tronick and Reck 2009; Weinberg and Tronick 1998). This ubiquity of altered maternal affect also prompts an inquiry

into what mechanisms are responsible for attenuating maternal cortisol levels that may be high as those in Cushing's disease or major depression following birth.

Remarkably, during the postpartum period, neuroendocrine changes in HPA function appear to be blunted compared to elevated states during pregnancy and the peripartum period (Altemus et al. 1995; Carter et al. 2001; Walker 2010). An initial putative explanation involves the absence of placental CRH following placental expulsion, which during pregnancy contributes to the feed-forward cycle of the maternal HPA axis during pregnancy, ultimately driving elevated maternal cortisol. Elevated levels of progesterone produced by the placenta, which are reported to have antianxiolytic properties, also drop precipitously following parturition and may interact concomitantly with changes in HPA function during this transition (O'Keane et al. 2011). Unfortunately, there is scant research addressing this possibility. Substantial evidence from both animal and human studies has revealed powerful regulatory effects of lactation on neuroendocrine function and suggests that breastfeeding contributes to attenuation of maternal HPA activity (Carter et al. 2001; Russell et al. 2001), plays a protective role in reducing risk for postpartum depression (Groer et al. 2002; Tu et al. 2006), and promotes the responsive behavior that underlies the maternal–infant bond (Reck et al. 2004). Cortisol also plays a direct role in supporting the energetic demands of lactation, for instance, cortisol mobilizes stores of gluteofemoral fat accumulated during pregnancy to fuel milk production (Ellison 2001; McNamara et al. 1995), and in concert with prolactin and insulin, alters the transcription factors that encode milk proteins during lactogenesis (Akers 2002; Ellison 2001; Hinde and Milligan 2011; Lillycrop et al. 2007; Quesnell et al. 2007).

Lactation paradigms have implicated the prosocial neuropeptide oxytocin in suppressing the stress response in rodents, primates, and also in humans (Altemus et al. 1995; Altemus et al. 2001; Carter et al., 2001; Heinrichs et al. 2001; Windle et al. 2004). Elicited by the suckling stimulus of the infant, a release of oxytocin into maternal circulation is accompanied by reductions in ACTH and cortisol (Chatterton et al. 2000; Neumann 2001; Windle et al. 2004). The importance of breastfeeding in attenuating the HPA axis to baseline during the postpartum period cannot be understated—in fact, the dyadic act of breastfeeding may restore maternal HPA allostasis and promote prosocial behavior foundational to mother–infant interaction, in addition to reducing cortisol concentrations in breast milk (Kulski and Hartmann 1981; Petherick 2010). Exciting new research has even documented infant behavioral calibration to glucocorticoids in milk among macaques, revealing sex specific effects on temperament (Hinde 2012; Sullivan et al. 2011).

6.6 What We Do Not Know: HPA Activity in a Non-Western Context

Despite considerable interest in how the maternal HPA axis navigates the transitions from pregnancy through parturition, and the related consequences for infant health, there is a paucity of data addressing variation in the diurnal cortisol rhythm among

pregnant women immersed in dramatically different nutritional and infectious disease ecologies (Nyberg 2009; 2012). Evidence from a recent study conducted among the Tsimane', a population of forager-horticulturalists of the Bolivian Amazon, supports the notion of pregnancy and parturition as a major physiological stress event: pregnant females demonstrated a 101% increase in midday cortisol compared to nonpregnant women, with the maximum morning value exceeding the average by 352% (Nyberg [in preparation](#)). Unfortunately, in the absence of data of on maternal stress during pregnancy, it is not possible to determine the degree to which psychosocial stressors further potentiate hypercortisolism during pregnancy. This study did not find robust support for diminished reactivity to infection in pregnant compared to nonpregnant women, although this study relied on subjective morbidity as a proxy for reactivity as opposed to an objective biomarker of infection (Nyberg [in preparation](#)). Interestingly, lactating Tsimane' women exhibited similar cortisol profiles compared to nonlactating women, confirming the hypothesis that breastfeeding serves an important role in attenuating HPA activity following birth. These findings also indicate that the dampening effects of breastfeeding are at their strongest in the few months following birth. It is likely that increased frequency and duration of suckling provide neural stimuli that promote oxytocin release, consequently diminishing HPA activity, although other prosocial neuropeptides such as prolactin and vasopressin are also implicated (Carter 2003; Feldman et al. 2007; Heinrichs et al. 2003; Levine et al. 2007).

Ongoing research in conjunction with the Cebu longitudinal health study in the Philippines has also reported elevations in cortisol during pregnancy, although peak concentrations occur during the second trimester (Thayer and Kuzawa [in preparation](#)). These studies are among the first to document naturally occurring variation in HPA activity across healthy pregnancies in non-Western contexts.

6.7 HPA Development and the Brain

These findings also have important implications for the timing of offspring brain development, particularly the hypothalamus and the hippocampus, which are the seats of initiation and regulation of the stress response. Considerable debate has been waged over when the HPA axis is believed to reach adult-typical maturity, with some studies suggesting that the typical cortisol rhythm comes on board anywhere from 4 weeks to 20 weeks after birth in breastfed infants (de Weerth et al. 2003; Groschl et al. 2003), with others suggesting a moderate circadian rhythm by three months (Gunnar and Donzella 2002), and still others suggesting that it is not fully established until age 2 or later, with a considerable degree of variation in timing between children (Jessop and Turner-Cobb 2008). This developmental window is a time characterized by rapid brain growth and synaptogenesis, especially within the hippocampus, which is situated as the primary inhibitory feedback center of the HPA response with the highest density of glucocorticoid receptors (GRs). The hippocampus is vital for both cognition and memory and attains 85% of its volume by 4 years of age (Giedd et al. 1996; Lupien et al. 2009). Exposure to elevated levels of GCs before the HPA

axis can invoke its negative feedback circuitry thus presents a competing threat to postnatal brain growth: among their many effects on neurological development, glucocorticoids are known to inhibit neurogenesis and contribute to neural apoptosis in the neocortex, hippocampus, and anterior cingulate cortex, although GCs may exert divergent effects on the amygdala (Brunson et al. 2001; Kern et al. 2008; McEwen 1999; McEwen 2003; Pruessner et al. 2010; Sapolsky 2003; Tottenham and Sheridan 2009). Recent work suggests looking beyond GCs alone to understand how DHEA, an antiglucocorticoid, may also protect the brain and especially the hippocampus, during vulnerable developmental windows until weaning (Campbell 2011). Though not central to this review, further study of its involvement and coordination with postnatal adrenal development warrants consideration.

Preliminary results from a study of diurnal cortisol among Tsimane' children under the age of four suggest that the HPA diurnal rhythm is less well entrained, with overall output being lower and children exhibiting dramatically more within-person variation compared to other age groups (Nyberg 2009). While this evidence is not necessarily conclusive of the hypothesized "hyporesponsive" period, at the very least, it suggests that the nature of the HPA rhythm in young children in this remote subsistence population is highly disorganized (Nyberg 2009).

Despite the neurotoxic effects of elevated cortisol concentrations, not all early life stress should be conceptualized as "bad." For instance, the diurnal rhythm is especially sensitive to early social exposures to prime the HPA response and epigenetically activate receptors throughout the body and brain (Gunnar 1998; Gunnar and Donzella 2002; Lupien et al. 2009; Tottenham and Sheridan 2009). These early social exposures which entail mild stressors are in fact necessary to establish homeostasis, coordinate many of the body's circadian rhythms, and prime the negative feedback circuitry of the HPA axis (Cole 2008; Miller et al. 2009; Stetler et al. 2004; Stetler and Miller 2005).

If the infant does not display the adult-typical pattern of HPA activity, with the capacity to invoke the inhibitory feedback in the hippocampus following stressors, what mediates the infant's experience of stress? Previous research points to the dyadic interaction between the mother and infant in the early postnatal period as a means of bridging provisioning until the child has established its own diurnal rhythm, also implicating maternal behavior as a significant mediator of infant stress. Though alloparenting and direct paternal care have undoubtedly played an important role in the human developmental niche (Gettler et al. 2011; Kramer 2011), this review focuses explicitly on the linked transitions between mother and infant.

6.8 Dyadic Regulation of Maternal and Infant Interaction

Mothers may actively maintain the hyporesponsiveness of the offspring HPA axis, directly buffering the neurobiological effects of distress, helping to regulate emotion in the first few months of life, and diminishing the early effects of adversity (Chen et al. 2010; Gunnar 1998; Gunnar et al. 1996). Within developmental

psychology, researchers have underscored the mutual nature of this maternal–infant interaction (Reck et al. 2004). Rather than representing an idealized synchronicity, however, reciprocal interaction may be better characterized as the process of “interactive repair,” as it entails a process of matching, mismatching, and repair (Beck 1995; Cohn et al. 2012; Paulson et al. 2006; Reck et al. 2004; Tronick and Reck 2009). In controlled experiments, mothers with postpartum depression consistently rank as more unresponsive in their interactions with their infant (Flykt et al. 2010; Weinberg and Tronick 1998). A recent study indicated that higher quality maternal behavior was associated with more rapid cortisol attenuation in infants following a stressor (Albers et al. 2008). Still others have implicated maternal touch and feeding as critical dampeners of the stress response and inflammatory processes in infants (Walker 2010). From this perspective, maternal postpartum depression thus emerges as a formidable public health concern not just for maternal well-being but for its interference with the interactive process that helps regulate the infant’s stress response (Brummelte and Galea 2010; Cohn et al. 2011; Hipwell et al. 2000; Tronick and Reck 2009).

The burgeoning field of behavioral epigenetics holds great promise in identifying the neurobiological basis for the priming of the HPA reactive scope, which may translate to differential feedback efficiency and reactivity across the lifespan (Champagne and Meaney 2001; Oberlander et al. 2008; Szyf et al. 2005). Amid the salient developmental and epigenetic pathways by which environmental information is transmitted to offspring, recent attention has been granted to phenotypic inertia, which extends across generations, potentially reflecting a running average of past environments (Kuzawa and Thayer 2011). The case of the priming of the offspring HPA axis and its consequences for stress reactivity, however, underscore that this cross-generational information is transmitted not solely during fetal development or later via cues in breast milk but may also be signaled through behavioral pathways from the mother to infant during this early period of overlapping provisioning (Kuzawa and Quinn 2009). For instance, Champagne and Meaney (2001) demonstrated that behavior is stably transmitted in a nongenomic fashion across generations in rats, who in cross-fostering studies inherit the behavior from their nursing mother, not their biological mother. The vast majority of the literature on behaviorally induced epigenetic changes is derived from similar animal models, most notably from “aloof rat mothers” whose reduced licking and grooming behavior is associated with increased offspring stress reactivity, greater methylation of the promoter regions of the GR gene, and reduced receptor efficacy (Fish et al. 2004; Meaney 2010; Weaver et al. 2004). Whether an analogous process among mothers experiencing postpartum maternal depression elicits similar epigenetic changes in the human infant and under what conditions these effects may be reversible are far from clear. Oberlander et al. (2008) offered the first evidence among humans, reporting that altered methylation status of the human NR3C1 gene in newborns is contingent on prenatal maternal mood. Another recent study revealed that gene-specific DNA methylation patterns in infant leukocytes were associated with exposure to maternal depression (Devlin et al. 2011). These important findings may offer a glimpse into epigenetic processes linking maternal mood and behavior to altered

offspring HPA stress reactivity. We are in the infancy of what is certain to be a dramatic and exciting time for behavioral and developmental biology (Miller 2010; Roth and Sweatt 2011) and for elucidating the epigenetic underpinnings of neurobiology of attachment and the transmission of stress responsivity across generations (Champagne and Meaney 2001; Liu et al. 1997; Weaver et al. 2004).

6.9 Proximate and Ultimate Perspectives of HPA Function

Thus far, our understanding of stress during pregnancy has been largely defined by studies of HPA activity in US and industrialized populations. Documenting HPA trajectories in healthy pregnancies across diverse ecological contexts may help to expand the global range of variation in neuroendocrine activation and to better delineate the thresholds at which maternal stress buffering is exceeded. In addition, collection of longitudinal data will yield insight into how intraindividual variation in HPA activity shifts throughout the course of these linked physiological transitions. Greater clarification of the naturally occurring variation in HPA activity across pregnancy is a critical first step in identifying developmental windows associated with adverse health outcomes for mother and fetus. Furthermore, as maternal cortisol may reflect, in part, a downstream effect of CRH of fetal-placental origin, further inquiry into the placental mediators of the maternal-fetal HPA axes would enhance our understanding of its remarkable buffering capacity (Rutherford 2009; 2012; Power and Schulkin 2005). For instance, since maternal fat intake and its contribution to circulating leptin also contribute to the regulatory “brakes” on the maternal HPA axis and have been associated with offspring hippocampal function (Oates et al. 2000; Walker et al. 2008), finer grained details on maternal nutrition in terms of both micronutrient levels and energetic status would better illuminate these relationships. Future studies could greatly benefit from the inclusion of correlates of HPG function, metabolic expenditure, and insulin usage. This chapter has been purposefully narrow in focusing on cortisol as a measure of HPA axis function, but changes in GCs operate in a rich hormonal and metabolic milieu and are therefore likely to involve vastly complex, interdigitating interactions with other reproductive hormones, particularly with the sex steroids estradiol and progesterone produced via the hypothalamic-pituitary-ovarian axis (Bloch et al. 2003; Clancy 2012). Though relatively underexplored, the importance of the HPA elevation in suppressing the maternal immune response during pregnancy represents another compelling avenue for future research. Continued work in comparative primatology will also prove invaluable in determining how patterns of HPA activity are related to gestational and developmental timing across primate taxa, especially with respect to brain development and metabolic programming. Finally, linking these early life exposures to downstream health outcomes such as birth weight, growth trajectories, HPA activity, and cognitive function across the lifecourse will contribute to the growing understanding of the early life origins of health disparities.

Recognizing the dangers in the ambiguity of the stress term later in his career, physiologist Hans Selye wrote: “I should have called my phenomenon the ‘strain reaction,’ which causes ‘stress,’ in parallel with the use of these terms in physics” (Selye 1956, p. 51). In fact, there may be few biological examples that better embody Selye’s original model of strain and stress than human birth, where pregnancy, birth, and the postpartum recovery period may each present physiological stressors for mother and infant. This process also produces inordinate mechanical strain given the constraints of the female pelvis and fetal head, posing a unique developmental dilemma—obstetrical or energetic—to the timing of human birth (Rosenberg and Trevathan 2001). As a result of our secondary altriciality, sensitive periods for brain development were also extended, which required considerably greater postnatal maternal investment and buffering.

An additional challenge stemming from our altricial births entails how to match fetal lung and organ maturation to coincide with a relatively earlier birth. The solution to this question is suggestive, given the known role of glucocorticoids on fetal tissue acceleration and in coordinating the timing of parturition: this may provide a key piece of evidence in determining that maternal–fetal–placental HPA elevation is not simply a spandrel (Gould and Lewontin 1979), driven as a result of escalating female reproductive hormones during pregnancy. Rather, we should consider whether shifts in the HPA axis across pregnancy reflect an evolutionary adaptation co-opted to resolve changes in gestational timing for humans and our hominin ancestors who were giving birth to increasingly large and big-brained infants (De Silva 2011). Finally, given the inherent metabolic stress posed by human pregnancy, we must also conceptualize how psychosocial stress potentiates individual differences in HPA trajectories throughout pregnancy, which is inherently metabolically stressful, even under the best conditions.

In conclusion, this chapter has provided a broad overview of how the maternal and infant HPA axes negotiate the linked physiological transitions of pregnancy, birth, and lactation. This approach highlights the overlapping, contingent, and dialectical nature of these stages of the reproductive cycle and also emphasizes the importance of psychosocial and behavioral pathways in modifying infant stress neurobiology in the first years of life beyond programming effects occurring in utero. This extended developmental period means that if unaddressed, early adversities posed by gestational stress, maternal postpartum depression, psychosocial stress, and socioeconomic inequalities may leave an indelible mark on HPA trajectories, potentially shifting later life risk for depression, cardiovascular disease, and the metabolic syndrome. However, the very nature of early developmental plasticity of the HPA axis, which allows physiology to be modified in response to early social and environmental cues, posits that phenotypic and epigenetic changes in the stress response may be reversible in the presence of social enrichment and alloparental buffering, suggesting that early experience is not necessarily destiny (Chen et al. 2010; Flinn et al. 2011; Gluckman et al. 2010; Sapolsky 2003).

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Chapter 7

Genome–Environment Coordination in Neurobehavioral Development

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Keywords Epigenetics • Early experience • Critical windows • Brain development
• Serotonin

7.1 Introduction

How do we become who we are? Are we *tabula rasa*, blank slates randomly scrambling for imprintation of information, or are we merely the constructions of our selfish genetic blueprints? Current scientific philosophy tells us we are neither preprogrammed nor do we possess unadulterated free will. While mammalian neurobehavioral development is biologically constrained, it is also sensitive to experience. Neurophysiological patterning guides motivation and emotion that we use to navigate our environments. Our environments, however, often present unexpected challenges. We develop our strategies for responding to stress throughout prenatal and postnatal development. How does this neurobehavioral development unfold? It proceeds according to exceedingly elegant and precisely timed interactions between the genome and the environment. These interactions begin at conception and may last a lifetime but may be particularly potent at critical periods in development. During these critical periods of embryonic and early postnatal development, even the slightest variability in the coordination between the genome and the environment results in some of the breathtaking neurobehavioral variability in stress adaptation we observe in infant mammals. This chapter will examine some examples of genome–environment coordination that impacts prenatal and early postnatal neurobehavioral development in nonhuman primates. I will discuss how certain regions of the genome may put individuals at risk for disadvantageous neurobehavioral

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development following early stress and possible mechanisms for how this risk may occur. Next I will introduce the reader to the diverse role of epigenetics in the effects of early environment. Finally, I will consider the potential consequences of gene–environment coordination across generations. The goal of this chapter is to provide examples of the complexity of the inheritance and development of stress response strategies and to highlight new avenues for understanding why some nonhuman primates wither when challenged, while others thrive.

7.2 Early Environment and Neurobehavioral Development

It has long been known that early environment plays an essential role in neurobehavioral development (Bowlby 1952). The term “environment,” however, has multiple meanings. To quantitative geneticists, the environment includes any observed variance unaccounted for by genetic factors. To microbiologists, ultraviolet light, temperature, and salt concentration are potent environmental moderators of bacterial phenotypes. To psychologists, the environment often refers to the quality of one’s psychological experiences. Disruption of early attachment relationships, for example, is considered one of the most potent psychological stressors. Thus, occurrences of abuse, neglect, low socioeconomic status, or family discord profoundly affect neurobehavioral development. This chapter will focus on the role of psychological experiences in neurobehavioral development.

In nonhuman primate research, we have the ability to either observe natural variation in early life psychological experiences or experimentally manipulate the environments of developing infants. Some nonhuman primate studies, much like human and rodent studies, capitalize on natural variation in early social life, including observation of quality of parental care and social relationships (Hinde and Simpson 1975; Fairbanks and McGuire 1988; Fite and French 2000; Maestripieri et al. 2006; Kinnally et al. 2010). Alternatively, the infant can be exposed to stressful circumstances such as repeated separations from the mother or family group (Higley et al. 1992; Dettling et al. 2002), permanent maternal separation (nursery, peer, or surrogate rearing: Harlow and Zimmerman 1959; Capitanio et al. 2005; Mendoza et al. 1978), fostering infants to abusive mothers (Maestripieri et al. 2006; McKormack et al. 2006), or manipulating ease of finding food in a foraging device (variable foraging demand: Andrews and Rosenblum 1994; Parker et al. 2006). Less well studied in nonhuman primates are the experimental effects of more positive experiences, such as environmental enrichment, good-quality parent–offspring relationships, and social stability, on neurobehavioral development. This remains an important potential avenue of research.

In rhesus macaques (*Macaca mulatta*), one of the most commonly used experimental early life manipulations is maternal deprivation (called nursery- or peer-rearing, NR; Harlow and Zimmerman 1959; Higley et al. 1992; Suomi 1991). First used in nonhuman primates by Harry Harlow in the 1950s (Harlow and Zimmerman 1959), maternal separation includes the removal of the macaque infant’s primary attachment figure: their mothers. Because macaque species are matrilineal, macaque infants are believed to form little to no attachment to their fathers. Though this

maternal deprivation manipulation has been applied using slightly different protocols in different laboratories and for different purposes over the last 50 years, common elements include the following. Infants are removed from their mothers on the first day of life (Capitanio et al. 2005) or once they are more independent from their mothers (Suomi 1991). Once they reach 1–6 months of age, macaques are pair-housed with peers and, later in adolescence, are typically housed with larger social groups of peers (Higley et al. 1992). Of course, the differences in timing of each of these phases likely impact neurobehavioral development greatly, and different NR protocols have been demonstrated to have different effects on macaque infant development (Rommeck et al. 2009). It is critical in interpreting published NR studies to understand the potential impact of the maternal deprivation protocol used. The majority of studies I will discuss in this chapter include removal from mother on the first day of life, with continuous pairing or group peer housing until adolescence.

This type of early environmental stress tends to reprogram how individuals adapt to daily life challenges. Since variation in stress response contributes to every aspect of mammalian life, including somatic and mental health, quality of social life, and reproductive success, the effects of early experiences can last a lifetime. Stress responsiveness and adaptation can be observed at physiological and behavioral levels. Dimensions of physiological and behavioral stress response are typically consistent within individuals, indicating that it is a basic part of their individual makeup, or trait-like (Friedman and Rosenman 1971; Bohnen et al. 1991). The physiological stress response includes the coordination of the autonomic nervous system with the hypothalamic–pituitary–adrenal (HPA) axis (see Nyberg 2012; Nemeroff 2004; McEwen and Gianaros 2010). The coordination of these two systems to maintain homeostasis in the presence of a challenge enables the individual to mobilize energetic resources needed and conserving those that are not needed. The autonomic nervous system enables a fast response to stress, increasing heart rate and decreasing metabolism and stimulating epinephrine release from the adrenal medulla. The HPA axis responds to stress by regulating the level of steroid hormone cortisol that is released into the bloodstream. Inputs from brainstem nuclei (raphe nuclei, locus coeruleus, and substantia nigra), limbic, and cortical regions modulate the ability of the hypothalamus to secrete corticotropin-releasing hormone (CRH) and the pituitary gland to secrete adrenocorticotropin (ACTH), which stimulates the adrenal cortex to secrete cortisol. Cortisol negatively feeds back to multiple sites in the brain to shut down cortisol output. The process of stress response includes the activation of multiple central nervous system and peripheral pathways, including neurotransmitters (e.g., serotonin, dopamine, norepinephrine) and hormones (cortisol, vasopressin, neuropeptide Y, epinephrine). Mammalian trait behavioral responses to stress are even more complex to characterize, but seem to vary on a spectrum from activational (bold, impulsive, proactive) to inhibited (shy, avoidant, anxious: Kinnally et al. 2008; Sih et al. 2004).

Early life stress reorganizes these stress response systems and related behavior compared with infants that experience fewer challenges. Nonhuman primate infants that experience early life maternal deprivation often display dysregulation of physiological and behavioral stress adaptation. Some maternally deprived individuals are characterized by heightened response and slow recovery from HPA activation, represented by higher levels of circulating cortisol (Higley and Linnoila 1992; Capitanio

et al. 2005; Coplan et al. 1996) or extended sympathoadrenal system activation, indicated by increased heart rate and release of epinephrine (Mathew et al. 2002). Behaviorally, NR infants react to stress with disinhibition (activity or impulsivity, Suomi 1991). These responses to challenge are generally considered disadvantageous because they are energetically costly and predict poor health later in life (Wegman and Stetler 2009). Some argue, however, that activational responses to stress observed in NR infants may be an adaptive response to ensure mobilization in adverse conditions (Champoux et al. 2002).

Of course, such stressful early experiences do not affect all infants in the same way (Belsky 1980). Some infants may be more resilient or, alternatively, more sensitive to early life stressors. One of the factors that affect how an individual responds to the environment is their genetic makeup. Individual structure of genes that contribute to stress response, such as neurotransmitter and hormone-related genes, appears to be particularly important in the effects of environment on the individual. Variation in these genes can moderate the effects of early environment, buffering or exacerbating the effects of stress on neurobehavioral development.

7.3 Genes and Genomes

At this point, it is worthwhile to briefly define aspects of the “genome.” The genome is composed of deoxyribonucleic acid (DNA), a material that is in the nucleus of each (nucleated) cell in our bodies. DNA is composed of sequences that include four components called nucleotides or bases: adenine (A), guanine (G), thymine (T), and cytosine (C). Unique sequences of DNA are transcribed into ribonucleic acid (RNA), which is often (but not always) then translated into protein. The process of being transcribed and translated generally defines a “gene.” It is via this process, characterized by the concept of the “central dogma” of genetics (Crick 1970), that genes have traditionally been associated with traits.

Our genome includes more than genes, however. There are large stretches of DNA between our genes. Once believed to be “junk” DNA, we now know that within these spans of DNA are gene regulatory regions, or “promoters.” DNA sequences within these regions can facilitate or inhibit gene transcription. Transcriptional complexes, including polymerases and transcription factors, may bind within these promoters, based on their sequence. Variation in this scaffolding for transcriptional machinery may affect how efficiently the gene is transcribed. This means that while two individuals may share the same gene, they may still differ in the structure of DNA that regulates the expression of that gene. One potential source of variation in gene expression between individuals is polymorphism, or population variation in the structure of the DNA. Polymorphisms may be at a single nucleotide at a particular genomic locus or may include longer, often repeated, strings of sequences. One of the best-characterized structural variants is the serotonin transporter linked promoter polymorphism (*5-HTTLPR*) in the regulatory region of the serotonin transporter (*5-HTT*; henceforth, gene names are italicized) gene (see Box 7.1).

Box 7.1 Candidate genes that modulate early environmental influences

5-HTT: Serotonin (5-HT) transporter, takes up extracellular serotonin
 5-HT1A: Serotonin receptor 1A, partial mediator of 5-HT action
 TPH2: Tryptophan hydroxylase 2, rate-limiting enzyme of 5-HT production
 MAOA: Monoamine oxidase A, breaks down 5-HT
 DRD1: Dopamine receptor 1, partial mediator of dopamine action
 GR: Glucocorticoid receptor, partial mediator of cortisol action
 CRH: Corticotropin-releasing hormone, stimulates cortisol release
 AVP: Arginine vasopressin, regulates water balance
 NPY: Neuropeptide Y, breaks down fat for energy
 BDNF: Brain-derived neurotrophic factor, supports cell growth
 OPRM1: Mu-opioid receptor, partial mediator of opioid action

5-HTT helps regulate function of the neurotransmitter serotonin (5-HT) in the brain. Serotonin is a vasoconstrictor and is found primarily in the gut, but is also an important neurotransmitter. Serotonin neurotransmission has been linked with feeding behavior, growth and reproduction, and mood regulation. *5-HTT* is also expressed throughout the body, but when expressed in the brain, seems to be associated with emotion regulation aspects of serotonin function. The strongest evidence of this association is that one of the most commonly prescribed antidepressants, Prozac®, also known as fluoxetine, preferentially targets *5-HTT*. The *5-HTTLPR* polymorphism is a 19-bp insertion in rhesus macaques, and it appears to be orthologous (that is similar to, but not derived from, the same evolutionary ancestor) to the human 44-bp insertion region. Since we have two copies of each gene in our genome, three genotypes are possible: long allele/long allele (l/l) homozygosity (possessing two versions of the insertion region), short allele/short allele (s/s) homozygosity (possessing two versions of the gene without the insertion), and long allele/short allele (l/s) heterozygosity (having one of each). Having one or two short alleles of the gene results in lower *5-HTT* expression; thus, the short allele is considered the low-expressing allele (Lesch et al. 1996). The neurobehavioral impact of the polymorphism is usually only observed under certain environmental conditions.

7.4 Gene–Environment Interaction

When the effect of a particular genotype on a phenotype differs in one environmental context compared with another, this is called a gene×environment interaction (Falconer and MacKay 1996). *5-HTTLPR* has been demonstrated to moderate the effects of the environment on neurobehavioral development in humans and macaques. Adult humans that experience early life stress and who also have at least one short *5-HTTLPR* allele are at increased risk for developing psychiatric problems such as depression (Caspi et al. 2003), although there is variability in the strength and

significance in studies attempting to replicate that finding (Risch et al. 2009). Some of the most telling experimental work in this area has been conducted in rhesus macaques. In NR monkeys, low-expressing *5-HTTLPR* alleles are associated with greater alcohol consumption (Barr et al. 2004) and show slower motor development (Champoux et al. 2002) and aggression (Schwandt et al. 2010). This gene–environment interaction may extend to other types of early life stressors. Infant rhesus macaques that experienced maternal abuse and were also carriers of the short *5-HTTLPR* allele displayed greater physiological stress reactivity than non-abused infants (McCormack et al. 2009). Using a well-characterized and ecologically relevant “variable foraging demand” (VFD) stress paradigm, one group has shown a similar effect in bonnet macaques (*Macaca radiata*, Coplan et al. 2011). Briefly, when infant bonnet macaques are between three and eight months of age, they and their social groups (including their mothers) are required to forage for their food in a foraging device (a modified cart with wood chips to hide food, see Rosenblum and Paullly 1984 for full description). VFD subjects and their mothers/social groups were alternately required to forage either little or extensively for food in 2-week blocks over 12 weeks. “Low foraging demand” (LFD) control subjects were able to readily retrieve food from this device. Infants that experience VFD stress and also carry one or two short *5-HTTLPR* allele exhibit higher CRH in cerebrospinal fluid, a possible indicator of higher overall HPA activity in these animals (Coplan et al. 2011).

Other genes that are important for stress response have also been shown to moderate the effects of early experience in nonhuman primates. The *MAOA-uVNTR* polymorphism (*rhMAOA-LPR* in rhesus macaques) is located on the X chromosome and consists of an upstream variable number of tandem repeats (uVNTR) including 2, 3, 3.5, 4, or 5 30-bp repeats in humans (Sabol and Hu 1998) or 5, 6, or 7 18-bp repeats in rhesus macaques (Newman et al. 2005). The number of repeats in this promoter region impacts the production of monoamine oxidase A (MAOA), an enzyme responsible for the oxidation/inactivation of the monoamines norepinephrine and 5-HT (Sabol and Hu 1998). “High activity” *MAOA-LPR* alleles (3.5 and 4 repeats in humans; 5 and 6 repeats in rhesus macaques) are so named because they confer greater transcriptional efficiency (Sabol and Hu 1998; Newman et al. 2005). Our group has previously shown that infant rhesus macaques that carry the low-activity *rhMAOA-LPR* genotype and are reared in small social groups are at higher risk for expression of aggressive behaviors during a stressful situation, while those reared by mothers alone in a restricted environment exhibit greater rates of behavior thought to reflect anxiety (Karere et al. 2009).

Single nucleotide differences within gene regulatory regions have also been demonstrated to moderate the effects of early environment. A single nucleotide polymorphism (SNP) in the promoter of the gene that encodes the dopamine receptor type 1 (*DRD1*), which is thought to be involved with the experience of reward, is linked with higher alcohol consumption in macaques, but only in males that experienced early maternal deprivation (Newman et al. 2009). Two SNPs, one in the promoter *CRH* gene and one in the neuropeptide Y (*NPY*) gene promoter, have also each been linked with an increased stress response (HPA and behavioral activation during a stressful social separation) as well as greater propensity for alcohol consumption in macaques that experienced early maternal deprivation (*CRH*: Barr et al. 2009, *NPY*: Lindell et al. 2010). Structural genetic variation is widespread across the genome, and

it seems possible, if not likely, that many more gene variants will be demonstrated to moderate the effects of early life stress in macaques. For example, functional polymorphisms have been discovered in regulatory regions of the macaque mu-opioid receptor gene (*OPRM1*, Schwandt et al. 2011), tryptophan hydroxylase 2 (*TPH2*, Chen et al. 2010), and brain-derived neurotrophic factor (*BDNF*, Cirulli et al. 2011). Future research will determine whether environmental factors can moderate the effects of these polymorphisms on neurobehavioral development.

Given the number of variants that moderate the effects of experiences on neurobehavioral development, we might expect that there may be epistasis, or interactions between multiple loci, that influences neurobehavioral development as well. I have observed that this is, in fact, the case (Kinnally et al. 2010). My colleagues and I investigated the combined effects of *rh5-HTTLPR* and *rhMAOA-LPR* genotypes and early maternal deprivation on the quality of behavioral response to stress in infant rhesus macaques. We found that emotional dysregulation was most pronounced in individuals that carried the low-activity *rh5-HTTLPR* and high-activity *rhMAOA-LPR* genotype. This gene×gene interaction was accentuated by the experience of nursery rearing. These results point to the exciting possibility that gene×gene or gene×environment interactions that predispose infants toward particular behavior patterns can be exacerbated or attenuated by genetic or environmental factors.

Until now, we have assumed that the potency of gene–environment interactions is equal across development. This is likely not the case. Since gene–environment interactions begin at conception, we might expect the moderating effects of *5-HTTLPR*, for example, would be evident in utero. This has recently been demonstrated in non-human primates: moderate exposure to alcohol during the entire course of gestational development influences infant neurobehavioral development in rhesus macaques in a genotype-dependent manner (Kraemer et al. 2008). Infants with the short *5-HTTLPR* allele that experience gestational alcohol stress are judged by experimenters to be more irritable (“fussy” and “negative” response to temporary separation from their mothers, as opposed to “calm”). These infants also display great responsivity of the HPA axis to stress: plasma cortisol is the most elevated during maternal separation in these infants. This work suggests that some gene–environment interactions occur prenatally. Since the prenatal environment is comprised of nutritional, physical, and molecular transductions of the mother’s psychological and physical environment (Rutherford 2012), these findings highlight the need for understanding how prenatal gene–environment interactions are coordinated at the molecular level.

7.5 Genome–Environment Coordination

Understanding how the structure of DNA moderates the effects of early stress is an important step to characterizing the complexity of genome–environment coordination during neurobehavioral development. Yet the mechanisms of influence of *5-HTTLPR* and other polymorphisms on the effects of early stress are still largely unknown. One of the most obvious possible effects of gene and environment is to influence RNA production or gene activity. Several efforts to demonstrate a gene×environment interaction on gene activity have not yielded positive results,

however (Ichise et al. 2006; Jedema et al. 2010; Kinnally et al. 2008, although see Cirulli et al. 2011).

Thus, it remains to be explained how *5-HTTLPR* exerts its influence on behavior. One hypothesis regarding the mechanism of genotypic effects is that structural variation in DNA exerts its strongest effects on gene activity during prenatal development. We know that *5-HTT* dysregulation at a critical point in emotional development shapes neurobehavioral trajectories. The effect of a *5-HTT* antagonist, such as antidepressant fluoxetine, is to occupy *5-HTT* such that the brain and body are using less *5-HTT*. Treatment with fluoxetine (Prozac©) early in life results in enhanced emotional reactivity in response to stress later in life in mice (Ansorge et al. 2004) and in humans (Oberlander et al. 2008). This effect has been compared to having a low-expressing *5-HTTLPR* genotype early in development. Therefore, when higher emotional reactivity is observed in connection with *5-HTTLPR* genotype, it may be due to long-lasting downregulation of *5-HTT* activity in the brain at a specific developmental time point (Maciag et al. 2006).

It is also possible that early stress compounds smaller main effects of *5-HTTLPR* genotype on gene expression and neurobehavioral development, leading to an observed gene $\times$ environment interaction. If early stress exerts long-term effects on *5-HTT* expression and behavior, we would expect to observe *5-HTT* dysregulation soon after the experience of an early stressor. Lower post-stressor *5-HTT* expression in peripheral blood mononuclear cells (white blood cells) is observed in infant rhesus macaques that experience early life stress (maternal deprivation or aggression, Kinnally et al. 2008) and is associated with behavioral disinhibition during stress at an early stage in development (Kinnally et al. 2008). These findings suggest that *5-HTT* impairment, when induced by stress at a critical period in development, may lead to emotion dysregulation that may be long lasting.

An alternative explanation for observed genotypic effects is that traits associated with certain genotypes are generated through secondary, but correlated, causes. One group examined the relationship of *5-HTTLPR* genotype with adult brain morphology vs. *5-HTT* activity in macaques (Jedema et al. 2010). While carrying the short *5-HTTLPR* allele was not associated with *5-HTT* expression in relevant brain areas, it was associated with morphological deficits in stress pathway structures. This association may be moderated by early life experiences. Bonnet macaques that experienced variable foraging demand stress and carried the short *5-HTTLPR* allele displayed reduction in the volume of the corpus callosum in the brain, which is involved in emotion regulation (Jackowski et al. 2011). These studies highlight the potential importance of developmental regulation of *5-HTT* and other stress-related molecules in brain morphological development.

7.6 Genomic Plasticity and the Environment

So far, I have reviewed ways that the effects of certain experiences have different effects on an individual based on structural variation in the individual's genome. The genomic mechanisms of neurobehavioral plasticity in response to the environment

are still largely unknown, however. The simplest way for the environment to modulate neurobehavioral development would be for the environment to reconstruct the conformation of genes (called genetic recombination) based on the host's experiences. In nature, this is not usually the case. One can imagine that if it were, eventually environment-based genomic changes would limit the individual's ability to respond to changing environments, and therefore be maladaptive. However, there are some examples in nature in which the environment can change DNA sequences. Mutation of nucleotides can occur via exposure to a teratogen or mutagen, such as alcohol or radiation. However, most mutations are corrected via DNA repair. Another type of genomic rearrangement that occurs routinely is the recombination of genes that encode our immune response in response to pathogens to build our immunity (Jung and Alt 2004). Finally, transposons and retrotransposons, or “jumping genes,” first discovered by Barbara McClintock in 1950, are portions of ancestral DNA that opportunistically copy themselves and re-insert into the genome (McClintock 1950). The potential role of the early environment in directing (retro)transposition of DNA is an important direction for research.

While we do not yet know whether the environment may play a prominent role in structural changes to the genome, there is substantial evidence that plasticity in genomic *activity* (production of RNA and protein) is widespread across species. For example, nonhuman primate studies have demonstrated that multiple stress pathway genes are changed following different types of early life stress. Blood and limbic brain *5-HTT* and *5-HT1A* activity is reduced in macaques that experienced peer rearing (Ichise et al. 2006; Spinelli et al. 2010; Kinnally et al. 2008). Early repeated separation results in reduced hippocampal glucocorticoid (GR) receptors and *5-HT1A* in marmoset monkeys (*Callithrix jacchus*; Arabadzisz et al. 2010; Law et al. 2009).

For these changes in gene expression to be maintained long-term, some genomic element must be permanently reorganized. Instead of allowing for large-scale changes in DNA structure in response to changing environments, which may be maladaptive, evolution may have put into place mechanisms for gene *activity* to be changed by experiences. For example, there are chemical modifications that can be added to gene regulatory regions that may be temporary or permanent. These are called epigenetic modifications, and include histone modifications and DNA methylation (Bird 1986). The field of epigenetics holds great promise for our understanding of genome–environment coordination in neurobehavioral development.

7.7 Epigenetics in Neurobehavioral Development

Epigenetic plasticity, or changes in histone modification or DNA methylation patterns, may mediate or moderate some of the effects of early life stress. DNA methylation is the addition of a methyl group to cytosine-guanine (CpG) dinucleotides (see Sterner et al. 2012). When it occurs within gene regulatory regions, DNA methylation typically inhibits gene expression. DNA methylation may be a particularly strong candidate for the changes in gene activity we have described following

early stress because it is thought to be relatively stable once set. In general it should be: its primary functions are to maintain cellular differentiation and to prevent the expression of potentially harmful “jumping genes,” or transposons (Reik 2007).

One of the most exciting discoveries of the role of epigenetics in mammalian neurobehavioral development built on a long-studied area of research on the effects of maternal care on developing infant rats. We have long known that higher levels of maternal care early in life tend to lead to lower behavioral and physiological stress reactivity in infant rats (Denenberg 1964; Levine 2001). In a long-term and elegant series of experiments, one group has demonstrated an epigenetic pathway that may mediate these effects of early experience. First, they demonstrated that lower expression of hippocampal glucocorticoid receptors (*GRs*), which process circulating cortisol, heightens the individual stress response in rats. This is believed to occur because *GR* in the hippocampus helps shut down the HPA axis, so lower levels of *GR* promote greater stress reactivity (Francis et al. 2001). Next, they discovered that *GR* is expressed at a lower level in the hippocampi of infant rats that experience poor maternal care early in development. This effect of early experience is not limited to rats: McGowan and colleagues confirmed that expression of *GR* is also reduced in the hippocampi of humans that experienced childhood abuse (McGowan et al. 2009). This early life reprogramming has long-term implications, as these experience-dependent changes are transmissible between generations via apparently non-genetic mechanisms in rats (Champagne et al. 2006; Meaney 2001; Francis et al. 1999).

Intriguingly, an epigenetic mechanism for these phenomena has recently been demonstrated in both rats and humans. Greater DNA methylation within a *GR* regulatory region in hippocampus following lower maternal care (in rats) and childhood abuse (in humans) is linked with lower *GR* expression in humans and rats and enhanced stress reactivity in rats (Weaver et al. 2004; McGowan et al. 2009). This groundbreaking discovery demonstrates that changes to the epigenome following early life experiences change the course of neurobehavioral development. But it is not yet known whether epigenomic plasticity is the exception or the rule in psychobiological development. Since this discovery, epigenetic plasticity following stress has been reported in several other gene regulatory regions: estrogen receptor 1b (*ER alpha1b*) in the medial preoptic area of the hypothalamus in infant rats (Champagne et al. 2006), *CRH* in the paraventricular nucleus (PVN) of the hypothalamus in adult mice (Elliott et al. 2010), brain-derived neurotrophic factor (*BDNF*) in prefrontal cortex (PFC) in infant rats (Roth et al. 2009), and arginine vasopressin (*AVP*) in the PVN in infant mice (Murgatroyd et al. 2009). These epigenetic changes appear to mediate some of the effects of early stress on behavioral and physiological stress reactivity, as treatment with presumably demethylating drugs (histone deacetylase inhibitors, e.g., valproate) reverse the neurobehavioral effects of early stress in some cases. It remains unknown whether the epigenomic plasticity described in these studies is restricted to a subset of genes or is widespread across the genome. It appears, nonetheless, that the epigenetic reprogramming may play a role in gene–environment coordination in early postnatal development.

Even if the number of genes that are epigenetically reprogrammed following early stress is few, epigenetic marks still may play a large role in genome–environment

coordination. Stress-induced epigenomic plasticity is one mode of influence on neurobehavioral development (Weaver et al. 2004; Roth et al. 2008), but there are over 22 million genomic CpG sites that may be differentially methylated in each cell and organ. The developmental programming of the vast majority of the epigenome has not yet been characterized, and its role in the impact of early stress is largely unknown. Further, the derivation of DNA methylation programming may vary across the genome. While methylation patterns in some gene regulatory regions may be sensitive to environmental cues during postnatal development (Weaver et al. 2004; Champagne et al. 2006; Roth et al. 2008; Murgatroyd et al. 2009), methylation patterns within other gene regulatory regions may be set before birth. They may be partially inherited (Jones and Takai 2001; Schalkwyk et al. 2010), set during prenatal development, (Kaminsky et al. 2009) or dependent on DNA structure (Brandeis et al. 1994). The role of these marks in the effects of early stress is largely unknown, although we have recently discovered that global DNA methylation in peripheral blood, presumably because it reflects neural DNA methylation, accentuates the effects of early life stress in bonnet macaques (*Macaca radiata*; Kinnally et al. 2011), regardless of their developmental origins. As thousands of genes are involved with stress response (Alter et al. 2008), future work in the epigenetics of nonhuman primate development should seek to characterize the origins of epigenetic marks and place the role of epigenetic plasticity in stress pathway genes within this broader framework.

Another exciting potential role of these epigenetic marks is to explain some of the functional effects of candidate gene polymorphic regions described earlier in this chapter. Several studies in humans have recently demonstrated a link between low-expressing alleles of functional polymorphisms and greater average methylation of CpG “islands” within the regulatory regions of genes (*5-HTT*, Philibert et al. 2008a, b; *MAOA*, Philibert et al. 2009; *BDNF*, Mill et al. 2008; *5HT_{1A}*, Lu et al. 2008). My colleagues and I have also demonstrated this association in nonhuman primates: l/s or s/s *rh5-HTTLPR* genotype was associated with greater methylation of the *5-HTT* CpG island in blood DNA, consistent with a human study (Philibert et al. 2008). If genotype and early life stress are associated with similar methylation signatures, this would provide a molecular platform for direct interaction between structural genetic variation, epigenetic variation, and the environment. It is also possible that neurobehavioral variation associated with allelic variation actually arises due to links with DNA methylation patterns. This remains a critical avenue of research in this field.

7.8 Genome–Environment Coordination Across Generations

To understand the role of both early experiences and the genome on neurobehavioral development, it would be scientifically rigorous to examine the role of each in experimentally manipulated environments. Life, however, is not experimental. Mammals are born to their parents and usually live with their parents.

We share our genes with our parents, as they did with theirs. We also share a common early environment with them while they are raising us, which may resemble the environment they themselves were raised in. As such, our development depends on our genes, our environments, their interaction, and their *correlation*. Therefore, our genes and our environments are inextricably entwined in guiding development. These processes may be transmitted across generations, but their respective influences remain unknown, as they cannot be easily scientifically controlled.

The study of epigenetics may help us to resolve some remaining questions about the role of genome–environment coordination in inheritance and development of neurobehavioral traits. We have described studies that have demonstrated epigenomic plasticity in mature neurons, which influence neurobehavioral development in response to early experiences. Epigenomic plasticity is not restricted to neurons but has been documented in multiple tissue types (each et al. 2009), including germ line cells (Franklin et al. 2010), which are passed to offspring. If epimutations are inherited by these offspring, it may explain some transgenerational non-genetic inheritance of neurobehavioral traits. This idea is highly controversial, however, because mechanisms are in place to erase large parts of the epigenome during embryogenesis (Morgan et al. 2005). A recent study has provided an example of the intergenerational transmission of epigenetic changes following stress, however: DNA methylation within the regulatory regions of specific candidate genes in sperm was altered following adult stress in male rats and associated with similar methylation patterns in the brains of male offspring reared apart from fathers (Franklin et al. 2010). This data suggests that the effects of early life stress were transmitted to the next generation via epigenetic rather than genetic or environmental inheritance in this study. One alternate explanation for this finding may be that plasticity to epimutation is heritable. Some offspring may be genetically predisposed to epigenomic plasticity (Chong et al. 2007). It is also possible that epigenetic erasure may be incomplete in some epigenomic regions or that cellular memory processes exist that allow reprogramming of DNA methylation patterns following erasure. Clearly, more research in the area is required.

Indeed, it remains unknown whether epigenetic inheritance may play a role in the intergenerational transmission of neurobehavioral traits in nonhuman primates. There have been some important examples of the intergenerational transmission of traits in nonhuman primate neurobehavioral development. Some appear to be genetically or prenatally primed: adolescent rhesus macaques display levels of aggression and affiliation that are more similar to their biological mothers than to their genetically unrelated foster mother (Maestripieri 2003). Others are more environmentally sensitive. The quality of rhesus macaque maternal care (Fairbanks 1989) or abusiveness (Maestripieri 2005) is tightly linked with the quality of care the individual received in infancy. One explanation may be that cycles of care are perpetuated via learning. It also possible that cultural influences play a role: the social group may enforce certain behavioral propensities of its members. Finally, the role of epigenomic inheritance in this intergenerational transmission remains to be established.

7.9 Summary

I hope I have convinced readers that the genome is not a fixed platform upon which development proceeds nor are we blank slates for the environment to mold. Rather, primate neurobehavioral development is a dynamic, lifelong, feedback-dependent process that is constrained and facilitated by both heritable and environmental factors. We are only just beginning to discover the biological mechanisms for the coordination that occurs between the genome and the environment to allow us to adapt to the challenge. The future of this field of research will require the uniting of evolutionary, psychological, neuroscientific, and genetic approaches to determine why and how some animals psychologically and physically wither when challenged, while others thrive.

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Chapter 8

Building Marmoset Babies: Trade-Offs and Cutting Bait

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Keywords Cooperative breeding • *Callithrix* • Reproductive outcomes • Maternal investment • Multiple births

8.1 Introduction

The ultimate evolutionary goal of an organism is to put as many replicates of its DNA into the next generation as possible. Primates are long-lived organisms that devote considerable resources to each replicate—i.e., individual offspring. The trade-offs involved in physiological and behavioral “decisions” regarding what to invest in any particular primate offspring at a specific point in time versus what to invest in somatic maintenance and possible future offspring are likely to be complex.

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Common marmosets (*Callithrix jacchus*) are a particularly fascinating species in which to examine the manner in which investment trade-offs take place. Marmosets are the smallest anthropoid primates. They display suites of traits that are characteristic of primates as a whole, including adaptations for arboreality, diurnality, a relatively slow maturation and reproductive pattern, and an omnivorous diet. However, they also display traits that are unusual in anthropoid primates and are likely tied to the secondary reduction in body size that occurred in the callitrichid lineage (Ford 1980; Marroig and Cheverud 2005). Unusual reproductive traits include ovulation of multiple ova per cycle leading to production of litters that are typically twins, a postpartum estrus that results in production of up to two litters per year, suppression of reproduction in all but one or two females in a territory, and a cooperative breeding system in which all group members participate in infant care. Infant care includes not only physical transport but provisioning weanling infants with solid food. For reviews of marmoset reproductive strategy, see French (1997), Tardif (1997), Digby and Saltzman (2009), Saltzman et al. (2009), and Yamamoto et al. (2009).

This cooperative reproductive system has been proposed to be driven by the purported high energetic expense of reproduction. As expected with their small size, marmosets have the highest birth mass, relative to maternal weight of any anthropoid primate, and this relationship is frequently cited as the selection force leading to their cooperative breeding system. However, comparison of the degree to which New World monkey females receive assistance in infant care relative to birth mass and growth rates suggests that the relationship is not straightforward and there are many different strategies employed by small New World monkeys to balance present reproductive demands with those of somatic maintenance and future reproduction (Tardif 1994; Garber and Leigh 1997). The strategy adopted by marmosets results in many reproductive steps in which the female's investment may be modified including what litter size to gestate and how much to invest in each infant, what litter size to support through lactation and how much to invest in each infant, amount of time spent carrying, amount of time spent provisioning, and, ultimately, whether to reproduce or not.

In this chapter, we will review what is known regarding the manner in which captive common marmoset females make physiological and behavioral “decisions” regarding investment in reproduction. We will concentrate on studies in our laboratory that have examined effects of variable maternal energy availability (through dietary manipulation or naturally occurring variation in maternal condition) or variable fetal/infant demand (through naturally occurring variation in litter size) on outcomes throughout the reproductive cycle—i.e., from ovulation that begins the process through weaning of the resultant offspring. We will then relate these findings to what is known regarding reproduction in wild common marmosets and attempt to integrate all of these findings into an understanding of reproductive strategy in this species. We end with a brief discussion of the way in which the marmoset example illustrates the importance of integrating an understanding of both adaptation and constraint in theories on reproductive strategy. All references to marmosets in this chapter, unless otherwise indicated, refer to common marmosets (*Callithrix jacchus*).

8.2 Captive Studies

8.2.1 *Ovulation*

Ovulation is the culmination of the process of folliculogenesis taking place in the ovary. Folliculogenesis results in an oocyte and its associated support cells (i.e., the ovarian follicle) maturing to the point that sustained luteinizing hormone (LH) exposure will result in expulsion of the oocyte (ovulation) and subsequent formation of a corpus luteum. Folliculogenesis is controlled by both intra- and interovarian feedback mechanisms (Saltzman et al. 2011). Marmoset females who are not dominant within their group often display suppressed ovulation, likely due to disruption of normal LH pulsatility (Abbott et al. 2009). Work by Saltzman et al. (1997a, b) provides an excellent overview of the relation of proximate social factors to physiological and behavioral suppression of captive marmoset females.

The process of folliculogenesis culminating in ovulation is, therefore, sensitive to social cues in the marmoset. It is also sensitive to environmental cues in terms of the number of ova ultimately ovulated. In captivity, marmosets have produced litter sizes varying from 1 to 6, with 2–3 per litter being the most common. Litter sizes of 1–3 have been documented in the wild (Dixon et al. 1992; Bales et al. 2001), with identifiable litters of 3 being extremely rare. In the captive setting, maternal body condition is related to ovulation number and litter size, with females who are larger or are in positive energy balance (i.e., gaining weight) during the follicular phase of a cycle being more likely to ovulate larger numbers of ova (Tardif and Jaquish 1997).

8.2.2 *Pregnancy*

A long pregnancy (143 days) that produces more than one relatively precocial offspring offers many opportunities to adjust investment throughout gestation. With pregnancy loss assessed by urinary steroid monitoring, Heger et al. (1988), found that 28% of pregnancies were lost prior to day 40, a figure that is lower than estimates for humans (73%; Bolage 1990) or baboons (60%; Kuehl et al. 1992). However, marmosets display a higher percentage of spontaneous pregnancy loss in mid- to late pregnancy, with 16–22% of pregnancies aborting during that period (Heger et al. 1988; Jaquish et al. 1996). The developmental trajectory of marmosets is delayed compared to humans and Old World monkeys (Merker et al. 1988; Smith and Moore 1988), so it is perhaps not surprising that pregnancy loss is more common later in pregnancy in this species. Marmosets have relatively frequent in utero litter size reduction, frequently occurring relatively late into pregnancy. In an ultrasound survey of 39 marmoset pregnancies proceeding to term, 7.2% had a reduction of litter size in utero from either two to one or three to two (Jaquish et al. 1996).

The relationship of spontaneous pregnancy loss and in utero litter size reduction to maternal condition is not as well studied as that between maternal condition and

ovulation. However, there are some findings to support the idea that these losses are related to maternal condition. Identifiable illness was reported to be associated with a large percentage of aborted pregnancies (Jaquish et al. 1996). Similarly, marmoset females weighed significantly less during early pregnancies in which they subsequently experienced litter size reduction than during pregnancies with no litter size reduction (Tardif and Jaquish 1994).

The effect of manipulating maternal condition was examined by limiting pregnant females to 75% of estimated ad libitum caloric intake during either mid- or late pregnancy (Tardif et al. 2004). The effects were strikingly different between the two periods. All females ($n=8$) who were restricted during midpregnancy (the period of exponential placental growth) aborted their pregnancies. Of females who were not restricted until late pregnancy, 4/7 went to term with normal-sized neonates while 3/7 delivered preterm. In late pregnancy, both the female's prepregnancy weight and her weight loss were related to preterm delivery—females who started smaller and females who lost more grams per day during restriction were more likely to have preterm deliveries.

8.2.3 *Lactation*

Based upon caloric consumption during gestation and lactation, Nievergelt and Martin (1999) found a negligible difference in consumption during gestation, where at peak lactation the daily caloric consumption of a captive marmoset female doubles. Lactation, therefore, is a substantial energetic cost to the marmoset mother. This daily cost is substantially higher than that for larger bodied primates, such as baboons (Roberts et al. 1985).

We examined the relationship between infant growth, milk composition, litter size, and maternal size in captive marmosets (Tardif et al. 2001). Large and small mothers supported comparable growth in singletons and had similar milk composition. However, small mothers appeared to be challenged when rearing twins. Small mothers rearing twins had lower percentage milk fat and lower gross milk energy than large mothers with twins, and they supported significantly less growth, in terms of grams/day/litter. Small mothers rearing twins also were significantly more likely to lose weight during lactation and were more likely to be infertile in the subsequent year.

We subsequently examined the effects of restricting caloric intake during lactation in females rearing twins who all fell into the "large" category as defined in Tardif et al. (2001). This study involved four dams that were fed ad libitum and five dams that were restricted to 75% of estimated peak lactational caloric intake. Both controls and restricted dams were fed by placing the dam in one half of the home cage for four feeding periods of 1.5–2 h, spread throughout the day from 0800 to 1700 h. Food was available to the group only during that time. The mesh door between the two halves of the cage was constructed such that infants could move between the sides once they were mobile. This feeding regime was used from postpartum day 5 to day 65.

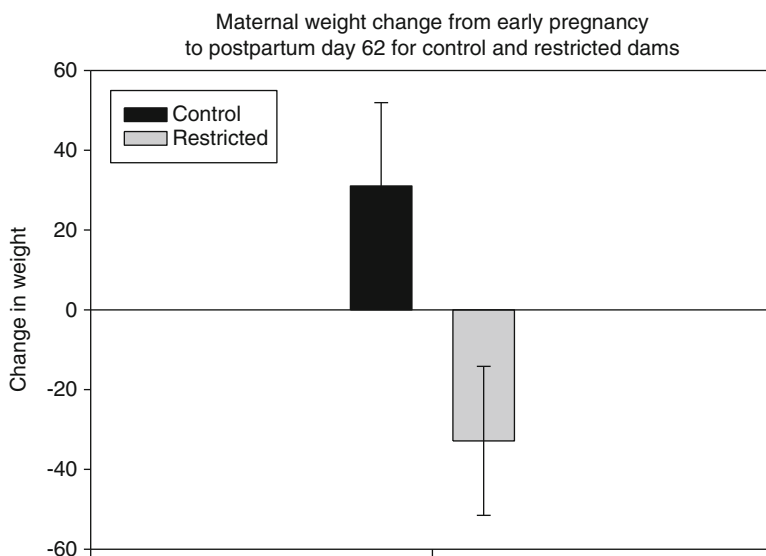


Fig. 8.1 Maternal change in weight (in grams) from birth to day 62 postpartum for controls (separately fed ad libitum) and restricted (separately fed at 75% of expected ad libitum consumption). See text for more details on feeding regimen

Figures 8.1, 8.2, and 8.3 illustrate the changes in maternal condition and infant growth for restricted versus control lactating females. The weight gain of the control females during lactation (Fig. 8.1) was similar to that of the large dams nursing twins in a nonmanipulated environment (Tardif et al. 2001)—an average gain of around 0.5 g/day in each case. Restricted females, however, lost weight during lactation—an average of around 30 g over the course of lactation or around 0.5 g/day.

Infants from restricted and control dams did not differ in birth weight. However, infants of restricted dams gain significantly less weight during the preweaning period (Figs. 8.2 and 8.3). After day 62, the difference was no longer significant, suggesting that the infants of restricted dams may have undergone catch-up growth.

8.2.4 Maternal Behavior

The most notable infant care behavior in marmosets, as with other primates, is transport of the infants. In captivity, infants are carried continuously for about the first month of life. From one to about 3 months of age, they are carried less and less often, both as a result of rejection by carriers and due to their spontaneous interest in moving off the carriers and exploring their environment. After about four months of age, they are rarely carried unless there is a disturbance in the group (Ingram 1977; Tardif et al. 1986; Yamamoto 1993).

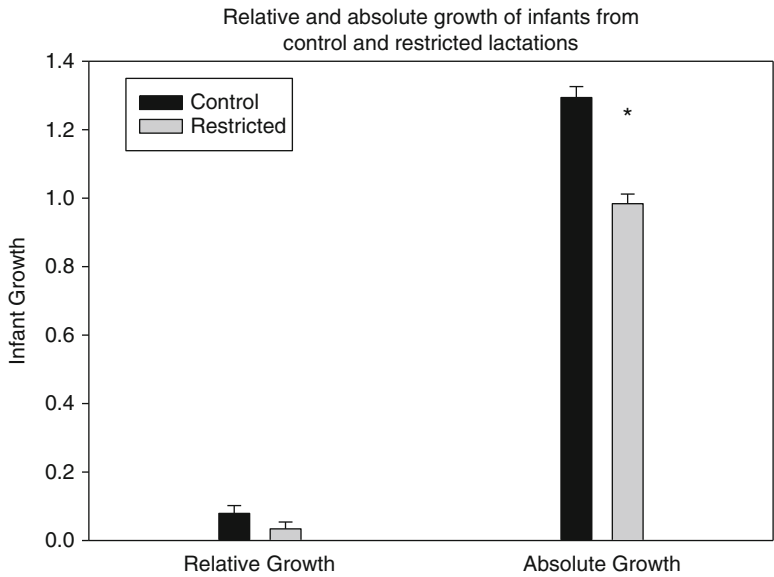


Fig. 8.2 Relative (g/g/day) and absolute (g/day) growth in infants, days 0–62, from control and restricted dams. Controls dams separately fed *ad libitum* and restricted dams separately fed at 75% of expected *ad libitum* consumption. See text for more details on feeding regimen

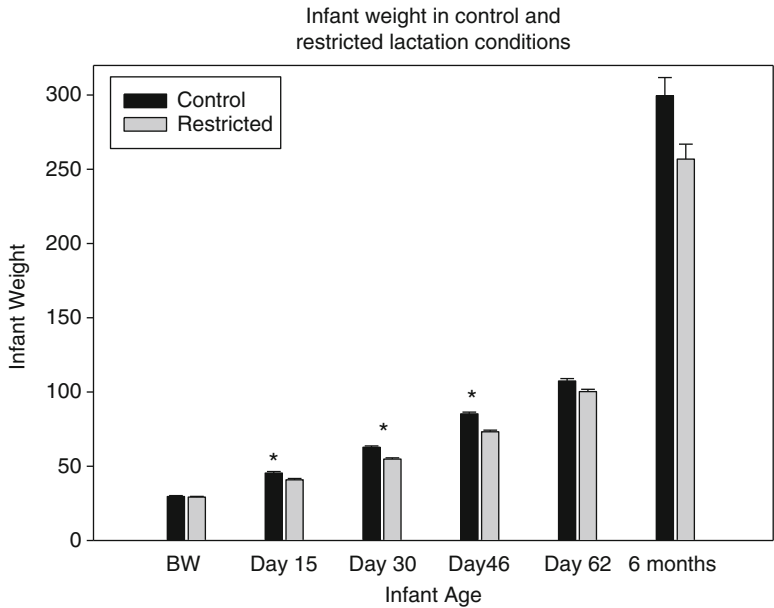


Fig. 8.3 Infant weight (grams)×infant age for infants from control and restricted dams. Control dams separately fed *ad libitum* and restricted dams separately fed at 75% of expected *ad libitum* consumption. See text for more details on feeding regimen

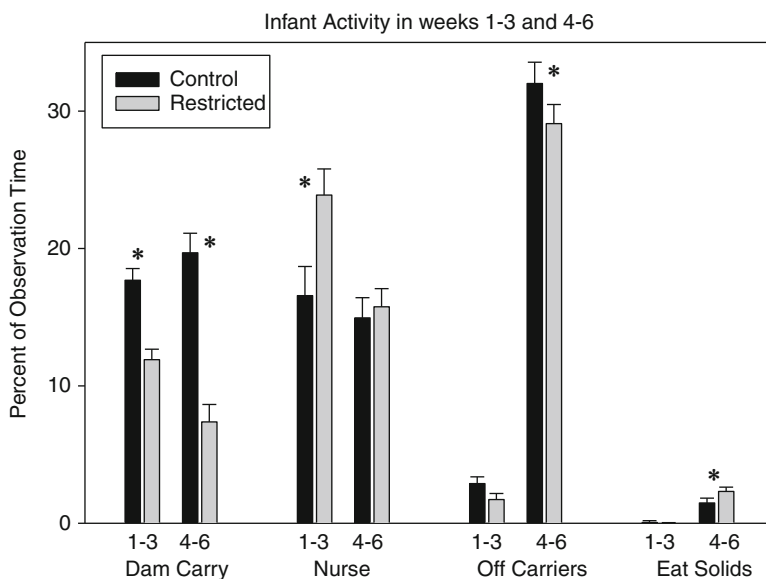


Fig. 8.4 Percent of observation time that infants from control versus restricted dams participated in selected behaviors. Control dams separately fed ad libitum and restricted dams separately fed at 75% of expected ad libitum consumption. See text for more details on feeding regimen

Common marmoset mothers typically carry infants about 20–30% of the time. Pryce (1993) provides an excellent model of the roles of motivation to retrieve and reject carried infants in producing patterns of infant care seen in a communal care species like marmosets. Both the mother’s drive to retrieve the infants as desirable objects and from signals related to breast fullness and the mother’s drive to reject the infants will determine the length of time she carries infants. One factor that appears to be important in marmosets as a determinant of rejection is the drive to perform other activities such as feeding. Studies in captivity and the wild indicate that marmosets and tamarins are poor “multitaskers” and are much less likely to travel or forage while carrying infants (Goldizen 1987; Price 1992; Tardif 1997).

Do marmoset mothers who are under more severe energetic constraints spend less time carrying infants? Our study of naturally occurring differences in maternal size and litter size did not indicate that small dams nursing twins were less likely to carry infants; however, they did have a lower frequency of nursing bouts during the preweaning period. In the controlled restriction study (Fig. 8.4), restricted dams did carry infants less often; however, they nursed them more often during the preweaning period (weeks 1–3). Taken together, these results suggest that nursing behaviors are not grossly affected in a consistent manner by maternal energetic constraints. However, time spent carrying infants during non-nursing periods may be reduced when the mother is restricted. In a separate study of maternal behavior toward twins versus triplets during the first week following birth, we found strong effects of having a supernumerary infant on maternal behavior (Tardif et al. 2002).

Mothers with three infants had shorter carrying bouts, and significantly more bouts ended with maternal harassment. This finding that marmoset mothers appear to tolerate only a limited amount of time transporting infants, regardless of litter size, supports the contention of Harper (1981) that “there may be lower and upper limits for frequency or intensity of offspring stimulation that, on average, serve as reliable boundaries, below or above which it would be uneconomical to invest at all or at current levels.”

8.3 Marmoset Maternal Investment in the Wild

Significantly less information is available on maternal investment of marmosets in the wild. One of the longest field studies of *Callithrix jacchus* is the 10-year study at Nisia Floresta (Digby and Barreto 1993; Arruda et al. 2005; Yamamoto et al. 2009) involving up to 14 breeding groups. Data on maternal condition and infant growth are not available for this population; data on frequency of parturition and survival of offspring are available.

Data on interbirth intervals and limited data on female weight change suggests that, as in captivity, losses are occurring throughout pregnancy in wild marmosets. Yamamoto et al. (2009) report that interbirth intervals are significantly longer in groups with more than one breeding female (7.5 months) than in groups with only one breeding female (5.7 months). With a gestation period of 4.7 months and an average postpartum ovulation, in captivity, at around day 10, an interbirth interval of approximately 5 months would be expected for a successful postpartum estrus following a successful parturition. The interbirth intervals observed in the wild suggest that there is either a longer anovulatory period following parturition or there are likely undetected early pregnancy losses. Also reported for this population are weight changes in three females indicative of being in late gestation with no evidence of live infants at any point, suggesting that there are also incidences of late pregnancy loss in this population. The relation of any of these pregnancy losses in wild common marmosets to maternal condition is unknown. However, Bales et al. (2001) report a strong association between higher maternal weight and number of live births in the golden lion tamarin (*Leontopithecus rosalia*).

Marmoset infant survival is related to maternal breeding tenure. First parturitions with live offspring often suffered infant mortality prior to 5 months of age, particularly for females who were secondary breeders in a group. Arruda et al. (2005) defined groups containing these females as “pseudo-polygynous” in that, while two females became pregnant and often both carried pregnancies to term, the most common final outcome was only one female successfully weaning any offspring. The end of reproductive tenure is also associated with increased likelihood of infant mortality (Tardif et al. 2008). For seven dominant breeding females followed throughout their reproductive tenure, infant survival averaged 89% for their first two litters but only 51% for their last two litters. Particularly intriguing is the finding that the age of infant loss differed between early and late tenure,

with all of the early tenure loss being during the weaning/postweaning period while 36% of the late tenure loss was during months 0–2 when infants are subsisting almost entirely on milk.

8.4 When to Invest and When to “Cut Bait”

Female marmosets exist in a reproductive environment that is unusually competitive. As opposed to most primates—indeed as opposed to most mammals—many females live long into adulthood without reproducing. Physiological and behavioral factors result in limited to no successful reproduction in females who are not dominant in their territory. Physiological suppression of subordinates has long been recognized (Abbott et al. 2009). More recently, well-documented cases of infanticide by dominant females of the offspring of subordinates (Digby and Saltzman 2009), both in captivity and in the wild, reveal the extent to which dominant females will attempt to ensure that the resources of the cooperative breeding group are available for her infants. Females who have the opportunity to reproduce as the dominant female in an established territory may, in theory, produce as many as 24 viable offspring (4 per year for up to 6 years) in their reproductive lifetime (Smucny et al. 2004; Tardif et al. 2008).

The strategy adopted by marmosets results in many reproductive steps in which the female’s investment may be modified including what litter size to gestate and how much to invest in each infant, what litter size to support through lactation and how much to invest in each infant, amount of time spent carrying, amount of time spent provisioning, and, ultimately, whether to reproduce or not (Fig. 8.5). Data from captive studies suggest that, for most if not all of these steps, physiological pathways exist that allow for maternal condition to be used as a cue, though the specific manner in which the cue is sensed and transduced is generally not known.

In terms of ovulation, social cues appear to be the primary driver of whether or not females undergo suppression of ovulation. The adaptive arguments regarding how this physiological “decision” is made have been explored recently in Yamamoto et al. (2009), Digby and Saltzman (2009), and Saltzman et al. (2009) and, in the broader sense of cooperative breeding, in general, by Emlen (1995; Emlen et al. 1998). These discussions generally propose that there is advantage to the nondominant female of extreme flexibility as to whether to reproduce when reproduction is unlikely to be successful without the significant resources of an established territory and a minimum-sized social group, but chances of gaining the dominant position in a territory are unpredictable, and dispersal is a risky proposition.

The possible adaptive significance of environmental cues affecting ovulation number has not, until recently, been discussed. It was long assumed that ovulation numbers higher than two were an artifact of captivity; however, with reports of identifiable, viable triplet litters in the wild, it is now clear that the same factors may on occasion operate in the wild, raising the interesting possibility that the effects of environmental cues on ovulation number might be relevant to wild populations. Rutherford

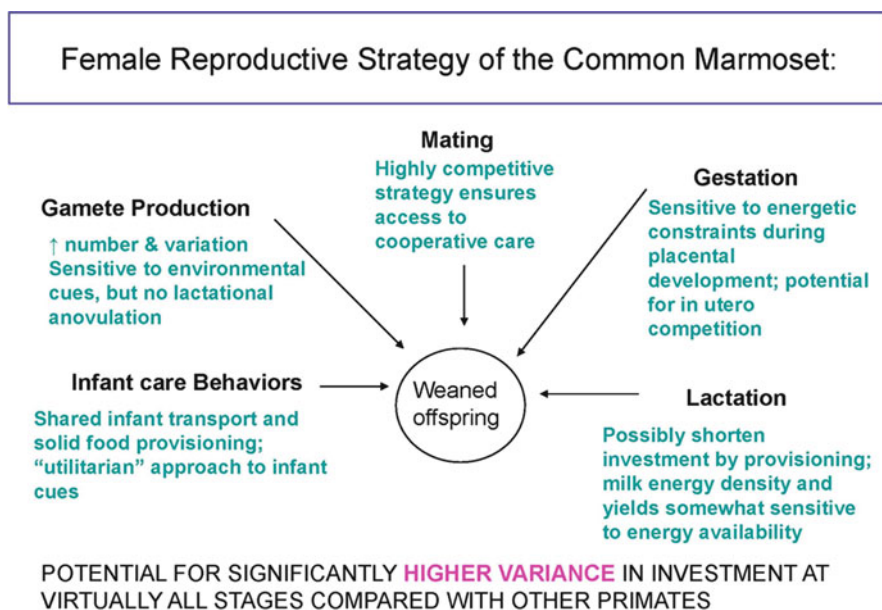


Fig. 8.5 Choice points for altering investment in reproduction by marmoset females

(Rutherford and Tardif 2008, 2009a, b) has recently proposed the interesting possibility that this litter size variation might result in variable in utero competition for resources. This variable competitive environment in utero might be a means to affect postnatal outcomes, even if the ultimate outcome is not to rear three offspring at a time. In addition, the potential for litter size reduction in utero throughout pregnancy may mean that additional fetuses can be maintained at minimal cost.

Data from captive marmosets indicates, as expected, that mothers are less likely to completely abandon a reproductive attempt (i.e., “cut bait”), the further into the attempt they have ventured. Restriction of maternal energy availability has a much more marked effect in early or midpregnancy than in late pregnancy or lactation. In late pregnancy and lactation, mothers with restricted reserves or with higher demand are most likely to proceed to produce viable offspring. In late pregnancy, they have the physiological option of litter size reduction. During lactation, investment in those offspring, as assessed by their growth, is reduced when mothers have low resources and/or high demand.

Perhaps as importantly, the demand appears to take a toll on the mothers, even in the relatively benign captive environment, such that small mothers lactating for twin offspring are less likely to reproduce in the coming year. It is possible that these females, in a wild environment, would simply have forgone reproduction. However, it is interesting to note that the final reproductive event in a female’s tenure as a dominant breeder in the wild is characterized by poorer outcomes, including a higher likelihood of losing infants during the early lactation period.

A scenario in which nondominant females are variably sensitive to the condition of the dominant female, or in which the cues provided by the dominant female vary according to the likelihood she can retain her dominant status, would result in the reproductive pattern seen in the wild. Nondominant females would be expected to periodically attempt reproduction, often with marginal success. In such a scenario, sensitivity of investment to environmental constraints would be extremely valuable. Dominant females, on the other hand, need to balance their investment in present reproduction with the ability to maintain dominant status and invest in future reproduction.

8.5 Implications and Future Directions

As indicated from the breadth of the chapters in this volume, the miraculous and complex process of building a baby can be examined from a myriad of directions. However, this complex process ultimately serves a straightforward evolutionary goal—to put as many replicates of an organism’s DNA into the next generation as possible, relative to the competition (i.e., conspecifics). For that reason, the processes involved in “baby-building” bear the marks of selection pressures that have shaped those processes over time. Primates are a lineage in which those selection pressures have resulted in long-lived organisms that devote considerable resources to each DNA replicate—i.e., individual offspring. A modal litter size of one, a relatively long gestation period, an even longer lactation period with relatively low quality milk, and a strong, prolonged physical association between mothers and offspring are all part of the adaptive landscape of primate reproduction.

Starting with this adaptive landscape, callitrichid primates have undergone reduction in body size linked with dietary diversification (Marroig and Cheverud 2009, 2005). It is proposed that production of litters and a fertile postpartum estrus in callitrichid primates is likely the result of selection pressures stemming from small body size, such as increased predation (Eisenberg 1981), driving a higher reproductive output. Some models propose that cooperative breeding, and associated female reproductive suppression, would follow selection for litter production in an anthropoid primate, while others propose that it preceded and is a necessary prerequisite for production and rearing of litters (reviewed in Caine 1993). In either case, the callitrichid lineage represents a fascinating group in which to examine reproductive adaption, given that it has undergone selection pressures that likely acted counter to those that shaped the underlying adaptive landscape of primate reproduction. Table 8.1 lists reproductive traits of female marmosets that are part of their primate ancestry (representing phylogenetic constraint) and those that most likely represent the unique evolutionary trajectory of the group.

As described in this chapter, we are beginning to decipher the outcomes of the “decisions” made by marmoset females as to whether to invest in a given reproductive event. Marmoset females are exquisitely sensitive to environmental cues—social and energetic—and these cues appear to affect whether and how much

Table 8.1 Female marmoset reproduction: constraints and adaptations

Phylogenetic constraints	Possible adaptations related to smaller size
Underlying hypothalamic–pituitary–gonadal function for single ovulations	Increased baseline ovulation number and susceptibility to cueing signals
Hemochorial placenta, simplex uterus, slow fetal growth rate	Prolongation of early gestation events with increased sensitivity to cueing signals
Low milk energy density, slow growth rates	Relatively short lactation period, provisioning of infants during the weaning period
Strong attraction to and tolerance of infants	Modifications in attraction and tolerance that result in cooperative care and in infanticide by dominant females of subordinates' infants

females invest in all phases of reproduction. We do not, however, yet understand the underlying mechanisms that result in these “decisions.” Adaptive alterations in neural, endocrine, and autocrine systems that sense environmental changes and signal those changes to systems controlling reproductive function can be hypothesized for marmosets, based upon what is known regarding function in other well-characterized species. For example, many single gene changes in autocrine factors (e.g., bone morphogenic protein 15, BMP15, growth and differentiation factor 9, GDF9) are known to alter ovulation number and sensitivity of ovulation number to maternal energy availability in sheep and these well-characterized effects offer a set of likely candidates for selection in marmosets (Tardif and Ross 2009). Researchers are now poised to hunt for these candidates and the recent sequencing of the marmoset genome (<http://www.hgsc.bcm.tmc.edu/project-species-p-Marmoset.hgsc?pageLocation=Marmoset>) will be instrumental in this discovery process. Bernstein (2010) offers an elegant description of how endocrine and autocrine systems may leave a “signature” of the selection processes which have shaped a given biological process. We are now poised to identify such signatures in the systems that control reproductive “decision-making” in marmoset monkeys. One intriguing possibility is that changes in genes controlling the growth hormone—IGF axis could link selection for small body size with altered reproductive function in these smallest of the anthropoid primates, as IGF signaling is known to play important roles in folliculogenesis, placentation, and fetal growth as well as controlling post-natal growth. Marmosets, therefore, are an intriguing natural experiment with much remaining to be discovered from them about the ways in which reproduction “decisions” are made.

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Part III
Milk: Complete Nutrition for the Infant

Chapter 9

Lactational Programming of Infant Behavioral Phenotype

Katie Hinde

Keywords Milk • Cortisol • Temperament • Development • Maternal Effects

9.1 Introduction

Imagine a magic potion. This potion includes all of your calories and hydration for the day. It has fatty acids for your brain, amino acids for your muscles, and essential vitamins and minerals for your cellular processes. This potion provides immunoglobulins to protect you from pathogens and hormonal cues about your mother and the environment. This potion delivers bacteria that colonize your gut and then continues to provide specialized nutrients for those beneficial bacteria. Oh, and one last thing, your mom makes it just for you. This magic potion, of course, is milk.

The synthesis of milk by mammary glands is the defining characteristic of our mammalian class. Identifying the composition of milk, and the volume produced, is foundational to understanding lactation strategies in all mammalian taxa. As you are reading this sentence, hundreds of scientists around the world are investigating what exactly milk is composed of (we still don't know!), how milk is synthesized, and how infants assimilate milk. Most milk science, however, is applied, and our knowledge of milk is primarily pieced together from the dairy industry, cancer research on mammary gland biology, and agenda-driven contrasts of formula-feeding vs. breast-feeding. Much less is known about milk from an evolutionary biological perspective, and a systematic understanding of the magnitude, sources, and consequences of variation in mother's milk largely eludes us. For example, gross milk

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composition has been described for fewer than 40 primate taxa. From the data that are available, it is clear that milk composition varies among taxa as a function of phylogeny, ecology, diet, life history, and maternal behavior (reviewed in Oftedal and Iverson 1995; Hinde and Milligan 2011). Additionally, maternal parasite load, parity, and energy balance¹ have all been shown to influence milk composition and yield among individual mothers within primate taxa (reviewed in Hinde and Milligan 2011).

Milk, however, is not merely a product of the mother and her environment. Mother's milk reflects a complex physiological and behavioral negotiation between the mother and the infant. This negotiation begins during pregnancy when the mammary gland functionally develops and is potentially sensitive to fetal signals (Hinde and Milligan 2011). Postnatally, mothers can behaviorally restrict nipple access, thereby down-regulating milk synthesis, and infants can throw tantrums to gain nipple access, consequently up-regulating milk synthesis (Hinde and Milligan 2011). Lastly, what an infant does with the milk he ingests is crucial to understanding what milk is. Indeed, determining milk's myriad influences on infant developmental trajectories is critical not just from an evolutionary perspective; it also has implications for global public health. Despite the benefits to be gained from such research, at the time of publication of this book, we still know relatively little about infant development as a function of mother's milk, and the ways that milk shapes infant behavior is particularly under-explored.

The goal of the present chapter is to familiarize the reader with the limited body of knowledge on mother's milk and infant behavior and thereby motivate future investigations on the complex inter-relationships among early nutrition, neurodevelopment, and behavioral phenotype. After briefly summarizing what is known about mother's milk and infant growth, I will provide a conceptual framework for "behavioral phenotype" and discuss attributes of mother's milk that have been associated with infant behavioral phenotype. To date, this has only been directly studied in rodents and rhesus macaques, and cortisol (corticosterone in rodents) is the milk constituent that has received the greatest research effort. I will then explore the potential proximate mechanisms by which cortisol and other milk attributes mediate metabolic and neurobiological development and thereby influence infant behavior.

¹Energy balance reflects the ratio of energy intake vs. energy expenditure. When these are equal, an individual is in neutral energy balance and is neither gaining nor losing body mass. Negative energy balance is when an individual's energy expenditure exceeds energy intake, requiring the mobilization of body reserves for somatic maintenance and body mass decreases. Positive energy balance occurs when energy intake exceeds energy expenditure and individuals are gaining mass.

9.2 Milk and Infant Development

The volume of milk and its energetic density—the kilocalories per gram from fat, protein, and sugar—influence infant growth rates, both among (Riek 2008) and within species (Table 9.1). Such a relationship is not surprising given that mammalian infants rely entirely on milk energy for somatic maintenance and growth during the early postnatal period, and milk often remains a significant source of calories during transitional phases to solid foods (Langer 2003, 2008; Sellen 2007). Experimental manipulation of dietary intake in baboons revealed that mothers in negative energy balance significantly decreased milk yield, though milk energy density remained constant, and their infants stopped growing (Roberts et al. 1985). Similarly, milk yield has been most predictive of infant growth for rhesus macaque and human infants. This is because milk yield varies to a much greater extent than does milk energy density among mothers (Hinde et al. 2009; Hinde 2009; Butte et al. 1984). For small-bodied callitrichine primates like marmosets that have a higher metabolism and “faster” life histories, infant growth may be more sensitive to milk energy than for more slowly growing anthropoids. Indeed, among common marmosets, small mothers rearing twins produced lower fat concentrations in milk and had lower milk energy output, and their infants grew more slowly than did the infants of larger mothers (Tardif et al. 2001).

Most mammalian infants, however, are not allocating milk energy solely to somatic growth and development. This is particularly true for infants of taxa characterized by social complexity. Infants begin to behaviorally engage with conspecifics early in the postnatal period, and both literally and figuratively take their first steps

Table 9.1 A selection of representative publications in which studies have demonstrated that individual differences in milk composition and/or volume, among mothers within a single taxa, are positively correlated with infant growth rates

Taxon	Common names	Representative references
Bovidae	Domestic cow, water buffalo	Wilson et al. (1969) and El-Masry and Marai (1991)
Cervidae	Iberian red deer, black-tailed deer	Landete-Castillejos et al. (2001) and Sadler (1980)
Marsupialia	Tamar wallaby, ringtail possum	Trott et al. (2003) and Munks and Green (1997)
Pinnipedia	Sea lion, fur seal, gray seal, Southern elephant seal	Iverson et al. (1993), Mellish et al. (1999), Lydersen et al. (1995), Hindell et al. (1994) and Arnould and Hindell (2002)
Primates	Baboon, common marmoset, rhesus macaque, human	Roberts et al. (1985), Tardif et al. (2001), Hinde et al. (2009) and Butte et al. (1984)
Rodentia	Cotton rat, Sprague–Dawley rat	Rogowitz and McClure (1995) and Del Prado et al. (1997)
Suridae	Domestic pig	Averette et al. (1999) and Revell et al. (1998)
Ursidae	Polar bear, black bear	Arnould and Ramsay (1994) and Oftedal et al. (1993)

into their social world (Altmann 1980; Fairbanks 2000). Infants are energetically dependent on mother's milk to sustain activity and social interactions. We know that activity patterns are sensitive to energy balance and ecological gradients (humans, Dauncey 1990; *Macaca fuscata*, Jaman and Huffman 2008), in particular infant and juvenile play behavior decreases under poor ecological conditions (humans, Bock and Johnson 2004; *Trachypithecus leucocephalus*, Li and Rogers 2004; *Rattus norvegicus*, Sivi and Panksepp 1985; *Saimiri sciureus*, Stone 2008). Presumably, infants growing up in social groups in marginal ecological conditions are limiting energy expenditure because the milk they receive from their mother cannot sustain play behavior. We can extrapolate further to hypothesize that variation in milk synthesis among individual mothers—as a function of their nutrition, health, body mass, and residual reproductive value—may affect infant activity patterns with lasting consequences for behavioral phenotype. Indeed, the early expansion of the infant's behavioral repertoire is coincident with critical windows of neurodevelopment (Fairbanks 2000). A handful of studies in rodents and primates are beginning to demonstrate that mother's milk contributes to the organization of behavioral phenotype in offspring.

9.3 Behavioral Phenotype

Before we can delve into milk's influences on infant behavioral phenotype, it is important to operationalize the term. For our purposes here, behavioral phenotype is the observable *behavioral* characteristics of an individual resulting from the interaction of its genotype with the environment, often manifested in a suite of covarying behaviors (Johnson et al. 1976). When an individual's behavior and/or response to stimuli are consistent across time and situation, it is considered a stable, trait-like quality of that individual. For example, when exposed to a novel conspecific, individual monkeys will approach, retreat, or remain stationary in response. This experimental manipulation in primates, known as the "Intruder Challenge," reliably differentiates individuals along a spectrum from socially impulsive to socially inhibited (*Macaca fascicularis*, Manuck et al. 2003; *Chlorocebus pygerythrus*, Fairbanks 2001; *Callithrix kuhlii*, Kinnally et al. 2006). The terms for the phenomenon of stable, individual differences in behavior vary widely among disciplines and include personality, temperament, coping style, behavioral syndrome, and behavioral dispositions (Gosling 2001; Weinstein et al. 2008; Sih et al. 2004; Stamps and Groothuis 2010; Hinde and Capitano 2010; Koolhaas et al. 2010). Similarly, the terms for the traits that characterize specific dimensions of this phenomenon often reflect a particular method or theoretical approach (e.g., bold, impulsive, confident, extroverted) (Weinstein et al. 2008). Despite this lexical variability,² there is substantial

² When describing published studies in detail, I will use the same terms used by the investigators conducting the research. Elsewhere I will primarily use "behavioral phenotype," the most inclusive term for individual behavior.

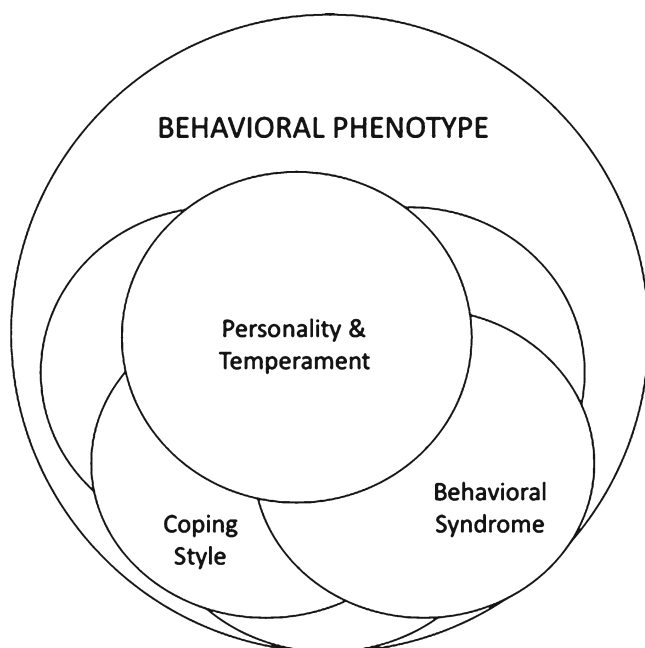


Fig. 9.1 Various terms have been used to describe individual differences in behavior. “Behavioral Phenotype” subsumes overlapping categories of individual differences in behavior that are stable across time and context

but imperfect semantic overlap among disciplines (Stamps and Groothuis 2010; Uher 2011) (Fig. 9.1). For a comprehensive treatise on the theory, methods, and terminology among these complementary approaches, I direct the reader to an excellent review by Uher (2011).

Personality, long the domain of psychology, has become increasingly relevant to the fields of animal behavior, primatology, and biological anthropology because stable individual differences in behavioral phenotype can have consequences for fitness (Smith and Blumstein 2008; Réale et al. 2007). Behavioral phenotype determines how individuals forage and defend food resources (*Branta leucopsis*, Kurvers et al. 2010; *Dama dama*, Bergvall et al. 2011), detect and evade predators (*Amatitlania nigrofasciata*, Jones and Godin 2010; *Marmota vancouverensis*, Blumstein et al. 2006; *Fringilla coelebs*, Quinn et al. 2011), acquire and combat pathogens (*Homo sapiens*, Cohen et al. 2003; *Macaca mulatta*, Capitanio et al. 2008), court and retain mates (for review see Schuett et al. 2010), and produce and rear offspring (*Parus major*, Both et al. 2005; *Papio cynocephalus*, Silk et al. 2009). A meta-analysis across insects, fish, birds, and mammals revealed that greater “boldness” was associated with improved survival and greater reproductive success (Smith and Blumstein 2008). For male primates, higher-ranking males often have priority access to estrus females (*Eulemur fulvus rufus*, Kappeler and Port 2008; *Propithecus verreauxi*, Kappeler and Schaffler 2008; *Macaca mulatta*,

Widdig et al. 2004; *M. fascicularis*, de Ruiter et al. 1994; *Papio cynocephalus*, Alberts et al. 2003; *Gorilla beringei beringei*, Bradley et al. 2005; *Pan troglodytes*, Boesch et al. 2006; for a meta-analysis see Cowlshaw and Dunbar 1991), and behavioral phenotype may influence rank acquisition. For example, juvenile vervet monkeys (*C. pygerythrus*) that were socially impulsive, e.g., they quickly approached a novel male during the Intruder Challenge, were more likely to achieve alpha status as adults, especially if they were larger and had low levels of the serotonin metabolite 5-HIAA (Fairbanks et al. 2004). Behavioral phenotype may also affect female reproductive success; wild baboon females that are characterized as more sociable, after controlling for rank, are more likely to produce an infant that survives the first year of life compared to females that are less sociable (*Papio cynocephalus*, Silk et al. 2003, 2009).

Although the above examples suggest that behavioral phenotype ought to be under directional selection, multiple behavioral phenotypes are thought to be maintained within a species as a result of numerous evolutionary forces. Because behavioral phenotype represents a set of correlated behavioral traits that are both polygenic and pleiotropic—multiple genes contribute to each personality dimension and individual genes can contribute to multiple dimensions of personality—many behavioral phenotypes emerge (Sih et al. 2004; van Oers and Mueller 2010; Stamps and Groothuis 2010). Frequency-dependent selection may occur within the social group or population as individuals of different behavioral phenotypes interact with one another (Wolf et al. 2007; Wolf and Weissing 2010, reviewed in Dingemanse and Wolf 2010). Further to this, evidence is mounting that larger group size favors the development of traits that convey individual identity (alarm calls in sciurids, Pollard and Blumstein 2011; olfactory cues in *Mesocricetus auratus*, Johnston and Peng 2008; for reviews see Tibbetts and Dale 2007; Beecher 1989), which may in part account for the variability of behavioral phenotypes. Individual behavioral phenotype in socially complex mammals may be important for establishing reputation and facilitating coordination and cooperation (van Schaik and Kappeler 2006; Bergmüller et al. 2010). Fluctuating ecological conditions across time and space are unlikely to consistently favor a particular behavioral phenotype in such a way that underlying genes attain fixation (Nettle 2006; Sih et al. 2004; van Oers and Mueller 2010; Dochtermann and Roff 2010). For a deer in the meadow, being twitterpated can be dangerous when “man is in the forest,” but not so much if the deer, the man, and the meadow are in Yosemite National Park.

Given that ecological conditions vary and social partners change, why then don't individuals retain maximal behavioral flexibility so that they may respond optimally in all contexts? Researchers think that behavioral phenotype emerges as a function of tradeoffs (reviewed in Sih et al. 2004; Stamps and Groothuis 2010). An example would be the tradeoff between responding quickly vs. accurately. For example, consider the case of a juvenile vervet foraging on the margin of the social group. Nearby, the bushes rustle. Is it the wind, a leopard poised to pounce, a buddy eager to play, or a Thompson gazelle grazing placidly? Perfect knowledge takes investigation, which would be incredibly risky if it is the leopard. On the other hand, running away at every fluttering leaf is energetically costly. The main

currency of selection is reproductive success, dependent on both survival and energy; therefore, most individuals are likely to fall at intermediate points along a spectrum from bold to shy. In this way, behavioral phenotype affords organisms a readily accessible, but necessarily imperfect, system for engaging with their environment and the other organisms in it.

Lastly, behavioral phenotype is a product of ontogeny and is sensitive to inputs and experiences during development (Groothuis and Trillmich 2011; Trillmich and Hudson 2011). Returning to the rustling bushes example above, nonthreatening stimuli regularly elicit alarm calls from vervet infants and juveniles. Over time, by monitoring the lack of a response from adults, they learn to accurately identify and signal the presence of actual predators (Seyfarth et al. 1980; Seyfarth and Cheney 1980, 1986). Since this calibration of predator response involves social learning, we can predict that the composition of the behavioral phenotypes in a social group affects the development of an individual's behavioral phenotype in addition to the genetic predisposition that individual may have along a bold-shy, or impulsive-inhibited, personality dimension. Indeed, organisms adaptively organize themselves in response to cues from their environment by directly assessing the local ecology and their own condition as well as via signals from their mother or other individuals. This process is necessarily contingent on phenotypic plasticity during development.

Metabolism, growth, immune function, neurobiology, reproduction, and health throughout life are all known to be responsive to conditions during early development (for comprehensive reviews see West-Eberhard 2003; Hochberg et al. 2011), but behavioral phenotype may also be organized by early environment, as initially and most dramatically demonstrated by Harlow (Blum 2002). More relevant to this chapter, Meaney and colleagues have demonstrated in Long-Evans rats that variation among mothers in maternal care—specifically, arched back nursing position and frequency of licking/grooming during nursing—programs exploratory, playful, and fearful behaviors after weaning (Szyf et al. 2007; Parent and Meaney 2008; Fish et al. 2004). Macaque mothers under conditions of variable foraging demand were more rejecting of their infants who were consequently less playful and exploratory and, as juveniles, were less sociable and more likely to be subordinate in newly formed groups (Andrews and Rosenblum 1994; Andrews et al. 1993; Rosenblum et al. 2001). To date, these and the many other investigations of maternal influences on the development of infant behavioral phenotype (reviewed in Sachser et al. 2011; Maestripieri 2009; Fairbanks 1996) have not ascertained if mother's milk may have contributed to these outcomes. This is particularly unfortunate because mother's milk is the postnatal continuation of early nutritional programming which has well-established consequences when mediated through the placenta during fetal development (Rutherford 2012). Moreover, variable foraging demand can alter hypothalamic-pituitary-adrenal (HPA) axis regulation in mothers (Coplan et al. 2006), and cortisol in milk, as discussed below, has been implicated in the ontogeny of infant behavioral phenotype. Indeed, the HPA axis, its regulation and reactivity, is often identified as underpinning behavioral phenotype (reviewed in Sullivan et al. 2011; Koolhaas et al. 2010; Sapolsky 1999).

9.3.1 *Mother's Milk and Behavioral Phenotype in Rodents*

A series of elegant experimental studies in Wistar rats (*R. norvegicus*) by Angelucci, Catalani, and Casolini's research group in the Department of Human Physiology and Pharmacology, University of Rome represents the most comprehensive investigation of ingested glucocorticoids on behavioral, cognitive, and physiological outcomes for any mammal. Their studies indicate that ingestion of glucocorticoids via milk have beneficial programming effects in offspring that persist into adulthood. In their study design, rat dams are administered corticosterone (200 µg/ml) via their ad libitum water intake following parturition. The levels of corticosterone ingested are within the physiological range following a mild stressor and increase corticosterone concentrations in the dam's peripheral circulation and milk (Angelucci et al. 1983, 1985). Importantly, corticosterone administration did not alter maternal energy balance or behavioral care of pups. Dams administered corticosterone did not differ from controls in their latency to retrieve pups removed from the nest, the time they spent in the nest, body mass, or indices of thermoregulation (Catalani et al. 1993). As juveniles, individuals who were reared by corticosterone-supplemented dams, and therefore ingested corticosterone via milk, had better spatial memory performance; they learned to find the hidden platform in the Morris water maze faster than did controls. Once they learned how to perform in the maze, they also escaped to the platform faster than did controls (Catalani et al. 1993; Casolini et al. 1997). In adulthood, individuals reared by corticosterone-supplemented dams had lower corticosterone responses to stressors and demonstrated better coping behavior (less anxiety, more exploration) during stress challenges, e.g., the elevated plus maze and the dark-light test (Catalani et al. 2000, 2002; Meerlo et al. 2001). Additionally, for males reared by corticosterone-supplemented dams, the density of glucocorticoid receptors was increased in the hippocampus, which enhances the down-regulation of the HPA axis following a stressor (Catalani et al. 2000). These results support the stress inoculation hypothesis that moderately challenging conditions during development better prepare individuals to cope with stressors later in life (see Fairbanks and Hinde 2012).

9.3.2 *Mother's Milk and Behavioral Phenotype in Primates*

Compared to rodents, we know much less about how mother's milk contributes to behavioral phenotype in primates due mostly to their much longer life span. The research to date has been focused on infants, and we are awaiting the maturation of those subjects before investigating juvenile and adult outcomes. During infancy, however, milk has been associated with behavioral phenotype in rhesus macaques (*Macaca mulatta*) assigned to the breeding colony at the California National Primate Research Center in Davis, CA. These animals live in 1/2 acre outdoor corrals in intact social groups composed of close kin, distant kin, and non-kin. Most colony

infants undergo a 25-h biobehavioral assessment (BBA) between 3 and 4 months of age, which occurs concurrently with peak lactation in the mother. BBA consists of a battery of tests that assess aspects of temperament, HPA axis regulation, coping behavior, health, and appetite (described in greater detail in Hinde and Capitanio 2010; Capitanio et al. 2005; Golub et al. 2009; Sullivan et al. 2011). As of 2011, over 3,250 infants have been assessed in this program. During the 25-h infant assessment, milk is collected from a subset of mothers. In a sample of 44 mothers, we found substantial individual variation in milk cortisol concentrations, which were positively correlated with plasma cortisol concentrations (Sullivan et al. 2011). Cortisol concentrations were higher in the milk of mothers rearing sons than in the milk of mothers rearing daughters. Additionally among mothers rearing sons, the higher the cortisol concentrations in the milk, the more infants were characterized as “Confident,” a factor score derived from ratings of trait adjectives for confident, bold, active, curious, and playful. This result remained even after accounting for the energy density of milk, which in rhesus macaques is higher for sons (Hinde 2007, 2009). Similar to studies in rodents, this result suggests that glucocorticoids ingested during development may exert a stress inoculation effect. However, cortisol concentrations in milk were not associated with the other temperament factors of “Vigilant,” “Gentle,” or “Nervous,” and cortisol in milk was not associated with any temperament factors for daughters (Sullivan et al. 2011). Lastly, the sources of interindividual variation in milk cortisol concentrations have not yet been determined.

A single study from humans suggests that cortisol in breast milk may also contribute to temperament in our own species (Glynn et al. 2007). Breast-feeding mothers with higher plasma cortisol concentrations, used as a proxy for milk cortisol concentrations, rated their infants as significantly more fearful than did breast-feeding mothers with lower plasma cortisol concentrations when infants were 2 months of age. Importantly, maternal peripheral cortisol concentrations were not associated with infant fearful temperament ratings among mothers who were formula-feeding their infants. These data, drawn from both formula- and breast-feeding mothers, suggest that the cortisol ingested via milk directly contributes to infant fearful temperament, rather than maternal cortisol influencing behavioral care of the infant or the mother’s rating of her infant’s temperament (Glynn et al. 2007). It is unclear why the human results differ so markedly from findings in both monkeys and rats, in which ingested glucocorticoids produce less fearful individuals, and this difference warrants further investigation.

The above studies on maternal cortisol concentrations in rhesus macaques and humans reflect concurrent measures of infant behavioral phenotype and milk, but further research in rhesus macaques has demonstrated that milk during initial behavioral development predicts infant temperament and coping behavior later in infancy. At 1 month of age, rhesus macaque infants begin to substantially explore the world beyond their mother’s ventrum. Infants take further and further forays into the physical and social world, regularly running back to the secure base that is their mother or being retrieved by her when they wander too far (Machado 2012). At this time, their only source of calories to support this behavioral activity is milk.

From the infant's perspective, the value of milk is not just a function of energy density but also the amount of milk that the mother produces (Hinde and Milligan 2011). The available milk energy—the number of kilocalories that a mother produces in a standardized period of time—is a function of both milk energy density (kcal/g) and the milk yield (g) (Hinde and Capitanio 2010; Hinde 2009). Importantly, milk yield varies much more among rhesus mothers than does milk energy density, and therefore yield, not energy density, is the strongest predictor of available milk energy (Hinde 2009).

In a sample of 59 mother–infant dyads, we found that the available milk energy produced by the mother when the infant is a month old predicts subjective measures of temperament and objective measures of behavior during biobehavioral assessment over 2 months later (Hinde and Capitanio 2010). Specifically, mothers who produced greater available milk energy during the early postnatal period had infants that were characterized as more “Confident”—more playful, bold, active, and exploratory—all traits that we would expect to be sensitive to energy balance. Moreover these infants showed better adjustment and behavioral coping during the 25-h separation from their mother and social group. They moved around their new environment, ate and drank, and engaged with novel objects. Infants whose mothers produced low available milk energy were less exploratory, playful, bold, and active. We interpreted this to indicate that these infants had a more conservative behavioral phenotype that minimized energy expenditure. Importantly, these temperament and behavioral outcomes reflected available milk energy from months earlier, not at the time of assessment, suggesting that early nutrition organizes, or *programs*, infant behavioral phenotype during critical windows of development. As a result, the behavioral activity patterns and responsivity of infants are seemingly calibrated to maternal and environmental conditions (Hinde and Capitanio 2010).

Unfortunately, nonhuman primate research on this topic has lacked the gold standard of experimental manipulation, such as cross-fostering or maternal dietary manipulation, that enables us to establish causal relationships between mother's milk and infant outcomes. The correlational associations between milk and infant behavioral phenotype may instead reflect genetic correlations between mothers and infants, infant suckling demand, or differences in maternal behavioral care. Several lines of evidence, however, suggest that mother's milk has an independent effect on infant outcomes. Available milk energy during the early postnatal period, but not during peak lactation, predicted infant behavioral phenotype later in infancy. If this result was primarily due to underlying genetic correlations or infant suckling demand, we could predict that the effects would persist throughout early and peak lactation. Moreover, maternal characteristics that are often associated with maternal behavioral care—i.e., rank, parity, and mass—were covariates in the statistical models (Hinde and Capitanio 2010). Future research on this topic, however, should integrate experimental methods to more effectively disentangle maternal physiological investment from behavioral care to better understand contributions to infant developmental trajectories.

9.4 The Metabolic Role of Cortisol

As discussed above, the aspect of mother's milk most studied in conjunction with infant behavioral phenotype has been cortisol (corticosterone in rodents), but infant behavioral activity budgets are unquestionably a function of available energy. We can reconcile these two points by incorporating a broader perspective of cortisol. Although cortisol is often referred to as the "stress" hormone, cortisol performs routine metabolic functions, as well as stimulating and suppressing the stress response (Sapolsky et al. 2000; Nyberg 2012). Cortisol directly mediates the metabolism of carbohydrates, proteins, and fats and is instrumental in the energy-producing effects of glucagon and catecholamines (Barrett et al. 2010; Sapolsky et al. 2000). For example, glucagon requires cortisol to generate glucose from noncarbohydrates to maintain blood glucose levels while fasting (Khani and Tayek 2001; Barrett et al. 2010). Similarly, cortisol is necessary for lipolysis, the breakdown of lipids into free fatty acids (Djurhuus et al. 2004; Barrett et al. 2010). Particularly important for the present discussion, cortisol in the lactating mammary gland stimulates the production of proteins for milk (Akers 2002).

Energy utilization, and the metabolic role of cortisol, becomes particularly critical during challenging conditions, e.g., food shortages, predator encounters, and social conflicts. These are the same environmental conditions that have been implicated in the development of behavioral phenotypes (e.g., variable foraging demand) and regulation of the stress response. Suggestively, individual differences in energy metabolism are correlated with behavioral phenotype, although the causal direction is unclear—it may be that low resting metabolic rate predicts low reactivity or that low reactivity predicts low resting metabolic rate (Biro and Stamps 2010; Careau et al. 2010; Houston 2010). We can hypothesize that behavioral phenotype is organized in concert with the metabolism by energetic conditions, among other factors, during early development.

Some evidence indicates that infants employ physiological pathways to specifically process glucocorticoids ingested from mother's milk. However, disentangling the metabolic and stress response roles of ingested glucocorticoids in the developing infant is particularly challenging. Expression of glucocorticoid receptors in the intestinal tract is highest during infancy but declines to adult levels after weaning (Pácha 2000). Additionally, the activity and distribution of 11 β -hydroxy-steroid dehydrogenases, enzymes that either inactivate (11 β -HSD1) or enhance (11 β -HSD2) the physiological effects of glucocorticoids (Seckl 2004; Tomlinson et al. 2004), are different in rat pups before and after weaning (Pácha and Miksík 1996). Pácha's study did not differentiate between the two 11 β -HSD enzymes, so it is unclear if infants are suppressing or amplifying ingested corticosterone, or if there are inter-individual differences. Rat pups who were administered exogenous leptin had increased glucocorticoid receptor density in their hippocampus, which subsequently enhanced negative feedback in the HPA axis (Proulx et al. 2001). The hormone leptin primarily derives from adipose tissue and

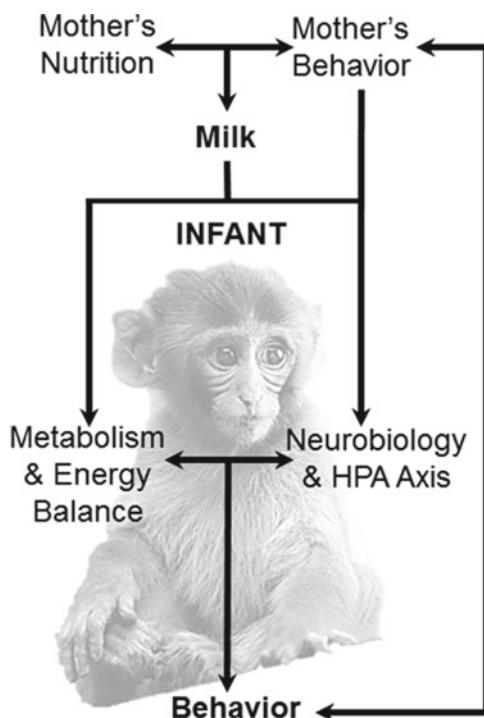
is directly proportional to body fat stores (Margetic et al. 2002). In other words, physiological indications of positive energy balance (e.g., elevated leptin) meant that pups returned to baseline faster following stress response activation of the HPA axis. In dairy calves, exogenous glucocorticoids elevate circulating leptin concentrations (Chilliard et al. 2005), which in turn suppress appetite (Wisse and Schwartz 2003; Broberger 2005) and may reduce infant suckling. In this way, glucocorticoids transferred from the mother via milk may effectively calibrate infant behavioral demands to maternal physiological state. Lastly, in rhesus macaque milk, cortisol concentrations are significantly and positively correlated with fat and protein concentrations (Sullivan et al. 2011) suggesting that milk cortisol possibly contributes to the assimilation of nutritive components in milk. Indeed, infants grow faster when milk cortisol concentrations increase from early to peak lactation (Hinde, unpublished data). However, corticosterone ingested via milk is not associated with pup growth in rats (Catalani et al. 1993). This difference between rodents and primates may be due to their very different life history strategies, but further research is needed.

9.5 Mother's Milk and Mind, Brain, and Behavior

The brain and mind determine how an individual perceives, experiences, and interacts with his world (Kandel and Squire 2000; Bunge 1985) and necessarily underlie the behavioral phenotype of an individual (Kinnally 2012; Machado 2012). How then might mother's milk affect infant neurodevelopment and subsequently behavior as described above, either directly or indirectly? Firstly, experiences gained through behavioral activity directly shape brain development (Fairbanks 2000), and mother's milk provides the energy required to sustain behavioral activity (Hinde and Capitanio 2010). Moreover early nutrition is instrumental in neural development (e.g., neurogenesis, synaptogenesis) and organization (e.g., maturation of neurotransmitter pathways) (Walker 2005), although we still know little about how specific milk constituents directly affect neurodevelopment (Milligan 2012). Well-recognized gut-brain pathways are sensitive to hormonal, energy, and nutrient signals that affect appetite, motivation, and energy homeostasis (Murphy et al. 2006; Alpers 2010; Kondoh et al. 2009; Tomé et al. 2009). Additionally along these pathways, commensal gut bacteria influence neurobiological functioning and the HPA axis (Forsythe et al. 2010; Rhee et al. 2009). Conversely, activation of the HPA axis also modifies the community structure of the intestinal microbiome (Bailey et al. 2011).

Gut-brain signaling pathways are likely to be particularly sensitive during critical periods of neurodevelopment (Machado 2012; Fairbanks 2000) when infants are reliant on mother's milk, becoming behaviorally active, and establishing their gut microbiome (Martin and Sela 2012). For example, neurons that express neuropeptide Y (NPY) and agouti-related peptide (AgRP) stimulate food intake via appetite regulation in the hypothalamus (Wisse and Schwartz 2003; Näslund and Hellström 2007). In rats and mice, there are minimal innervations for NPY/AgRP

Fig. 9.2 Conceptual model of pathways from mother's milk to infant behavior as mediated physiologically through infant energy balance and neurobiology, with feedback through maternal behavioral regulation of nipple access. Maternal behavior can additionally directly affect infant neurobiology and behavior (see Kinnally 2012; Machado 2012; Fairbanks and Hinde 2012). Photo by G. Lampard



neurons at birth, but this peaks postnatally before declining to adult levels following weaning (reviewed in Broberger 2005). These neurons are activated by low leptin concentrations, an “honest” signal of fat deposition (Wisse and Schwartz 2003; Broberger 2005). For mammalian infants, however, circulating leptin does not only reflect their own body fat depots but is additionally acquired from mother's milk. Leptin ingested from mother's milk has been implicated in lactational programming of infant growth and appetite through neural pathways (Savino et al. 2009). Additionally, energy intake via mother's milk mediates the perception and response to environmental stressors and insults. Stress responses in rat pups are reduced by the ingestion of high-fat milk (Trottier et al. 1998). Similarly, consumption of carbohydrates, the primary component of primate milks (Hinde and Milligan 2011), and the subsequent engagement of neural reward centers (Wisse and Schwartz 2003; Broberger 2005; Näslund and Hellström 2007) act as an analgesic in human infants and rat pups (reviewed in Walker 2005).

Taken together, these results paint a compelling picture for the potential of energetic and hormonal constituents in mother's milk to contribute to infant neurodevelopment and psychobiology and consequently shape infant behavioral phenotype (Fig. 9.2). Importantly, the infant is not a passive recipient of milk, nor does the mother passively synthesize milk (Wells 2006; Hinde and Milligan 2011). The behavioral negotiation between mother and infant over the frequency and

duration of nipple access and infant activity budgets can affect milk synthesis. For example, laissez-faire mothers that allow their infant greater latitude to explore and play may have infants with greater energy expenditure and experience longer intervals between nursing bouts. Less frequent nursing down-regulates lactose synthesis, reducing milk yield and increasing milk energy density (Hinde 2009; Hinde and Milligan 2011), but the effects on hormonal constituents are not known. Moreover maternal behavioral care is sensitive to environmental factors that may also have consequences for milk synthesis. In primates, social conflict and nutritional restrictions can increase peripheral concentrations of cortisol (Honest and Marin 2006; Abbott et al. 2003; Cameron 1996) and may therefore increase cortisol in milk. Although maternal behavioral care has well-established consequences for infant outcomes, the extent to which maternal behavioral care and physiological investment have convergent, additive, or possibly even divergent effects on the developing infant remains to be explored.

9.6 Future Directions

The goal of this chapter was to familiarize the reader with the mechanisms through which mother's milk contributes to infant behavioral phenotype, although much remains unknown. Our limited understanding of the biochemical mechanisms underlying glucocorticoid ingestion in infants and the consequences for metabolic canalization and psychobiological development requires rectifying, but in this way, glucocorticoids are not unique. As a science, we still know very little about the mechanistic and functional outcomes of most milk constituents in isolation, not to mention their myriad, synergistic interactions. Understanding the ontogeny of the complex neural pathways and the regulation of eating, tasting, digesting, metabolizing, and behaviorally utilizing energy sources is particularly crucial in the face of the childhood obesity epidemic in the United States and elsewhere in the world. Research on this topic, however, has largely overlooked the magnitude and sources of individual variation in the concentration of nutrients and hormones in milk. The paucity of data on both natural variation in breast milk among mothers and consequences for infant physiology, neurobiology, and behavioral phenotype provides a rich opportunity for future collaborative research among anthropologists, psychologists, nutritionists, neuroscientists, and animal behaviorists. The HPA axis, metabolism, and behavioral phenotype do not exist apart from one another in adulthood. We can therefore predict that the organization of these interconnected systems during ontogeny is similarly intertwined, and programmed, in part, by mother's milk. Research programs that integrate these systems are absolutely necessary to meaningfully advance our understanding of behavioral development.

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Chapter 10

Do Bigger Brains Mean Better Milk?

Lauren A. Milligan

Keywords Lactation • Milk composition • Encephalization • LCPUFA • DHA

10.1 Introduction

Life history theory proposes that individuals have a finite amount of energy that can be spent on either growth or reproduction, leading to a trade-off between fecundity and survival to maturity (Charnov 1993; Purvis et al. 2003; Stearns 1992). The subsequent pace of a species' life history reflects the trade-off between the potential gains for continuing to grow larger and the risk of dying before reproducing (Charnov 1993). The variation in the pace of life history strategies across mammals reflects the myriad ways in which energy can be partitioned to maximize fitness over the lifetime. On one end of the continuum of life history variation are primates who have been described as living “life in the slow lane” (Charnov and Berrigan 1993). As a result of their protracted life history strategy, primate mothers invest more heavily in each offspring during gestation and lactation compared to non-primate mammals (Dufour and Sauther 2002; Martin and MacLarnon 1990). However, because this investment is paid out over a longer period of time, the daily energetic burden of primate reproduction on the mother is relatively low (Dufour and Sauther 2002; Martin and MacLarnon 1990).

Primate milk composition demonstrates this trade-off between daily and total costs. Primate milk is relatively dilute and low in energy, with those species with the longest duration of lactation and the oldest ages at reproductive maturity (e.g., the apes) producing the most dilute milks (Hinde and Milligan 2011). The production of energetically dense milk among primates would be at odds with their extended period

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of infancy because it would deplete maternal body reserves before offspring became physically, socially, and behaviorally independent (Hinde and Milligan 2011). However, the production of low-energy milk appears to be at odds with other important hallmarks of primate life history: their relatively larger neonatal and adult brain sizes. While somatic growth may be “in the slow lane” in primates in general, and apes in particular, brain growth does not proceed on such a protracted schedule.

For many primates, more than 50% of brain growth occurs postnatally and thus overlaps with the lactation period (Leigh 2004). As the extreme example, human neonates are born with brains approximately 25% of adult brain size and have completed 90% of brain growth by the age of five, well over a decade before adult stature is attained (Bogin and Smith 1996; Leigh 2004; Robson and Wood 2008; Smith and Tompkins 1995). In human and nonhuman primates, increased relative brain size is accomplished by an increased growth rate rather than a longer duration of brain growth, precisely the opposite of what is seen with somatic growth (Leigh 2004; Robson and Wood 2008). How, then, can rapid brain growth during the postnatal period and the production of low-energy milks be reconciled?

This chapter addresses this question by examining the relationship between primate brain growth and development and milk composition, specifically milk fatty acids. This chapter unfolds across four sections. In the first section, I provide a brief introduction to fatty acids and why they are the molecules of interest in mammalian milk when discussing brain ontogeny. The second section utilizes published data on human and nonhuman primate milk fatty acid composition and relative brain sizes to determine if selection for larger relative brain size among primates (including humans) was accompanied by modifications in milk composition. The next section explores alternative mechanisms to milk composition for transferring brain-specific fatty acids from mother to offspring. In the final section, I switch the focus from how brains may have influenced milk composition over the course of primate and human evolution, to a discussion of how milk fatty acid composition influences brain growth. Both perspectives are critical to our understanding of whether “better” milk really does build bigger brains.

10.2 Milk as Brain Food

Among humans, rapid postnatal brain growth is best modeled as the continuation of the fetal rate of brain growth for the first 18 months postpartum (Leigh 2004). Martin (1981) proposed that this brain growth trajectory—a unique pattern among mammals—required milk constituents that could support rapid brain growth in the neonate. He went on to hypothesize that human milk composition should be species-specific due to the unique ontogenetic priorities of human neonates (Martin 1981, 1983). Implicit in Martin’s hypothesis is the idea that biological components that facilitate and support brain growth should either be found in human milk in higher concentrations than they are found in other nonhuman primate milks or should be found only in human milk. The hypothesis could also be expanded to predict variation in milk components depending on the degree and rate of postnatal brain growth among

primates. For example, neonatal chimpanzees (*Pan troglodytes*) have brains approximately 40% of adult brain size (DeSilva and Lesnik 2006) and complete brain growth just prior to weaning (Robson and Wood 2008). Although their total brain growth is slower in rate and significantly less than humans due to a smaller adult brain size, chimpanzees still experience the majority of brain growth during the postnatal period. This emphasis on brain growth during lactation suggests that selection may have favored an increase in milk components related to brain ontogeny over other nonhuman primates who complete the majority of brain growth in utero (e.g., *Macaca* species) (Leigh 2004).

A comparative analysis of the macronutrient or proximate composition (e.g., fat, protein, sugar, energy) of human and nonhuman primate milk composition suggests that human milk fits well within the overall primate pattern and is actually lower in energy and fat than milk from many nonhuman primates with smaller relative brain sizes or less emphasis on postnatal brain growth (e.g., rhesus macaques, *Macaca mulatta*; tufted capuchins, *Cebus apella*) (Hinde and Milligan 2011; Milligan 2007, 2010). Indeed, there is no correlation between milk energy density, percent energy from fat, or percent energy from sugar and relative brain size or neocortex size (Hinde and Milligan 2011). It is clear that an understanding of the relationship between milk composition and brain ontogeny in primates in general, and humans in particular, requires moving beyond generalized descriptions of the macronutrient composition of primate milk and investigating the individual components associated with facilitating and supporting brain growth and development. Investigations should focus on milk fatty acid composition, particularly long-chain polyunsaturated fatty acids (LCPUFA) and their 18-carbon polyunsaturated fatty acid (PUFA) precursors because of their integral role in brain growth and development.

10.2.1 Fatty Acids and the Brain

Fatty acids are molecules composed of a hydrocarbon chain, with a methyl group at one end (the omega end) and an acid group at the other. PUFA are fatty acids with more than one double bond between the carbons, and LCPUFA refers to PUFA with more than 14 carbons. Fatty acids between 16 and 24 carbons in length are important as structure in membranes (Cunnane 2005), and the lipid composition of membranes determines their shape, fluidity, elasticity, permeability, and bilayer stability (Carlson and Kingston 2007). Research on the relationship between fatty acids and brain growth and development primarily focuses on four fatty acids: linoleic acid (LA), alpha-linolenic acid (ALA), arachidonic acid (AA), and docosahexaenoic acid (DHA) (Table 10.1). LA and AA are omega-6 (n-6) fatty acids, while ALA and DHA are omega-3 (n-3) fatty acids.¹ These four fatty acids are highlighted because AA and DHA are the n-6 and n-3 fatty acids found in the highest concentrations in cell membranes (Carlson 2001) and together comprise a third

¹ n-6 or n-3 refers to the location of the first double-bonded carbon from the omega end of the fatty acid molecule.

Table 10.1 LCPUFA nomenclature, dietary sources, and function

Fatty acid	Chemical formula ^a	Abbreviation	Key dietary sources	Other sources
Linoleic ^b	18:2n-6	LA	Sunflower oil, corn oil	NA
Alpha-linolenic ^b	18:3n-3	ALA	Green, leafy vegetables; flaxseed; soybean oil	NA
Arachidonic	20:4n-6	AA	Terrestrial animal lipids, eggs	Synthesized from LA
Docosahexaenoic	22:6n-3	DHA	Fish lipids or oils, brain and marrow tissue	Synthesized from ALA

^aLCPUFA nomenclature is as follows: the number of carbons, followed by a colon, followed by the number of double bonds and the location of the first double bond from the omega end. For example, 18:2n-6 has 18 carbons and 2 double bonds, the first double bond located six carbons from the omega end

^bEssential fatty acids: these fatty acids cannot be synthesized from shorter chain fatty acids or by the mammary gland so must be obtained by the diet

of all lipids in the brain's gray matter (Gibson 1997), with DHA in particularly high concentrations in membranes surrounding neural synapses (Carlson 2001). AA and DHA can be obtained directly from the diet (Table 10.1) or can be synthesized in the liver from their 18-carbon precursors, LA and ALA, respectively (Fig. 10.1). The pathways from LA to AA and ALA to DHA require identical enzymes for adding in double bonds, leading to competition between fatty acids for these enzymes, particularly over access to Δ -6 desaturase (Fig. 10.1). As a result, there is a very intimate relationship between the dietary supply of LA and ALA and their LCPUFA metabolites (Innis 2003). For example, among mammals (including humans), diets high in LA inhibit synthesis of DHA, presumably by outcompeting ALA for access to Δ -6 desaturase (Brenna 2002; Carlson 2001; Innis 2003).²

The brain appears to be selective in the incorporation of fatty acids, preferring those with 20 and 22 carbons rather than their 18-carbon precursors because of their influence on the function and properties of the membrane bilayer, including their effects on gene expression in the brain (Carlson 1999, 2001; Carnielli and Sauer 1996; Innis 2000, 2003; Koletzko et al. 2001). Both DHA and AA cross the blood–brain barrier, but the specific transport molecules and the mechanisms by which they do so are unknown. The brain has relatively lower proportions of LA and ALA and relatively higher proportions of AA and DHA than other organs in the body, suggesting specific mechanisms allowing the brain to accumulate such large amounts of these fatty acids (Innis 2003). Moreover, once DHA is incorporated into the brain, it remains there, (Carlson 2001) with one possible exception: during the last weeks of human pregnancy, mothers lose approximately 3% brain volume as lipids, much of which is DHA, to the developing fetus (Holdcroft et al. 1997). Recent research suggests that LCPUFA are also involved in gene expression in the brain and central nervous system. Supplementation of infant baboons with DHA and AA with levels

² As indicated in Fig. 10.1, EPA (eicosapentaenoic acid: 20:5n-3) is also an n-3 LCPUFA metabolite of ALA. EPA is not highlighted in this chapter (nor in most research/discussions of human brain function) as its concentration in the brain is significantly less than that of AA or DHA.

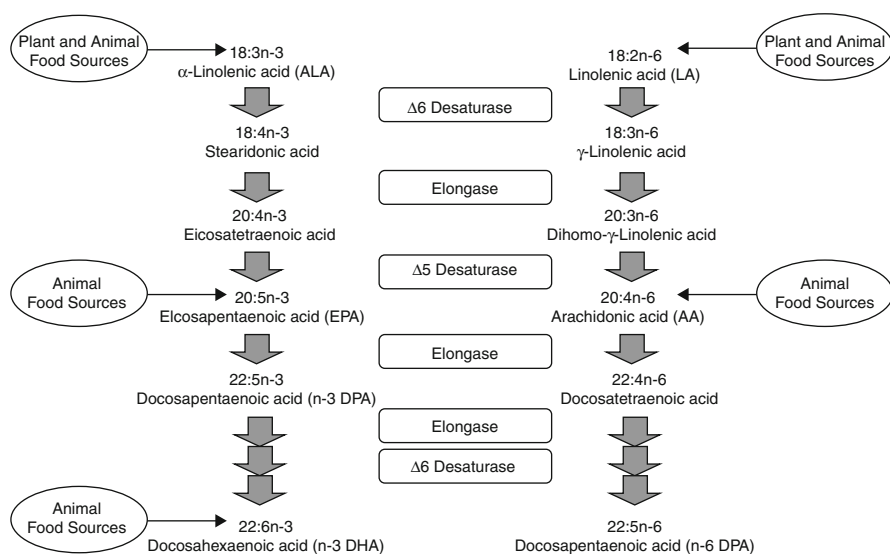


Fig. 10.1 Desaturation and elongation of ALA and LA to DHA and AA, respectively. Reproduced from Milligan and Bazinet (2008)

found in human breast milk (0.33% of total fatty acids as DHA and 0.67% as AA) influenced the expression (either up- or downregulation) of over 1,100 genes in the brain (Kothapalli et al. 2006, 2007). LCPUFA may therefore have a particularly important role in regulation of fatty acid metabolism in the brain of the baboon, and presumably all primates, including humans (Kothapalli et al. 2007).

Brain growth in mammals is associated with increased incorporation of LCPUFA in phospholipids located, primarily, in the cerebral cortex (Farquharson et al. 1992). The period of maximum accumulation is during the brain growth spurt, which among mammals usually occurs in utero (Huang and Brenna 2001). Thus, the placenta transfers most LCPUFA to the developing fetal brain. However, among some primates and most especially in humans, the brain growth spurt is perinatal. In humans, the brain selectively incorporates DHA from the third trimester (approximately 26 weeks of gestation) through the second year of postnatal life, and thus LCPUFA are transferred via placenta and mammary gland (Huang and Brenna 2001; Sheaff-Greiner et al. 1997).

10.2.2 Fatty Acids in Milk

Mammalian milks have approximately 150 fatty acids (Innis 2000), of which only seven (including LA) are present in proportions greater than 1% (Jensen et al. 1995). The proportion of short (less than 8 carbons), medium (8–14), and long-chain (15 or more)

fatty acids differs across mammalian species so that while all mammalian milks may have palmitic acid (a 16-carbon saturated fatty acid), the relative proportion of this fatty acid varies dramatically (Iverson and Oftedal 1995). Milk fatty acids are taken up from maternal plasma or adipose tissue or are synthesized *de novo* by the mammary gland (Iverson and Oftedal 1995). The mammary gland does not synthesize n-3 or n-6 PUFA or LCPUFA, and the presence of these fatty acids in milk reflects their consumption in the maternal diet, either past (maternal fat stores) or present. LCPUFA in milk also may represent metabolites of precursor fatty acids (e.g., LA or ALA) in maternal plasma. Biosynthesis of LCPUFA from n-3 or n-6 precursors (Fig. 10.1) depends on the quantity of both LA and ALA in the diet (Brenna 2002; Carlson 1999; Jensen et al. 1995), the ratio of n-3 to n-6 LCPUFA in the diet (Brenna 2002; Huang and Brenna 2001), and the ability to convert n-3 and n-6 LCPUFA into their longer-chain metabolites (Agostoni et al. 2001; Brenna 2002; Carlson 2001). Variation in conversion efficiency among species (discussed below) may produce different LCPUFA milk fatty acid profiles despite similar dietary intakes of n-3 and n-6 precursors. Therefore, milk fatty acid profiles are not simply a reflection of the supply of fatty acids in the maternal diet but also the interaction of dietary fatty acids with maternal abilities to synthesize and elongate fatty acids in the liver.

The first evidence in humans that higher maternal dietary intake of AA and DHA led to higher membrane concentrations of these fatty acids, relative to diets containing only LA and ALA, came from studies comparing formula-fed and breast-fed infants (reviewed in Carlson 1999; Koletzko et al. 2008). The most consistent finding of these studies is lower levels of DHA in the brains of formula-fed infants compared to those receiving various levels of DHA through breast milk (Gibson and Makrides 1999; Koletzko et al. 2008). In addition, among breast-fed infants, the proportion of milk DHA was found to be positively correlated with both visual and language development (Innis 2003). Based on these results, in 2002 the FDA approved supplementing infant formulas with DHA and AA. The current recommended concentrations are 0.2% of total fatty acids as DHA and at least 0.35% of total fatty acids as AA (Koletzko et al. 2001, 2008). Interestingly, these values match most closely those identified in milk from women consuming a Western diet and are not representative of the proportions of these fatty acids in milk cross-culturally (Brenna et al. 2007; Yuhas et al. 2006). This issue, and whether these values represent the ideal concentration for human infants, will be discussed in more detail in subsequent sections.

10.3 Fatty Acids in Human and Nonhuman Primate Milk

The human brain rapidly accumulates n-3 and n-6 LCPUFA for structure and multiple functions during the last trimester of gestation and first 18 months of infancy (Burdge 2004; Carlson 2001; Innis 2003). Therefore, the dietary supply (via the placenta or mammary) of these fatty acids must be sufficient to support brain growth. As it relates to milk, the concentration of LCPUFA and their incorporation into the

brain should be related quantitatively to the ultimate size and function of the brain (Martin 1995). An alternative hypothesis is that brain size is instead correlated with the concentration of the 18-carbon precursors (LA and ALA) and their conversion by the liver to AA and DHA. In this section, I investigate both hypotheses using data on milk composition from nine nonhuman (anthropoid) primates and four human populations (Table 10.2). These human populations were selected from the literature based on the variation in dietary intakes of LCPUFA, especially DHA. Data on relative brain size (encephalization quotient: EQ) are the same as those used by Hinde and Milligan (2011) in comparisons of proximate milk composition with brain size.³

10.3.1 *n-6 Fatty Acid Composition of Milk*

Captive living cebids (*C. apella* and *S. boliviensis*) have the highest mean values for percent composition of LA, followed closely by vegetarian human females (Table 10.2). Although cebids have relatively large brains (with capuchins second only to humans among the primates), it is likely that primate interspecific variation relates to differential consumption of foods rich in LA (e.g., corn oil) rather than encephalization. This hypothesis is supported by two observations: (1) the four human populations vary widely in LA percent composition, and (2) two of the human populations (women consuming Western and Nigerian/traditional diets) are similar in percent composition LA to wild living mountain gorillas and howler monkeys, both of which have lower EQ values than humans.

The percent composition of milk AA also appears to be unrelated to relative brain size. Larger relative brain sizes (represented by EQ) are not associated with higher proportions of milk AA ($R^2=0.005$; $p=0.84$; Fig. 10.2). The relationship is still not significant when mountain gorillas, the extreme outlier, are removed from analysis ($R^2=0.25$, $p=0.16$). For this analysis, I used only data from the Nigerian population to represent the percent composition of AA in human milk, as the other three diets are likely to be more divergent from the ancestral human diet (discussed in more detail below). It should be noted, however, that rerunning analyses with each of the remaining three human populations also failed to produce a significant relationship. In addition, the fact that humans consuming a Western diet have nearly identical proportions of milk AA to captive living rhesus macaques suggests that proportion of brain growth completed in utero (humans: 25%, rhesus macaques: 55%; Leigh 2004) also is unrelated to milk AA proportions.

The relationship between milk AA proportions and AA concentrations in the diet is less clear than that between milk LA and dietary LA. Although some cross-cultural studies indicate very little variation in milk AA composition (e.g., Yuhas et al. 2006),

³ With the following changes: *S. sciureus* values used for *S. boliviensis* and *G. gorilla* values for *G. beringei*.

Table 10.2 Human and nonhuman primate populations used in analyses with percent composition (mg/g) for milk LA, ALA, AA, and DHA (all values are mean $\pm$ SE unless otherwise indicated)

Species	<i>n</i>	LA (18:2n-6)	ALA (18:3n-3)	AA (20:4n-6)	DHA (22:6n-3)	Reference
<i>Alouatta palliata</i> ^a (howler monkey)	7	12.59 $\pm$ 0.60	15.06 $\pm$ 0.75	0.68 $\pm$ 0.09	0.03 $\pm$ 0.003	Milligan et al. (2008)
<i>Cebus apella</i> (tufted capuchin)	7	30.63 $\pm$ 1.35	2.91 $\pm$ 0.14	0.92 $\pm$ 0.08	0.31 $\pm$ 0.04	Milligan and Bazinet (2008)
<i>Callithrix jacchus</i> ^a (common marmoset)	4	3.29 $\pm$ 0.56	2.63 $\pm$ 0.43	0.30 $\pm$ 0.03	0.14 $\pm$ 0.06	Milligan et al. (2008)
<i>Saimiri boliviensis</i> (squirrel monkey)	8	30.39 $\pm$ 1.02	1.65 $\pm$ 0.21	0.92 $\pm$ 0.08	0.40 $\pm$ 0.03	Milligan and Bazinet (2008)
<i>Macaca mulatta</i> (rhesus macaque)	21	23.88 $\pm$ 0.54	1.55 $\pm$ 0.11	0.44 $\pm$ 0.01	0.44 $\pm$ 0.02	Milligan and Bazinet (2008)
<i>Macaca sinica</i> (toque macaque)	8	8.03 $\pm$ 0.98	2.55 $\pm$ 0.32	0.32 $\pm$ 0.02	0.12 $\pm$ 0.01	Milligan et al. (2008)
<i>Gorilla gorilla</i> (lowland gorilla)	4	8.03 $\pm$ 0.98	2.46 $\pm$ 0.86	0.55 $\pm$ 0.16	0.36 $\pm$ 0.25	Milligan and Bazinet (2008)
<i>Gorilla beringei</i> ^b (mountain gorilla)	5	10.56 $\pm$ 0.54	16.31 $\pm$ 1.19	2.08 $\pm$ 0.15	0.09 $\pm$ 0.04	Milligan et al. (2008)
<i>Pan troglodytes</i> (chimpanzee)	4	25.73 $\pm$ 2.28	3.56 $\pm$ 1.29	0.73 $\pm$ 0.16	0.36 $\pm$ 0.07	Milligan and Bazinet (2008)
<i>H. sapiens</i> Western diet	120	10.75 $\pm$ 4.22	0.59 $\pm$ 0.16	0.40 $\pm$ 0.10	0.32 $\pm$ 0.17	Gibson and Kneebone (1981)
<i>H. sapiens</i> Nigerian/traditional diet ^b	10	11.06 (5.4–13.8)	1.41 (0.64–5.45)	0.82 (0.38–1.48)	0.93 (0.70–2.16)	Koletzko et al. (1991)
<i>H. sapiens</i> vegetarian diet	12	28.82 $\pm$ 1.39	2.76 $\pm$ 0.16	0.68 $\pm$ 0.03	0.22 $\pm$ 0.08	Specker et al. (1987)
<i>H. sapiens</i> vegan diet	9	23.8 $\pm$ 1.40	1.36 $\pm$ 0.18	0.32 $\pm$ 0.02	0.14 $\pm$ 0.06	Sanders and Reddy (1992)

^aMilk samples collected from wild living individuals

^bMedian values (ranges)

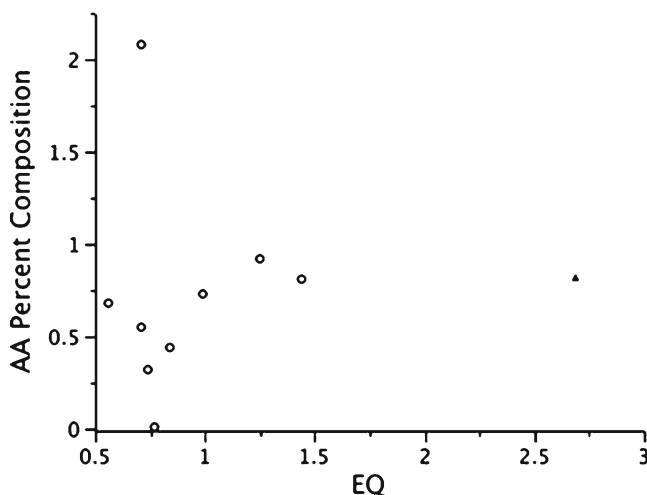


Fig. 10.2 Percent composition of milk AA by EQ. Nonhuman primates = *circles*; humans consuming Nigerian/traditional diet = *triangle*. The highest value (2.08%) is from a sample of wild living mountain gorillas with no known source of AA in their diet

there may be a relationship between the amount of animal products (primarily meat and eggs) in the diet and levels of milk AA (Table 10.2). For example, vegetarians have lower proportions of AA than the women on Western and Nigerian/traditional diets that consume animal products, and higher proportions than vegans, presumably because of the consumption of eggs by vegetarians. The high values in the mountain gorilla are extremely perplexing, as these females were not observed to consume any foods with a preformed source of AA (C. Whittier, personal communication). The pathway from LA to AA requires less energy (fewer steps for elongation and desaturation) than that from ALA to DHA (Agostoni et al. 2001, Fig. 10.1), which would suggest that LA obtained from the diet is readily metabolized into AA. However, data from humans using labeled LA indicate that little human milk AA originates from conversion of LA but instead comes from maternal depot stores of AA (Del Prado et al. 2001). It appears, therefore, that the picture is more complex and that the inclusion of AA in the diet (past or present) may increase milk AA among humans.

Importantly, the percent composition of AA in human milk (and by extrapolation, AA in the milks of nonhuman primates), may be unrelated to AA levels in the infant brain. Until 2002, human infant formulas lacked any preformed source of AA. Therefore, any AA in the formula-fed infant brain was presumed to come from LA that the infant synthesized *in vivo*. Comparing postmortem brain tissue of formula-fed and breast-fed infants revealed no significant difference in the concentration of AA (Farquharson et al. 1992; Makrides et al. 1994). This finding is critical to issues surrounding infant formula supplementation as it suggests that infants have a compensatory mechanism for AA and are not reliant on the dietary (milk) supply of this fatty acid.

This finding also may speak to issues in human (and perhaps, primate) evolution. AA is an essential component of neural tissues, and natural selection may have acted on infant metabolism in order to regulate the concentration of this fatty acid in the developing infant brain, regardless of dietary supply. Similar findings are reported for baboon neonates fed formula without AA, formula with AA (approximately 0.35% AA), and human breast milk (with 0.68% AA) (Sarkadi-Nagy et al. 2003, 2004). No significant differences were found in the concentration of AA in the brain among these groups, suggesting that the compensatory mechanism for AA synthesis in brain tissues may be part of our anthropoid, or at least Old World anthropoid (catarrhine), legacy.

10.3.2 *n-3 Fatty Acid Composition of Milk*

As was observed for LA, the proportion of milk ALA appears to be more reflective of diet than of relative brain size or proportion of brain growth completed postnatally. There is a strong influence of degree of folivory, or amount of leaves in the diet, and the proportion of milk ALA. Mountain gorillas and howler monkeys (both representing wild living populations) produce milks with approximately 15% of fatty acids as ALA, whereas more frugivorous wild primates, like common marmosets, have milks with approximately 3% of fatty acids as ALA. The proportion of ALA in human milk also is variable with respect to dietary strategy, with the lowest proportion found in women consuming a Western diet and the highest in vegetarians. Like nonhuman primates, these differences also are assumed to be a reflection of differences in inclusion of ALA-rich foods in the diet.

The proposed relationship between larger brain sizes and increased concentration of milk ALA, as the precursor fatty acid to DHA, is not supported by the available data. Regardless of which human population is used for the interspecific comparison, there was no significant relationship between percent composition of milk ALA and EQ ($R^2=0.22$; $p=0.103$). Further, the convergence of values among humans consuming a traditional diet (1.41% ALA) and rhesus macaques (1.55% ALA) fails to support a relationship between milk ALA concentration and the proportion of postnatal brain growth.

Cross-cultural meta-analyses of human milk fatty acid composition have found DHA to be the most variable fatty acid (Brenna et al. 2007; Yuhas et al. 2006). The percent composition of DHA was also found to be highly variable among the nine nonhuman primate species and the four human populations included in these analyses (Table 10.2). However, little variation is seen among populations that are presumed to lack a preformed source of DHA in their diet (wild living primates and vegan human females). Indeed, no significant differences were identified in percent composition of DHA among mountain gorillas, toque macaques, common marmosets, and vegan human females ($F=1.05$, $p=0.38$). Howlers were not used in this analysis, as they were significantly different from each of these species in post hoc pairwise comparisons. However, their significantly lower values for percent

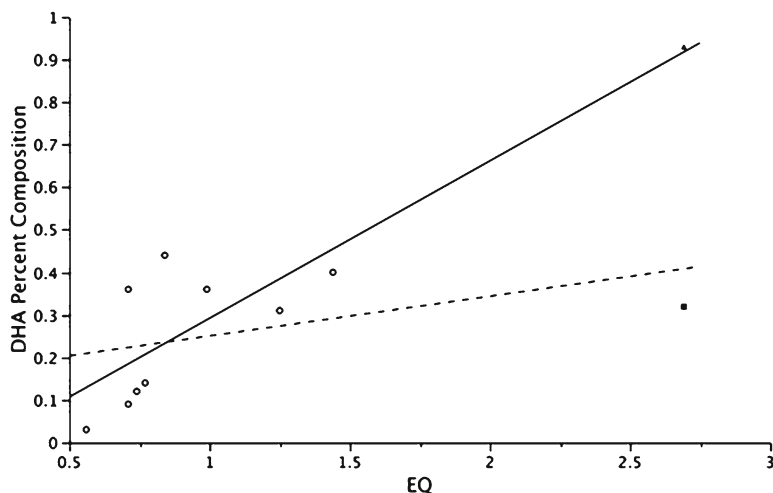


Fig. 10.3 Percent composition of milk DHA by EQ. Nonhuman primates=circles; humans consuming Nigerian/traditional diet=triangle, solid line ($R^2=0.81$, $p<0.01$); humans consuming Western diet=square, dashed line ($R^2=0.16$, $p=0.25$)

composition of DHA serve to strengthen the position that maternal diets lacking in this fatty acid are associated with low proportions in milk.

DHA in the milks of these wild living nonhuman primates and vegan human females can only be the result of elongation and desaturation from ALA, and the similarity among them suggests that anthropoid primate females may be limited in the amount of ALA in maternal plasma (diet, depot fat) that they can elongate and desaturate into DHA. Despite high consumption of foods rich in ALA (e.g., leaves), neither howler monkeys nor mountain gorillas were able to increase milk DHA proportions to the levels seen in species with a preformed source in their diet (e.g., captive living primates consuming Monkey Chow, which contains fish oils). One possible explanation is that metabolically, primate mothers may be constrained in the energy available to elongate and desaturate ALA; the ALA that was not synthesized into DHA would then accumulate in milk.

DHA is the brain-selective nutrient that has received the most attention with regard to its role in human brain evolution (Cunnane 2005). But as has been the case for LA, ALA, and AA, the variability among human populations in percent composition of milk DHA obfuscates an examination of the relationship between milk DHA percent composition and relative brain size. For example, if values from the Nigerian population are taken as the comparative human sample, there is a significant and positive relationship between the two variables ($R^2=0.81$, $p<0.01$; Fig. 10.3). In this example, humans have the highest mean value, more than twice the concentration found in any other nonhuman primate, and it therefore appears that species with larger relative brain sizes have higher milk DHA concentration. However, using DHA values from women consuming a Western diet negates this relationship

($R^2=0.16$, $p=0.25$; Fig. 10.3), and human milk DHA is either similar to or lower in concentration than that found in nonhuman primate milks. Thus, whether or not larger relative brain sizes in humans are associated with higher milk DHA concentration is entirely dependent on the human population that is selected. Clearly, a Western diet is a novel evolutionary niche and is unlikely to mimic the diet of our Paleolithic human ancestors or other hominins in regard to DHA consumption. However, it is not clear that the Nigerian population, with their high consumption of fish, is representative either.

These conflicting results suggest that it may not be possible to test the proposed relationship between DHA and brain size with the data at hand. However, several important conclusions can still be made with regard to human and nonhuman primate DHA metabolism:

- (1) The variability among humans (including the four populations from this analysis as well as other published findings, e.g., Brenna et al. 2007) indicates that they lack any sort of compensatory mechanism for increased milk DHA when faced with maternal diets that lack DHA, although it is such a mechanism that is proposed to have been under selection.
- (2) Increased consumption of ALA by humans and nonhuman primates results only in increased values of milk ALA rather than desaturation and elongation to DHA. Thus, the most efficient way to increase the proportion of milk DHA is through increased consumption of preformed sources of DHA.
- (3) Similar values in vegan humans (0.14% of total fatty acids) and wild living nonhuman primates (0.09–0.14%) suggest that there may be a minimum DHA concentration among all anthropoid primates without a preformed source of DHA in their diet. Foods rich in DHA are rare or absent in the diets of almost all nonhuman primates, and a vegan diet is a novel dietary strategy in humans.

Taken together, these observations suggest that if changes in relative adult brain size in the human lineage required higher milk DHA concentration, then there would have to be concomitant changes in maternal diet. The derived feature for humans, then, might not be milk composition but increased access to and inclusion of foods rich in DHA (Milligan and Bazinet 2008).

10.4 Moving Beyond Milk Composition

Natural selection does not seem to have provided humans with a unique mechanism for supplying DHA during lactation. This finding seems surprising, considering the apparent compensatory mechanisms for brain accretion of AA and the well-documented increased requirements for DHA in brain and central nervous system tissues among human infants relative to nonhuman primates (Agostoni et al. 2001; Carlson 2001; Gibson and Kneebone 1981; Gibson and Makrides 1999, 2000). If larger brains do in fact require more DHA, how are human infants getting it? In this section of the chapter, I address alternative targets for selection to increase the supply of LCPUFA for the developing fetal and infant human brain.

10.4.1 Selection on Milk Volume

Results presented in this chapter speak only to milk quality, not to the quantity of LCPUFA the infant was consuming. Data on milk composition reflect what the mother is physiologically capable of manufacturing, which is not equivalent to what the infant is able to extract over the course of lactation. If human infants ingest more milk than nonhuman primates, their intake of DHA will be higher despite similar proportions of this fatty acid in milk. However, if selection acted on volume and it is the derived feature of lactation related to our unique brain growth pattern (Hinde and Milligan 2011), what still requires explanation is the extreme variation among human populations in milk LCPUFA composition.

10.4.2 Selection on Conversion Rates

One way to increase milk DHA concentration without increasing DHA consumption would be to increase the rate at which ALA is converted to DHA, either in maternal or infant metabolism. This would be an alternative hypothesis to that proposed by Martin (1983), but the end result would be the same—increased DHA available for brain growth and development. Data on conversion rates from humans and baboons with regard to conversion efficiency are available, but they do not support this hypothesis (Brenna 2002; Burdge 2004; Farquharson et al. 1992; Huang and Brenna 2001; Sheaff-Greiner et al. 1997). The bioequivalence (defined as the relative efficacy of brain accretion between the two molecules) of ALA and DHA was estimated to be approximately 7:1 in human adults (Huang and Brenna 2001). Human neonates and infants may be even less efficient than adults in conversion to DHA. Without a preformed source of DHA in their diet, the rate of DHA formation from ALA in human infants may be inadequate in meeting neural requirements, especially in preterm infants who have an increased requirement for DHA (Salem et al. 1996). Findings are similar in baboons. The relative accretion of labeled DHA as a percentage of the dose received was seven times greater in baboons receiving DHA than those receiving ALA (Su et al. 1999). Additionally, preformed DHA was incorporated into fetal baboon tissues at least one order of magnitude higher than was DHA derived from ALA (Sheaff-Greiner et al. 1997). Finally, a large endogenous pool of ALA is not associated with increased conversion of DHA in infant or adult humans (Brenna 2002) or infant baboons (Sheaff-Greiner et al. 1997; Su et al. 2005).

Based on these findings, it could be suggested that Old World anthropoid primates, as a whole, are inefficient in conversion of ALA to DHA and that the most efficient method for increasing the proportion of DHA in milk, adult, or neonatal plasma is by direct transfer of DHA from circulating lipids from the diet or depot stores. It is interesting to note that there are several non-primate species with more efficient conversion between ALA and DHA, including pigs and rats (Brenna et al. 2009). This suggests that there are mechanisms that natural selection could act on

that would result in increased desaturation and elongation by maternal (or infant) metabolism, such as the upregulation of the enzyme Δ -6 desaturase.

Recently, such a potential target was identified (Caspi et al. 2007). The *FADS2* gene (fatty acid desaturase 2) encodes the Δ -6 desaturase enzyme, and its activity also is regulated by the concentration of LCPUFA in the diet. Particular allelic variants of the *FADS2* gene were associated with higher IQ scores among breast-fed children relative to those fed formula without DHA (Caspi et al. 2007). In addition, no IQ differences were identified between breast-fed and formula-fed children carrying a different allele. Thus, there is a gene-environment interaction whereby individuals with particular genotypes that receive breast milk (with some amount of DHA—milk composition was not measured) have higher IQs, and thus presumably higher cognitive function, than those with alternate genotypes or those who are formula-fed without any DHA. It is important to point out that Caspi et al. (2007) did not identify the molecular mechanisms whereby these alternative alleles influence Δ -6 desaturase activity, although they did suggest it could be related to efficiency of fatty acid processing as a result of increased transcription of this enzyme. In addition, the distribution of these various genotypes across human populations is unknown, as is the date of appearance of these various alleles. However, if increased transcription of Δ -6 desaturase were critical for increases in brain size over the course of human evolution, one would predict a very low frequency and recent mutational event for allele variants that have alternative effects, particularly since the environmental factor they addressed (breastfeeding) was the only one available to infants until the mid-twentieth century.

10.4.3 *Metabolic Differences*

Selection for larger brain size and rapid postnatal brain growth also may have resulted in unique metabolism of fatty acids. For example, larger relative brain sizes may have been accompanied by selection on infant metabolism, such that any DHA that was ingested was preferentially used for brain growth and development. Chamberlain (1996) suggested one possible mechanism by which this could be accomplished. He argued that the enzyme ethanolamine phosphotransferase, which sequesters n-3 LCPUFA, might have been under selection over the course of human evolution. Thus, although conversion efficiency may be reduced in humans, the fate of the DHA may differ. This hypothesis remains to be tested.

10.4.4 *LCPUFA in Our Ancestral Diet*

The data that are most suggestive against the uniqueness of human milk come from captive living primates consuming a preformed source of DHA in Monkey Chow and human females who do not consume a preformed source of DHA. The

former that nonhuman primates may have similar physiological capabilities for transferring dietary DHA into milk DHA; the latter, that without dietary DHA human milk DHA concentrations are identical to or less than those from smaller-brained nonhuman primates. But is either of these populations a realistic representation of their species' "natural diet"? The primary dietary sources of DHA include brain tissue, bone marrow, and aquatic foods (e.g., algae, shellfish, fish), resources that are rare or nonexistent in the diets of most nonhuman primates. In the same regard, vegan and vegetarian diets are a strong departure from the proposed Paleolithic Diet (Cordain et al. 2005), which would have included fats of animal origin. What may be unique in humans, then, is the inclusion of preformed sources of LCPUFA, particularly DHA, in the diet (Milligan and Bazinet 2008). Thus, selection would not have needed to act on conversion rates, metabolic pathways, or milk volume for the simple reason that DHA was sufficiently present in the diet of our ancestors.

There is much debate in the anthropological literature over possible sources and amounts of DHA in our *Homo* and australopithecine ancestors (Broadhurst et al. 1998, 2002; Carlson and Kingston 2006; Cordain et al. 2001; Crawford 1992; Crawford et al. 1999; Cunnane 2005). The dietary niche of the earliest members of the genus *Homo* has been argued to include access to brain and marrow from animal carcasses, terrestrial sources of DHA (Blumenshine 1995; Blumenshine and Madrigal 1993; Brantingham 1998; Cordain et al. 2001; Madrigal and Blumenshine 2000). Others (e.g., Broadhurst et al. 1998, 2002; Crawford 1992; Crawford et al. 1999) argue for a diet based on marine and lacustrine fish and shellfish. Faunal remains dated to 1.95 million years ago from Koobi Fora suggest that hominins prior to *Homo erectus* may have been utilizing both terrestrial and lacustrine sources of DHA (Braun et al. 2010). Regardless of where the preformed sources of DHA were coming from, if high levels of DHA are found to be important for hominin encephalization, then at some point in human evolution, there would have been a need for a shift toward a consistent, predictable, and generous supply of DHA. Our modern diets with increased amounts of n-6 fatty acids and decreased amounts of n-3 fatty acids are strikingly different than what is believed to have characterized the diet of *Homo sapiens* for most of our existence. Indeed, one explanation offered for the small decreases in cranial capacity since the advent of agriculture is decreased DHA consumption (Cordain et al. 2005).

Considering the wide variation in human milk LCPUFA profiles, Agostoni (2005) offers an interesting perspective. He proposes that very low values of DHA or AA identified in human milk may not be problematic, nor is there such a thing as the correct concentration of these fatty acids. Rather, fetuses may become accustomed to the supply of fatty acids from their mother during intrauterine life, and infants would then be "imprinted" with a specific fatty acid pattern during gestation (Agostoni 2005). Following from models of developmental plasticity, their fatty acid metabolism may be programmed to the maternal environment and the infant's genetic background, and thus the fatty acid composition of the offspring's own mother's milk is the best for any infant because they calibrated their growth and development to these levels during the fetal stage (Agostoni 2005).

10.4.5 Placental Transfer

Finally, larger brain size may have selected for preferential placental transfer of LCPUFA among humans (and their ancestors who shared this brain growth trajectory). The human fetus obtains the majority of its LCPUFA from placental transfer of preformed LCPUFA (Rutherford 2012) rather than from the conversion of 18-carbon precursors (Brenna 2002; Carlson 1999; Carnielli and Sauer 1996; Koletzko et al. 2001). The human fetus is estimated to assimilate at least 400 mg of DHA per week during the last trimester (Lauritzen et al. 2001), with little ALA sequestered by the brain for production of DHA (Huang and Brenna 2001). However, the human fetal liver does have the ability to convert ALA (and LA) into DHA (and AA). Desaturase activities have been detected in aborted fetuses as young as 17 weeks gestational age (Brenna 2002). Like infants and adults, however, human fetuses appear to be relatively inefficient at this process, and total whole body conversion is highly dependent upon the supply of LCPUFA in the maternal diet (Brenna 2002; Burdge 2004; Carlson 2001).

With inefficient conversion of ALA by the offspring, the demand for DHA therefore is mainly on the mother. Consequently, maternal plasma concentrations of DHA must increase during pregnancy by either increased dietary consumption of DHA, increased mobilization of DHA from body stores, increased maternal abilities to convert ALA to DHA, or increased maternal abilities to transfer DHA (Burdge 2004). Maternal plasma concentrations of DHA have been shown to increase throughout the course of gestation without increasing dietary intake of DHA, possibly due to the effect of increased estrogen (Burdge 2004; Giltay et al. 2004). Higher levels of circulating estrogen are associated with upregulation of DHA synthesis from ALA (Giltay et al. 2004). Therefore, increased concentrations of circulating estrogen in humans may result in increased placental transfer of DHA, regardless of dietary intake of DHA. To my knowledge, there have been no comparative studies of circulating estrogen and DHA synthesis in nonhuman primates, so it is not possible to say whether this feature of human gestation is derived or ancestral.

Rutherford and Abrams (in press) offer an additional mechanism for increasing placental transport of LCPUFA: increased placental surface area as a result of the intensive invasiveness of the human placenta. They argue that the human placenta is unique in the increased chorionic villous surface area that is in contact with maternal circulation and that both passive and active transport of LCPUFA increase with increasing placental surface area. Therefore, even with diets similar in DHA, human mothers would be able to transport more of this fatty acid across the placenta than nonhuman primates with less invasive placental morphology.

Interestingly, Capellini et al. (2011) found no association between increased placental invasiveness and neonatal encephalization. However, increased placental transfer of LCPUFA may be critical for postnatal brain growth and may explain human neonatal body fat composition. At birth, human neonatal body fat has higher concentrations (three to four times) of DHA and AA than the mother's body fat

(Cunnane 2005). Cunnane (2005) estimates that the reserve DHA in the newborn human could provide all the DHA needed for growth and development of the brain and body for 50 days. He refers to this supply as insurance: because the pathway from ALA to DHA is inefficient and susceptible to inhibition, a supply of preformed LCPUFA across the placenta reduces the possibility of compromises in early brain development (Cunnane 2005). Human neonates have larger stores of body fat at birth relative to nonhuman primates, a feature also argued to be related to the need for energy reserves for brain growth (Ellison 2001; Kuzawa 1998). Taken together, these observations suggest that encephalization may have required not just an increase in neonatal body fat but also an increase in particular types of fats (e.g., DHA) in the neonate. Data on the composition of body fat in neonatal nonhuman primates is currently unavailable, and thus this hypothesis remains untested.

10.5 This Is Your Brain on Milk

Any or all of the above proposed targets of selection may have been important in increasing neonatal and infant brain LCPUFA concentration in response to changes in brain size over the course of human evolution. All, however, depend on the assumption that there is an *optimal* amount of DHA (and presumably AA) required for normal human brain growth and development (and thus optimal cognitive and neurological function) among living humans today.

Interestingly, this optimal amount of DHA is unknown. There is much debate over what should be considered optimal cognitive development and how this should be assessed, making it difficult to determine the quantity of DHA that is considered sufficient and thus what constitutes insufficiency (Cunnane et al. 2000). Additionally, there is the issue that infant DHA levels can only be quantified through autopsy and are therefore an opportunistic measurement that is rarely made (Hoffman et al. 2009). Based on a very small sample size (from breast-fed infants of women consuming Western diets), Cunnane et al. (2000) suggest that human infants require approximately 20 mg of DHA per day. Breast milk with at least 0.2% of fatty acids as DHA is sufficient to meet this requirement, while formulas with only ALA as n-3 LCPUFA (usually as 1.5% of total fatty acids) are insufficient (Cunnane et al. 2000). Indeed, formula-fed infants were found to have half of the brain DHA observed in breast-fed infants (Cunnane et al. 2000). Increasing ALA levels only slightly increases circulating DHA levels (and presumably brain DHA concentration) but never to levels seen in breast-fed infants or those receiving formula supplemented with DHA (Koletzko et al. 2008).

Despite these dramatic differences in brain fatty acid (and thus brain cellular membrane) composition, it is still unclear whether human infants with diets completely lacking in DHA have any cognitive deficiencies. There are numerous long-term studies in humans that suggest improved verbal and problem-solving skills and higher IQ in breast-fed relative to formula-fed infants, even after controlling for potential

confounding variables such as maternal IQ (or education level), socioeconomic status, ethnicity, birth weight, and gestational age (reviewed in Anderson et al. 1999; Carlson 1999). Because these were not randomized, controlled trials, it is not clear whether the differences in cognition are solely due to differences in DHA intake, to other components in breast milk (e.g., hormones: Hinde 2012), or simply to the act of breastfeeding (Carlson 1999). Stronger support for a link between DHA supplementation and cognitive improvement, particularly visual acuity as a sign of neurodevelopment, can be found in studies that compare infants receiving formula with or without DHA (reviewed in Uauy et al. 2003). However, even many of these randomized controlled studies failed to find a significant correlation between DHA intake and cognitive function, with many even finding a negative correlation (Carlson and Neuringer 1999; Uauy et al. 2003).

Heterogeneity of study designs may be one reason for the discrepancy in findings (Hoffman et al. 2009), particularly in the metric used to represent cognitive function (Carlson and Neuringer 1999). For example, some studies measure specific skills such as language development, look duration (as a measure of processing speed), or problem solving, while others focus on more general measures, such as the Bayley Scales of Infant Development (Koletzko et al. 2008). DHA intake may have a stronger effect on particular measures, such as look duration (Carlson 1999), or some measures may have a stronger environmental effect, such as language development, thus diminishing the influence of supplementation. In addition, many studies measure the influence of breastfeeding only during the lactation period, but early nutritional insults may have effects at later points in the individual's life history (Wainwright 2002). Thus, many have argued for the need for longer-term studies that integrate multiple measures of cognition. One final issue confounding studies comparing breast- with formula-fed infants is the assumption that breast-fed babies represent a homogenous group. Human milk DHA is highly variable both within and across human populations (Brenna et al. 2007; Yuhas et al. 2006, Table 10.2), and thus not every breast-fed baby is consuming the same amount of DHA. And yet quantifying milk DHA composition (as well as the quantity of milk produced and the duration of lactation) is rarely integrated into these studies, as most are retrospective in design. This variation, along with Caspi et al.'s (2007) finding that the effects of breastfeeding on IQ vary by genotype, may be one reason why some studies fail to find any effect of breastfeeding on cognition.

Although this debate occurs outside of the anthropological literature, the question of whether better milk means better brains is directly applicable to the question posed by this chapter, whether bigger brains mean better milk. The lack of consensus in finding a correlation between milk DHA concentration and cognitive function may most likely result from the fact that an infant's cognitive development results from the interaction of various genetic and environmental factors (Anderson et al. 1999; cf. Caspi et al. 2007). Results from humans and nonhuman primates that indicate a lack of correlation between relative brain size and milk DHA further suggest that something as complex as cognition is unlikely to be completely dependent on one nutritional component.

10.6 Conclusions

The dilute, low energy content of primate milk matches their “life in the slow lane” as it relates their protracted schedule of somatic growth and development. Brain growth, however, occurs on at a more rapid rate, and for many nonhuman primates, and particularly humans, this period of rapid brain growth overlaps with the period of lactation. The derived human pattern of brain growth—rapid both during gestation and lactation—led to the prediction that human milk should have a correspondingly derived composition to support and facilitate the rapidly growing brain. And yet human milk is remarkably low in energy and similar in macronutrient composition to milks of other nonhuman primates (Hinde and Milligan 2011).

This chapter investigated the LCPUFA composition of human milk to determine whether human milk does indeed have a unique signature of brain-specific nutrients, specifically AA and DHA. Data from human and nonhuman primate milk do not indicate selection in the human lineage for increased concentrations of AA or DHA or for their 18-carbon precursors (LA and ALA) in milk as a result of the shift in the timing of brain growth and larger relative brain size. Human and nonhuman primate milk LCPUFA concentrations appear to be directly related to maternal dietary intake of n-3 or n-6 fatty acids, such that their increased consumption results in increased proportions in milk. Moreover, the range of variation in human milk DHA profiles (Brenna et al. 2007; Yuhas et al. 2006) is nearly identical to that of nonhuman anthropoids (Milligan and Bazinet 2008), as a result of variation in maternal consumption of preformed sources of DHA.

The strong influence of diet made it impossible to test for a unique human milk signature—which human population should be selected to represent the ancestral LCPUFA profile?—but such a finding in itself suggests a lack of evolutionary modifications in milk composition over the course of human evolution. If selection had acted on human milk production for increased LCPUFA concentration, one would predict that there will be less variation related to maternal diet in modern populations. Instead, the variation among human populations in LCPUFA concentration coupled with the similarity in response between humans and nonhuman primates to diets lacking in preformed DHA suggests that the mechanisms for transport of LCPUFA from maternal plasma and depot fat to milk in humans may be an ancestral trait shared among all anthropoid primates. Bigger brains do not appear to select for better milk.

Operating under the assumption that larger brains require higher concentrations of brain-specific nutrients such as DHA, attention should be directed away from milk composition and toward other possible targets of selection, including increased milk volume, increased enzymatic activity to preferentially sequester more fatty acids from milk, and an emphasis on placental transfer of LCPUFA. Underscoring any investigation is the necessity to quantify the DHA (and other fatty acid) requirements of a human brain during ontogeny relative to that of other primates and mammals and a better understanding of how these fatty acids are utilized by the developing brain. Findings have the potential to substantially alter our understanding of the

mechanisms regulating pre- and postnatal transfer of fatty acids and will direct future research investigations interested in understanding how humans built their bigger brain.

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Chapter 11

Infant Gut Microbiota: Developmental Influences and Health Outcomes

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Keywords Symbiosis • Immune system • Lactation • Commensal bacteria • Milk • Metabolic processes

11.1 Introduction

Ninety percent of all cells in the human body are not human at all, but bacterial. Human and other mammalian-associated bacterial populations, or microbiota, inhabit all exterior and interior surface niches of the body, including the skin, upper respiratory, and gastrointestinal (GI) tract (Blaser 2006). Of these, the gut microbiota are the most numerous and diverse. The typical human gut microbiota contains 500–1,000 different species (Sonnenburg et al. 2004) with a collective gene pool, or microbiome, that harbors 100 times more genes than the human genome (Hooper et al. 2002).

Gut microbiota *coevolved* with their hosts, signifying that over time those bacteria that had no negative impact on (i.e. commensals) or enhanced host fitness (i.e. mutualistic) came to commonly associate with particular hosts. A growing body of research has shown that gut microbiota substantially enhance host digestion, energy turnover, and absorption of nutrients (Bentley and Meganathan 1982; Canny and McCormick 2008; Dethlefsen et al. 2006). Gut bacteria also provide a vital barrier against intestinal pathogens, regulate immune development and response, and may

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facilitate gut–brain communication (MacDonald and Monteleone 2005; Mazmanian et al. 2005; Neufeld et al. 2011; Noverr and Huffnagle 2004; Savage 1977). However, these beneficial bacteria constantly compete with other bacteria in the host environment for predominance in the gut. At any given time, gut microbial populations are sensitive to host diet (Maslowski and Mackay 2011) and perturbations from other invading bacteria (Dethlefsen et al. 2006). The presence and relative proportions of individual species and bacterial groups in the gut may therefore vary greatly across individuals and throughout the lifespan, with varying consequences for host health (Ley et al. 2006a).

In primates, the dynamic host–bacterial relationship begins at birth, when maternal and environmental bacteria colonize sterile infant GI tracts. Major shifts in microbial composition continue over infancy with the introduction of solid foods and broader exposure to environmental bacteria (Palmer et al. 2007). During infancy, maternal milk is vital in promoting the growth of beneficial bacteria through both direct transmission and multiple biochemical and immunological factors that favor their establishment. The development and integrity of gut microbial communities during infancy may have implications for primate developmental trajectories after weaning, particularly in relation to metabolic and immune functioning later in life.

Across primates, vast differences in ecologies, diets, and duration of lactation (and in humans, differences in birth, breastfeeding, and hygienic practices) may lead to substantial interspecies and intraspecies variation in microbial development and community structure. While research on variation in primate gut microbiota owing to differences in phylogeny, ecology, diet, and pathogen exposure has increased in recent years (e.g., McKenna et al. 2008; Yildirim et al. 2010), these studies are still limited. Most of our knowledge on variation in mammalian gut microbial composition comes from clinical research on humans and mice (including experimental studies with germ-free and conventionally raised mice) and epidemiological studies of different human populations and risk groups—particularly formula vs. breast-fed infants, and Cesarean- vs. vaginally delivered infants. These models, despite their evolutionary novelty, have revealed complex relationships among early microbial exposure, lactation, diet, gut microbial community structure, and host metabolic and immune functioning. The emerging research suggests that alterations in gut microbial composition owing to modern dietary, hygienic, and medicinal practices are associated with a number of chronic diseases and conditions in industrialized populations, including obesity (Bäckhed et al. 2004; Turnbaugh et al. 2006), diabetes (Neu et al. 2010), inflammatory and immune disorders (Penders et al. 2007; Round and Mazmanian 2009; Shorter et al. 1972), and cancer (Zhang et al. 2011). Studies of variation in human gut microbiota therefore provide important insight into the impact of evolutionarily novel conditions on host health.

In this chapter, we review the current research on primate gut microbial composition and function, with a particular focus on humans and the role of maternal milk and weaning patterns in mediating infant microbial development. Throughout our discussion, we examine conditions associated with variation in microbial establishment and composition, and their associated health outcomes.

11.2 Overview of Primate Gut Microbiota: Composition and Function

The mammalian GI tract can be understood as a vast ecosystem harboring different bacterial niches, and mammalian gut microbiota as a vast organ performing multiple functions essential to host fitness (Hooper et al. 2002; Xu and Gordon 2003). The mouth, esophagus, stomach, and small and large intestines are inhabited by distinct microbial communities, with the most diverse and densely populated community inhabiting the distal gut (distal ileum, ascending colon, and rectum) (Mei Wang 2005; Savage 1977). As this microbial diversity increases, so does the number of associated metabolic and protective functions performed by them (Guarner and Malagelada 2003). Within primate species, gut microbial composition is fairly consistent at higher taxonomic levels, indicative of long coevolutionary histories, but substantially more varied at the species and strain level (Andersson et al. 2008). In humans, more than 99% of bacteria phylogenetic types (or phylotypes) in the distal gut belong to just five phyla: Firmicutes, Bacteroidetes, Actinobacteria, and to a lesser degree, Proteobacteria and Fusobacteria (Table 11.1). In humans, Firmicutes dominate, represented principally by the Clostridia class, which includes the *Ruminococcus*, *Clostridium*, and *Eubacterium* genera (Andersson et al. 2008; Dethlefsen et al. 2006). Bacteroidetes is generally the second most predominant group (Bäckhed et al. 2004; Bäckhed et al. 2005; Eckburg et al. 2005) represented primarily by *Bacteroides* genus, including *B. vulgatus*, *B. thetaiotaomicron*, *B. distans*, and *B. fragilis*. Actinobacteria is dominated by the *Bifidobacterium* genus. Anaerobic bacteria (which use fermentation rather than oxygen for cellular respiration) are the most abundant bacteria across all phylotypes. Facultative anaerobes (which can use either oxygen or fermentation for respiration) are present to a lesser degree (Marteau et al. 2001) and include *Escherichia*, *Lactobacillus*, and *Streptococcus* species.

Table 11.1 Major bacteria and functions of human gut microbiota

Major phyla	Common genera	Functions
Firmicutes	<i>Clostridium</i>	Protect gut surface tissue; carbohydrate and amino acid fermentation
	<i>Lactobacillus</i>	Carbohydrate fermentation; inhibit growth of pathogens; antidiarrheal
Bacteroidetes	<i>Eubacterium</i> , <i>Staphylococcus</i> , <i>Ruminococcus</i> , <i>Streptococcus</i> , <i>Enterococcus</i>	Carbohydrate fermentation
	<i>Bacteroides</i>	Carbohydrate and amino acid fermentation; immunoregulation
Actinobacteria	<i>Bifidobacterium</i>	Carbohydrate fermentation; bind to and inhibit growth of pathogens
Proteobacteria	<i>Escherichia</i>	Vitamin K synthesis
Fusobacteria	<i>Fusobacterium</i>	

Firmicutes and Bacteroidetes also dominate the gut microbiota of mice and macaques (McKenna et al. 2008), suggesting a long coevolutionary history of these phyla in mammals. Across primate species, gut microbial communities are distinct (McKenna et al. 2008; Yildirim et al. 2010), although phylogenetic differences strongly overlap with dietary adaptations. In fact, mammalian gut microbial compositions are better predicted by host dietary classification (i.e., carnivore, herbivore, omnivore, frugivore, folivore) and gut physiology (i.e., foregut or hindgut fermentation) than by phylogeny (Ley et al. 2008). Among humans and captive nonhuman primates, gut microbial compositions cluster by classification as omnivore/frugivore (humans, chimpanzees, baboons, spider monkeys, lemurs), hindgut fermenting omnivore/folivore (gorillas and orangutans), or foregut herbivore (colobines) (Ley et al. 2008). Interestingly, sex differences in microbial composition have been observed for macaques and mice, but not humans, the reasons for which are as yet unclear (McKenna et al. 2008).

Gut bacteria perform numerous critical functions for primate hosts, including enhanced energy extraction, protection against invading gut pathogens, and aiding of immune development and regulation. First, through the fermentation process, gut bacteria break down certain dietary-derived molecules, including some non-digestible food fibers, polysaccharides, oligosaccharides, and polyphenols, which hosts are otherwise unable to digest or absorb. Bacterial fermentation also produces short-chain fatty acids (SCFAs), such as acetate and butyrate, which are then used as energy sources by host cells and other beneficial bacteria (Gibson and Roberfroid 1995; Guarner and Malagelada 2003). Gut bacteria have also been shown to directly mediate lipid absorption and fat tissue deposition (Bäckhed et al. 2004). The extra energy harvested from gut bacteria provides a substantial advantage to hosts: for example, rats raised without gut bacteria require 30% more calories to maintain the same body mass as their conventionally raised counterparts (Wostmann et al. 1983).

The metabolic byproducts of gut bacteria are essential to other aspects of host fitness as well; for example, *Lactobacillus* bacteria degrade lactose into lactic acid (Sanders 1994), which increases the acidity of the gut and inhibits growth of harmful bacteria. Certain gut bacteria are mutualistic because they produce vitamins that considerably benefit the host. For example, *Escherichia coli* synthesizes vitamin K (Bentley and Meganathan 1982), important in blood clotting, bone growth, and maintenance of bone density.

Finally, gut microbiota form a critical barrier along intestinal surfaces that protect hosts from pathogens invading the intestinal tract, and are some of the first *antigens* (non-host molecules, Box 11.1) to stimulate the naïve infant immune system. As will be discussed in greater detail further on, this early bacterial stimulation influences the development and maintenance of immune system organs, cells, and responses, and “primes” the immune system to effectively and appropriately respond to pathogenic and nonpathogenic substances (Díaz Ropero et al. 2007; Macpherson and Harris 2004; Newburg and Walker 2007).

Before proceeding, it should be noted that much of our current knowledge of primate microbial diversity and function has emerged only in the last decade, aided

Box 11.1 Overview of the immune system

The immune system is an integrated system of specialized cells and molecules that recognize, eliminate, and contain damage resulting from invading pathogens and harmful antigen

Pathogen: a microorganism capable of colonizing host sites and causing disease. Includes *microparasites* (bacteria, virus, fungi, protozoa) and *macroparasites* (intestinal worms, ectoparasites)

Antigen: any foreign substance (e.g., bacterial cell membrane protein, bacterial toxin, pollen) capable of eliciting an immune response

Pathobiant: intestinal bacteria with pathogenic potential

Immune cells

Lymphocytes: white blood cells with antigen receptors that circulate in blood and lymph; the two major classes are T and B cells

T cells: mediate cytotoxic responses against virus-infected cells; activate B cells and phagocytic cells that ingest harmful particles and microorganisms. Upon activation by specific antigen, T cells may differentiate into T helper cells (e.g., T_H1 , T_H2 , T_H10 , T_{reg}) that promote targeted immune responses

B cells: secrete specific antibodies that mediate pathogen clearance

Dendritic cells: phagocytic cells that recognize and ingest infectious agents, then migrate to lymphoid tissues to present infectious antigen to T cells, activating immune responses

Toll-like receptors (TLRs): receptors on dendritic and other immune cells that recognize molecules from common pathogens (e.g., lipopolysaccharide on bacteria cell membranes)

Pathogen associated molecular patterns (PAMPS): molecular patterns that occur on pathogens, but not mammalian cells; recognition by dendritic cell TLRs initiates immune responses

Immune cell products

Immunoglobulins (Ig): antibodies secreted by B cells that bind to antigen and aid in pathogen clearance

IgG: present in breast milk, crosses the placenta during pregnancy to protect the fetus

IgM: present in breast milk, prevents pathogens from attaching to mucosal surfaces

IgA: its secretory form (sIgA) is the major immunoglobulin in breast milk, stays largely intact in the infant intestine, and transfers maternal immunity against many viral and bacterial pathogens to infants

IgE: protective against macroparasites, mediates immune responses (e.g., histamine production) that can produce symptoms of allergy, asthma, and hypersensitivity

Cytokines: proteins that are produced by and target immune cells in order to mediate immune responses

(continued)

Box 11.1 (continued)

INF- γ : secreted by T_H1 cells and activates phagocytic cells and inflammatory responses

IL-4, IL-5, IL-13: promote T_H2 activity, including antibody production and wound repair

IL-10 and TGF- β : associated with T_{reg} activity and have immunosuppressive effects

Lymphoid tissues and organs

Lymph nodes and spleen: sites of lymphocyte maturation; filter and present foreign antigens to T and B cells, aiding in immune cell activation and proliferation

Germinal centers: region in lymph nodes and spleen where B cell activation occurs

T and B cell zones: sites of B- and T-cell differentiation in lymphoid tissues, important in immune cell memory and antibody production

Gut-associated lymphoid tissues (GALT): innermost layer of the gastrointestinal wall. Contains immune cells and structural components that function dually to respond to invading pathogens and maintain non-responsiveness to host cells, commensal bacteria, and food antigens

Peyer's patches: lymphoid compartments within the GALT specialized to sample foreign antigen

by recent advances in gene sequencing techniques. These techniques have shown that the majority of intestinal bacteria actually belong to unknown, uncultured lineages (Dethlefsen et al. 2006). Extensive longitudinal and comparative sampling across human populations and captive and wild nonhuman primate species has also been limited (Ley et al. 2008). As both molecular technologies and population sampling continue to advance and broaden, so will our knowledge of the scope of primate microbial diversity and function. In the following sections, we draw on existing research from this dynamic field to highlight four key topics of gut microbiota relevant to infant development: the development of gut microbial communities during infancy, the influence of gut microbiota on immune development, environmental influences on microbiota development and composition, and the role of gut microbiota in metabolic and immune functioning from infancy to adulthood.

11.2.1 Development of Gut Microbiota During Infancy

Infant gut microbial communities are distinct from adult profiles in key aspects related to infant diet (especially maternal milk); they also undergo pronounced shifts in composition over the course of weaning and with increased environmental bacteria exposure (Edwards and Parrett 2002). Shortly after birth, full-term, vaginally delivered

infants are colonized by facultative anaerobes (e.g., *Lactobacillus* and *Streptococcus* species). Thereafter, *Bifidobacterium* often come to dominate the gut microbiota of breast-fed infants (Favier et al. 2002). With advancing age and weaning, the number of facultative anaerobes decreases and the number of obligate anaerobes (e.g., *Bacteroides* and *Clostridium* species) increases (Magne et al. 2006; Zhang et al. 2005). Introduction of solid foods and full cessation of breastfeeding are associated with major shifts in the infant microbiota (Favier et al. 2002). In industrialized populations, infant gut microbiota converge toward stable, adult-like phylotypic compositions (i.e., domination by Firmicutes and Bacteroidetes) by the first year of life, although community structure at the species and strain level remains highly variable among individuals (Palmer et al. 2007). Studies in nonindustrialized populations, however, have shown that microbial composition may fluctuate throughout childhood (Balamurugan et al. 2008; Hopkins et al. 2002). Substantial cross-cultural variation in the establishment of adult microbial profiles is expected because breastfeeding and weaning patterns are highly divergent across human populations, and maternal milk and the weaning process are major determinants of microbial compositions during infancy (McClellan et al. 2008; Obermeyer and Castle 1996; Sellen 2001).

11.2.2 Maternal Milk and the Establishment of Beneficial Gut Microbiota

Milk contains *antimicrobial*, *prebiotic*, and likely *probiotic* factors that function dually to promote the growth of beneficial gut bacteria and inhibit pathogenic bacteria from establishing and replicating in the infant GI tract (Table 11.2). *Antimicrobial* and other immune factors in milk mediate establishment of beneficial and pathogenic bacteria. Factors in milk such as epidermal growth factor, SCFAs, lactoferrin, and casein stimulate the growth of beneficial bacteria and support growth and repair of epithelial (surface tissue) cells (Edwards and Parrett 2002; Edwards et al. 1994; Hamosh 2001; Lawrence and Pane 2007; Petschow et al. 1999). *Lactoferrin* binds to gram-negative bacteria surfaces and opens membrane pores allowing *lysozyme* to enter and attack the bacterial cell interior (Ellison 1991). *Lactoferrin* also has a high affinity for iron, which decreases the amount of iron circulating in hosts that could be used by pathogenic bacteria for growth and replication (Lawrence and Pane 2007). Free fatty acids in milk have antimicrobial properties (Hamosh 2001), while maternal antibodies (*sIgA*, and to a lesser extent, *IgG* and *IgM*) (Box 11.1) secreted in milk bind to and facilitate killing of multiple pathogens, including pathogenic *E. coli*, *Shigella*, *Salmonella*, *Vibrio cholerae*, *Hemophilus influenzae*, *Clostridium difficile*, *Giardia*, and *Candida albicans* (Goldman 1993).

Probiotics are beneficial bacteria that directly establish in the gut (Lawrence and Pane 2007). Collectively, they produce nutrients for hosts (e.g., arginine, glutamine, SCFAs), compete with pathogens for intestinal colonization, increase production of mucus and *sIgA*, and stimulate mucosal cell immune responses and peristalsis (contractions of the intestinal tract) (Lawrence and Pane 2007). Bacteria commonly isolated from breast milk samples include *Bifidobacterium*,

Table 11.2 Factors in maternal milk that influence establishment and growth of beneficial gut microbiota in infants

Factors	Effects on microbiota	Common factors	Specific functions
<i>Prebiotic</i>	Undigested fermentable carbohydrates that support beneficial bacteria growth and establishment	Oligosaccharides and glycoconjugates (mucin, lactadherin, gangliosides, glycosaminoglycan)	Serve as energy for beneficial bacteria; inhibit pathogens from adhesion to gut; selectively nourish <i>Bifidobacterium</i> (oligosaccharides)
<i>Probiotic</i>	Bacteria isolated in human milk samples	<i>Bifidobacterium</i> sp. <i>Staphylococcus</i> sp. <i>Streptococcus</i> sp. <i>Lactobacillus</i> sp. <i>Enterococcus</i> sp.	Serve as a barrier to invading pathogens; produce nutrients and energy for host cells; stimulate infant immune system
<i>Immune factors</i>	Limit establishment and damage associated with pathogenic bacteria	Maternal antibodies (e.g., IgG, IgM, sIgA), leukocytes, cytokines, complement, TLRs Lysozyme, lactoperoxidase; α -lactalbumin, κ -casein; fatty acids (e.g., lauric and linoleic), lactoferrin Epidermal growth factor (EGF)	Targeted pathogen binding and clearance; stimulation and modulation of infant immune system Bacterial killing; antiadhesive; antimicrobial, limit iron available to pathogens (lactoferrin) Promotes epithelial barrier integrity

Reviewed in Edwards and Parrett (2002), Field (2005), Hamosh (2001), Lawrence and Pane (2007), Martín et al. (2004), Newburg (1996), Newburg and Walker (2007)

Lactobacillus, *Staphylococcus*, *Streptococcus*, *Bacteroides*, *Clostridium*, *Micrococcus*, *Enterococcus*, and *Escherichia* (Díaz Ropero et al. 2007; Martín et al. 2003, 2004, 2009). These bacteria have been isolated in fresh milk from women across different countries, and appear to be natural components of milk, not contaminants (Martín et al. 2004). The exact pathway by which these bacteria reach the mammary glands, however, has yet to be determined. Bacteria may be taken up by *dendritic cells* (DCs) (Box 11.1) in the gut lumen and then carried by DCs throughout the mucosal-associated lymph tissue (MALT), ultimately reaching mammary glands (Martín et al. 2004, 2009).

Prebiotics are polymers of carbohydrates that are not broken down or absorbed by the host, but are instead consumed by gut microbiota through fermentation (Gibson and Roberfroid 1995). The fermentation process produces numerous byproducts essential to host energy intake and other physiological processes, and in addition lowers gut pH levels (Bongers and van den Heuvel 2003), making the GI environment more inhospitable to invading pathogens. Prebiotics also prevent pathogens from adhering to mucosal surfaces (Newburg 1997) and stimulate production of the anti-inflammatory cytokine *IL-10* (Box 11.1) and other mucosal immune defenses (Roller et al. 2004). The primary prebiotics in milk are oligosaccharides, although some proteins (e.g., casein), peptides, and nucleotides may also have prebiotic functions (Lawrence and Pane 2007).

Oligosaccharides are the third most abundant solid component in human milk following lactose and lipids, with approximately 200 different structures identified to date. Milk oligosaccharides are complex sugars composed of the monosaccharides (simple sugars) glucose, galactose, *N*-acetylglucosamine, fucose, and sialic acid, a sugar derivative. These components are linked together in short chains by 13 potential α and β glycosidic linkages (covalent bonds between the sugars), resulting in a multitude of possible structural combinations containing 3 to 30 sugar residues. Given the number of possible combinations, it is somewhat surprising that only about 200 structures have been found, suggesting a structural constraint for bioactive functions. (Ninonuevo et al. 2006; Zivkovic et al. 2010).

Despite their abundance, human milk oligosaccharides (HMOs) are indigestible and instead act as prebiotics by furnishing nutrient substrates for beneficial bacteria. The β -glycosidic linkage between *N*-acetylglucosamine and galactose is of particular importance in this regard. Humans are incapable of splitting this bond, allowing HMO to reach the colon with minimal digestion (Gnath et al. 2000; Chaturvedi et al. 2001). Bacteria require specific enzymes to ferment HMO, especially sialidase, α -L-fucosidase, *N*-acetyl- β -D-hexosaminidase, and β -D-galactosidase. While many intestinal bacterial species produce the enzymes galactosidase and hexosaminidase, bacterial fucosidases (Katayama et al. 2005) and sialidases are less prevalent, and may be associated with bacteria that have coevolved with HMO delivered to the breast-fed infant gut. For instance, acidic oligosaccharides (i.e., those decorated with sialic acid) are specifically metabolized by *Bifidobacterium infantis* (Sela 2011), which is enriched in the breast-fed infant GI tract (Matsuki et al. 1999). In fact, among bacteria tested to date, only *Bifidobacterium* and *Bacteriodes* species are able to consume HMO as a sole carbon source

(Marcobal et al. 2010). *B. infantis* contains several unique gene clusters that permit it to transport and metabolize milk oligosaccharides within the cell (Sela et al. 2008), suggesting a coevolutionary relationship between this bacterium, milk, and the human host (Zivkovic et al. 2010).

The structural characteristics and diversity of milk oligosaccharides also directly inhibit the establishment of multiple pathogens. Acidic oligosaccharides help prevent pathogenic bacteria from adhering to the epithelial surface (Guggenbichler et al. 1997) and provide protection against rotavirus diarrhea (Ciarlet et al. 2001). Meanwhile, oligosaccharides decorated by fucose confer protection against pathogenic *Campylobacter*, cholera, *E. coli* toxin, and some caliciviruses (Newburg et al. 2004).

Interestingly, like gut microbial compositions themselves, the probiotic and prebiotic compositions of primate milks show some interspecific variation. For example, while human and macaque milks both contain a high abundance of *Streptococcus* and *Lactobacillus* bacteria, they differ in the presence and abundance of particular species in these genera (Jin et al. 2011). However, it is unknown whether differences in milk bacteria composition across primates are specifically adaptive or merely reflect individual differences in the maternal gut bacteria from which they may be derived.

Generally, as compared to other mammalian milks, primate milks have more complex and diverse oligosaccharides. Specific compositions and concentrations of oligosaccharides vary across species (including among the great apes), but not necessarily by phylogeny (Tao et al. 2011; Urashima et al. 2009). Human milk, however, appears to be unique among other primate milks (including those of more closely related great apes) in both overall oligosaccharide diversity and the predominance of type I oligosaccharides, which facilitate the growth of *Bifidobacterium* in the infant gut (Urashima et al. 2009). The differences in milk oligosaccharide composition across primates, and particularly between humans and nonhuman primates, may reflect differences in pathogen exposure and infection risk associated with increased sociality and group size (Tao et al. 2011). As stated earlier, because milk oligosaccharides bind to and inhibit the establishment of pathogens in the infant intestine, milk oligosaccharide diversity may track species-specific parasite prevalence and richness. Individual variation in milk oligosaccharide composition also appears to be greater within humans than within other primate species, and may reflect additional variation in human environments, diets, age, and blood types (Tao et al. 2011).

11.3 Gut Microbiota, Immune Development, and Immunoregulation

Gut microbiota interact with the immune system throughout life, providing both barrier protection against pathogens and ongoing “crosstalk” with the immune system that aids in the normal development of immune tissues and regulation of

immune responses. Alterations in microbial communities and subsequent immune signaling—which may begin at birth—may be a key component in the rising incidence of immune-mediated chronic diseases in industrialized nations (e.g., allergic hypersensitivity, inflammatory bowel disorder).

The link between gut microbiota and early immune function is readily apparent in experiments with “germ-free” mice, which are born and bred without gut bacteria (Macpherson and Harris 2004; Round and Mazmanian 2009). As compared to conventionally raised mice, germ-free mice have weaker immune responses and are more likely to die when challenged with bacterial pathogens (Macpherson and Harris 2004; Sprinz et al. 1961). The absence of gut microbiota in germ-free mice also results in a number of immune system abnormalities, including poorly developed gut-associated *lymphoid tissues* (Box 11.1), reduced production of *immunoglobulin A (IgA)*, reduced *T cells* in intestinal tissues, and fewer *germinal centers* and *T and B cell zones* in the spleen (Macpherson and Harris 2004; Round and Mazmanian 2009). Strikingly, these developmental abnormalities are reversed once germ-free mice are exposed to environmental bacteria and subsequently colonized (Hrncir et al. 2008; Macpherson and Harris 2004). Of course no animals are “germ-free” in their natural environments; nonetheless, these experiments demonstrate how tightly coupled microbial exposure and colonization are to multiple facets of immune system development.

Experimental research has elicited some specific pathways by which gut microbiota maintain immune regulation and integrity of the *gut epithelium* (the tissue lining intestinal surfaces). During infancy, gut bacteria stimulate the expression of *toll-like receptors (TLRs)* on intestinal epithelial cells and *DCs* in the GI tract (Lawrence and Pane 2007). Throughout the life, commensal bacteria continuously signal gut epithelial *TLR ligands* (surface molecule complexes), triggering the production of immune factors involved in tissue repair, cell protection, and stimulation of pro-inflammatory and anti-inflammatory immune activity (Rakoff-Nahoum and Medzhitov 2006). In infancy, TLRs on DCs are activated by commensal gut microbiota and invading pathogens, and subsequently “learn” to discriminate among different *pathogen-associated molecular patterns (PAMPs)*. Effective discrimination then results in appropriate *T-helper cell* activation and differentiation (i.e., T_H1 , T_H2 , T_H17 , and T_{Reg}) (Forchielli and Walker 2005). These T-helper cells stimulate the production of different *cytokines* and *immunoglobulins* (antibodies) to combat specific pathogens.

In brief, T_H1 - and T_H17 -associated cytokines (*IFN- γ* and *IL-17*) stimulate inflammatory and cell-killing activity important in bacterial and viral clearance. T_H2 -associated cytokines (*IL-4*, *IL-5*, *IL-13*) stimulate antibody production, particularly *IgE*, and proliferation of *basophils*, *eosinophils*, and *mast cells*, which are important in clearance of macroparasites (Kaiko et al. 2008). Balanced immune responses should clear pathogens, but limit inflammatory damage to hosts and “tolerate” (or not react to) nonpathogens. Unbalanced, excessive T_H1 and T_H17 activity is associated with autoimmunity (in which the immune response attacks host cells and tissues, e.g., Coeliac disease) and intestinal inflammation (e.g., inflammatory bowel disease, or IBD). Excessive T_H2 responses are associated with atopic and

allergic reactions (Rook 2009; Round and Mazmanian 2009). Vitality, intestinal microbiota continually stimulate T_{Reg} cells to release regulatory cytokines (*IL-10*, *TGF- β*), which suppress $T_{\text{H}}1$, $T_{\text{H}}2$, and $T_{\text{H}}17$ activity, and are thus essential to balancing T-cell responses and limiting epithelial damage caused by immune activation (Rook 2009; Round and Mazmanian 2009). Throughout the host life, gut bacteria promote and maintain immune homeostasis by first educating immune cells to distinguish among pathogenic and nonpathogenic bacteria, and later by continually stimulating T_{Reg} activity.

Importantly, infant GI tracts at birth are sterile and immune responses are $T_{\text{H}}2$ biased; colonizing bacteria may initiate production of IFN- γ , IL-12, and IL-10 and balance neonatal $T_{\text{H}}2$ biasing (Hrncir et al. 2008). This immune priming may involve specific bacteria and their biochemical properties, suggesting that the type of colonizing bacteria may be vital in mediating normal immune function later in life. For example, in studies with mice, unique surface polysaccharide structures on *B. fragilis* appear to selectively stimulate $T_{\text{H}}1$ cell proliferation and IFN- γ production following colonization (Mazmanian et al. 2005). *B. infantis*, *Lactobacillus salivarius*, and *Enterococcus faecalis* have all been shown to induce T_{Reg} cytokine responses through activation of DCs and transcription factors in the intestinal epithelium (Are et al. 2008; O' Mahony et al. 2008). Different *Lactobacillus* strains isolated from human breast milk have also been shown to exert separate immunostimulatory and immunoregulatory cytokine responses (Díaz Ropero et al. 2007).

11.4 Environmental Influences on Infant Microbial Composition

Throughout human evolution and recent human history, infants have been immediately exposed to and colonized by bacteria originating from maternal vaginal fluids, feces, and skin, as well as the surrounding non-sterile environment (commonly *E. coli*, *S. aureus*, *Lactobacillus*, and *Streptococcus* species). In contrast, infants delivered in hospitals and especially via Cesarean section are first exposed to environmental bacteria that persist under more sanitary conditions (e.g., *Clostridium*, *Enterococcus*) (Adlerberth and Wold 2009). As compared to vaginally delivered infants, Cesarean-delivered infants have delayed acquisition of *Bacteroides*, *Bifidobacterium*, and nonpathogenic *E. coli*, higher abundances of *Clostridium*, *Klebsiella*, and *Enterobacter* species (excluding *E. coli*), and lower ratios of anaerobic to facultative bacteria at 1 year of age (Adlerberth et al. 2006; Penders et al. 2006). The gut microbiota of prematurely born infants, who are placed in neonatal intensive care units at birth, are dominated by antibiotic-resistant bacteria and yeast (Adlerberth and Wold 2009; Ell-Mohandes et al. 1993). The combined effects of prolonged hospitalization, antibiotic use, incubation, and formula feeding on extremely low birth weight infants are associated with delayed colonization of anaerobes, diminished presence of *Lactobacillus* and *Bifidobacterium*, and decreased species richness overall (Gewolb et al. 1999).

Less sanitary conditions during birth and infancy may actually promote the colonization and growth of beneficial bacteria. For example, acquisition of beneficial bacteria such as *Bacteroides* and *Bifidobacterium* proceeds at a slower rate among infants birthed in industrialized as compared to nonindustrialized populations (Adlerberth and Wold 2009). And in a large Dutch cohort, infants vaginally birthed at home had higher counts of *Bifidobacterium* and lower counts of *E. coli* and *C. difficile* at 1 month, as compared to infants vaginally birthed in a hospital (Penders et al. 2006). In the same study, infants with older siblings also had slightly higher *Bifidobacterium* counts than did singletons (Penders et al. 2006).

The above conditions may reflect greater exposure to fecal bacteria in the environment, but may also reflect differences in access to and frequency of antibiotic use. In both infants and adults, antibiotic usage results in immediate shifts in community composition (Dethlefsen et al. 2008; Palmer et al. 2007), including significant decreases in community richness (Manichanh et al. 2010), reduced abundance of *Bifidobacterium*, *Faecalibacterium*, and Enterobacteriaceae (Bartosch et al. 2004), and subsequent overgrowth of *E. faecalis* and *C. difficile* (Bartosch et al. 2004; Waaij 1989). Antibiotic treatment has also been linked to overgrowth of *Campylobacter* bacteria in captive macaques (McKenna et al. 2008). While studies have shown that gut microbial diversity in subjects using antibiotics rebounded to pretreatment states within 4 weeks to 3 months following treatment (Dethlefsen et al. 2008; Jernberg et al. 2007), several species had not recovered at all by 6 months (Dethlefsen et al. 2008), and Bacteroidetes diversity was dramatically reduced at 2 years post treatment (Jernberg et al. 2007).

Negative influences on gut microbial development may also originate early in life through formula feeding, although this subject is intensely debated. The presence of beneficial bacteria in milk may be expected to promote the growth of those species in breast-fed infants, but research has not consistently shown a higher prevalence or abundance of either *Bifidobacterium* or *Lactobacillus* in breast-fed vs. formula-fed infants (Adlerberth and Wold 2009; Fanaro et al. 2003; Harmsen et al. 2000). However, conflicting results across studies could reflect changes in formula composition, as pre- and probiotics have been added to infant formulas in recent years (Adlerberth and Wold 2009). Indeed, infants fed oligosaccharide-enriched formulas harbor higher counts of *Bifidobacterium* than do infants fed non-enriched formulas, and do not significantly differ from exclusively breast-fed infants in *Bifidobacterium* abundance or prevalence (Penders et al. 2006). More consistently, however, research has shown that microbiota of breast-fed infants are dominated by *Bifidobacterium* (Favier et al. 2002; Kleessen et al. 1995), whereas microbiota of formula-fed infants are more varied, with a generally greater abundance of *Bacteroides*, Clostridia, and Enterobacteriaceae (Balmer and Wharton 1989; Benno et al. 1984; Penders et al. 2006; Tullus et al. 1989).

Factors in milk other than bacteria may account for the difference in *Bifidobacterium* dominance in breast-fed and formula-fed infants (Edwards and Parrett 2002; Lawrence and Pane 2007). While some modern infant formulas are enriched with synthetic oligosaccharides to promote *Bifidobacterium* growth, HMOs are unique in their ability to bind to and competitively inhibit the growth of

other bacteria in the infant gut, thus serving as independent receptors for a variety of different pathogens, and further contributing to *Bifidobacterium* dominance (Edwards and Parrett 2002; Newburg 1997). Lower iron content and lactoferrin in milk also decrease the availability of circulating iron in the infant (Kunz and Rudloff 2006; Newburg 1997). Iron is not needed for *Bifidobacterium* or *Lactobacillus* growth, but is required by other bacteria. The greater availability of iron in formula may therefore account for the increased presence of *Bacteroides*, Enterobacteriaceae, and Clostridia in formula-fed infants (Edwards and Parrett 2002).

The extended weaning process and weaning diet exert additional influences on microbial development by introducing more complex carbohydrates into the intestinal ecology. In the first year of life, infants do not digest carbohydrates well, due to limited chewing ability and low production of digestive enzymes (i.e., salivary and pancreatic amylase). Amylase and lipase in breast milk may aid in the digestion and absorption of starch in the small intestine, but the majority of fermentable carbohydrates and dietary fiber pass through undigested to the colon (Edwards and Parrett 2002). In breast-fed infants, the rate of carbohydrate fermentation by gut bacteria slowly increases from early to later weaning (from 1 month to 1 year after initial introduction of solid food). In contrast, the carbohydrate content in infant formula promotes early and increased growth of fermenting bacteria (Armstrong et al. 1992; Edwards and Parrett 2002). This shift in microbial composition results in an earlier and increased rate of energy extraction, and may explain in part why formula-fed infants have faster growth rates and an increased risk of obesity later in life (Owen et al. 2005).

To date, few studies have directly examined changes in gut microbial composition induced by the timing and type of solid foods introduced. However, in a recent analysis of European infants both pre- and post-introduction of solid foods, researchers found that while gut microbial populations were more diversified 4 weeks post-introduction, the timing of solid food introduction had no effect on postweaning composition (Fallani et al. 2011). At the same time, the influence of *preweaning* feeding method (breast milk or formula)—along with birth method and country of origin—continued to significantly influence postweaning microbial compositions. In particular, *Bifidobacterium* continued to dominate the gut microbiota of breast-fed infants, while formula-fed infants had higher proportions of *Bacteroides* and *Clostridia* species. Thus, the earliest influences on infant gut microbiota (environment, birth method, and breast- or formula feeding) appear to have lasting effects on gut microbial development and maturation (Fallani et al. 2011).

The effects of prolonged mixed-feeding strategies (breast milk with solid food supplementation) on infant gut microbiota have also not been well studied (Edwards and Parrett 2002). In many nonindustrialized populations in which traditional breastfeeding practices are still observed, weaning foods are introduced around 3 months, but infants may continue to nurse well past the first year of life (Sellen 2001). With mixed feeding, early introduction of carbohydrates could facilitate earlier maturation of gut microbiota and fermentation capacity, while ongoing nursing would provide infants with continued access to beneficial probiotic, prebiotic, and antimicrobial factors in milk. The quantitative and qualitative composition of such factors, however, varies across individual mothers and with the frequency and stage

of lactation (Chaturvedi et al. 2001; Prentice et al. 1983, 1984). More longitudinal studies with diverse populations are needed to better ascertain the role of complementary feeding and prolonged mixed-feeding strategies on infant gut microbial development.

Finally, animal studies have shown that psychological stress during infancy may also induce changes in GI tract activity—including mucus secretion, motility (movement of fecal matter through the GI tract), and the presence of inflammatory cytokines and stress hormones—which in turn influence the growth and adherence of particular bacteria species and strains (Collins and Berick 2009). In one experiment, inducing stress in weaned infant macaques by experimentally separating them from their mothers resulted in reductions in *Lactobacillus* populations and enhanced growth in *Campylobacter jejuni*—a commensal bacteria with pathogenic potential (a *pathobiont*). The decrease in *Lactobacillus* significantly correlated with increased displays of stress behavior (Bailey and Coe 1999). At present though, it is not known whether differences in maternal–infant interactions across human populations or primate species influence phylogenetic differences in gut microbial communities.

Interestingly, early perturbations in microbial composition may also induce changes in host behavior. Researchers have demonstrated that the release of adrenocorticotrophic hormone (ACTH)—a stress hormone that increases cortisol production—is reduced in young mice that are experimentally stressed and selectively colonized by *B. infantis*, but is increased when the mice are colonized by *E. coli* (Sudo et al. 2004). This relationship was only observed in very young mice, suggesting there may be a critical window during infancy when development of the brain's response to stress is sensitive to input from specific bacteria (Collins and Berick 2009).

In sum, it is apparent that infant gut microbial compositions are highly sensitive to early environmental, dietary, and perhaps even psychological conditions. But does the resulting variation in gut microbial composition negatively affect host health? We next briefly review emerging experimental and cross-sectional evidence suggesting that indeed certain bacterial compositions—particularly those associated with modern diet and hygiene—may be an important factor in the rising incidence of immune and metabolic disorders.

11.4.1 Gut Microbiota and Metabolic Disorders

While it is clear that variation in environmental exposure and host diet influence the presence and relative abundance of certain bacteria in the gut, it is also increasingly apparent that functional attributes associated with certain microbial compositions may greatly affect host metabolism. In particular, higher ratios of Firmicutes to Bacteroidetes have been widely observed in studies of subjects from industrialized populations and are further associated with obesity. In a recent comparative study (De Filippo et al. 2010), Bacteroidetes was shown to dominate the microbiota of children from a rural African village, while Firmicutes dominated the microbiota of

European children. The diets of the two populations appeared to be of greater significance in determining microbial composition than were ethnicity, sanitation, hygiene, geography, or climate (De Filippo et al. 2010). Additional studies have demonstrated that the microbiota of obese mice exhibit higher ratios of Firmicutes to Bacteroidetes and lower overall diversity as compared to their lean counterparts (Ley et al. 2006b; Turnbaugh et al. 2006; Turnbaugh et al. 2009b). Finally, in a comparison of the microbiota between obese and lean human adult twins, functional microbial groups associated with distinct metabolic pathways were shown to be correspondingly enriched or depleted in lean and obese subjects (Turnbaugh et al. 2009a). The majority of microbial genes associated with obesity-promoting pathways (“obesity-enriched”) belonged to the Actinobacteria (75%) and Firmicutes (25%) groups, with none belonging to the Bacteroidetes group. In contrast, 42% of “lean-enriched” genes belonged to the Bacteroidetes group (Turnbaugh et al. 2009a). In a striking follow-up study, switching mice from a “traditional” low-fat/high-fiber diet to a “Westernized” high-fat/high-sugar/low-fiber diet led to a shift in microbial composition and corresponding metabolic pathways in just 1 day, and increased adiposity in just 2 weeks (Turnbaugh et al. 2009b).

The comparative and experimental evidence suggests that high-fiber diets (typical of hunter-gatherer, horticulturalist, and rural agricultural populations) enrich the presence of Bacteroidetes—in essence “selecting for” those species that break down tough plant fibers (Maslowski and Mackay 2011). Conversely, the caloric excess of industrialized diets (which is evolutionarily novel) appears to enrich the presence of Firmicutes and associated “obesity-enriched” microbiomes. Thus, while excess fat and sugar (without an equivalent increase in energy output) may alone be expected to induce weight gain, the nutritional and caloric excess of typical industrialized diets favor obesity-enriched microbiomes—which, in a vicious cycle, promote increased energy harvesting and fat deposition.

Fortunately, owing to the very dynamic nature of gut microbiota, these obesity-enriched microbial populations may be malleable. In humans, the relative abundance of Bacteroidetes has been shown to increase following reductions in caloric or fat intake (Ley et al. 2006b) and the relative abundance of Firmicutes has been shown to decrease following gastric bypass surgery (Zhang et al. 2009). However, more research is needed to assess if therapeutic altering of the Firmicutes to Bacteroidetes ratio (i.e., through targeted administration of probiotics or antibiotics) is effective in inducing weight loss in obese individuals, or if such changes in composition merely follow alterations in the selective environment induced by dietary change.

11.4.2 Gut Microbiota and Immune Disorders

As previously discussed, gut microbiota form a barrier to protect vulnerable infant hosts from invasive pathogens, while initiating early immune “crosstalk” (signaling and activation among immune system components) that attenuates the development of the naïve infant immune system (Dimmitt et al. 2010). Because of the vital

immunoregulatory effects of gut bacteria, dysbiosis (alterations in gut microbial composition) may lead to immune dysfunction and disease (Round and Mazmanian 2009). For example, infants who are earlier colonized by *E. coli* and *C. difficile* and only belatedly colonized by *Bifidobacterium* and *Lactobacillus* have a higher risk of developing allergies later in life (Kalliomäki and Isolauri 2003; Penders et al. 2007). Among children and adults, gut microbial compositions of individuals with inflammatory bowel disorder (IBD), allergy, and asthma differ from those of non-affected individuals (Noverr and Huffnagle 2004; Penders et al. 2007; Round and Mazmanian 2009). Higher abundances of *pathobionts*, including *Clostridia* and *Enterococcus* species, have been associated with IBD risk in adults (Round and Mazmanian 2009). Similarly for nonhuman primates, a higher prevalence of *Campylobacter* species has been associated with severe intestinal inflammation in captive macaques (McKenna et al 2008).

The exact mechanisms by which altered gut microbiota in infancy may predispose hosts to abnormal immune responses in child or adulthood are unknown. Nor has it been conclusively demonstrated how immune development proceeds when certain beneficial bacteria are absent during infancy (or found at very low prevalence), or what effects many other common infant-associated bacteria have on early immune development. However, a central tenet of the “Hygiene” or “Old Friends” Hypothesis is that host immune systems evolved in concert with tolerated symbionts, including commensal microbiota and common intestinal parasites such as helminths. Without early and regular exposure to these “old friends”—which promote and attenuate immunoregulatory responses—hosts ultimately produce skewed inflammatory and/or hypersensitive responses to harmless environmental antigens (Rook and Brenet 2005; Rook 2009).

While the mechanisms of the hygiene hypothesis continue to be explored and debated, there is growing clinical interest in the use of *probiotics* (directly ingested beneficial gut bacteria) in treating gut-associated immune disorders. For example, research has shown that immune-associated gut inflammation (Round and Mazmanian 2009) and diarrhea (Resta-Lenert and Barrett 2003; Verna and Lucak 2010) may be alleviated through administration of antibiotics and probiotics to induce changes in gut microbial communities. Most promisingly, numerous controlled studies have demonstrated that probiotic supplements (primarily *Bifidobacterium*, *Lactobacillus*, and *Streptococcus* species) given to preterm and very low birth weight infants are highly effective in reducing their risk of mortality and necrotizing enterocolitis (death of intestinal tissues) (Deshpande et al. 2010).

Still, gut-mediated immune dysfunction has not been definitively linked to the absence or presence of any particular species. For example, specific pathobionts that trigger episodes of IBD are found in both healthy and unhealthy individuals, suggesting that these bacteria alone may not induce disease, but may trigger inflammatory conditions in susceptible individuals following dysbiosis or damage to the gut epithelium (Round and Mazmanian 2009). Probiotic therapy also appears to be ineffective in limiting the overgrowth of *C. difficile* and reducing the incidence or risk of remission of Crohn’s disease; probiotics may even aggravate inflammatory conditions among severely immunocompromised subjects (Verna and Lucak 2010).

Thus, more research is needed to better distinguish which candidates most benefit from probiotic therapy, as well as establish the particular bacterial species, strains, and dosages needed to effectively target specific disorders. Finally, although host factors influencing the presence of beneficial microbiota are likely relevant at every life stage, the use of probiotics and prebiotics during infancy may emerge as an important measure to counter negative environmental influences on gut microbial colonization, and promote the early and continued establishment of beneficial gut microbiota.

11.5 Conclusions: Human Gut Microbiota and Health from Infancy to Adulthood

For all primates, the origins of individual gut microbial diversity begin early in life, when microbial compositions are most dynamic owing to a number of dietary and environmental factors. Early colonization patterns may persist over time (Dethlefsen et al. 2006), as earlier-established bacteria continually outcompete newly introduced ones (Zoetendal et al. 2004). For humans in particular, this may increase the risk that altered gut microbiota associated with novel conditions during infancy (i.e., Cesarean birth, formula feeding, hygiene and antibiotic use) will have lasting, negative influences on later community structure and microbial-mediated metabolic and immune functioning.

While more research is needed to fully understand the relationship between early microbial development and later host health, promoting the establishment of beneficial microbiota during infancy should remain a goal of clinical practice and health research. The factors associated with key “healthy” and “less healthy” microbial phylotypes during infancy and adulthood have been fairly well identified and primarily reflect the influence of modern medicine, hygiene, diet, and even stress. During infancy, Cesarean births, premature delivery, and antibiotic administration promote colonization by bacteria that persist in hospital environments and may disrupt normal immune development, while formula feeding promotes colonization by bacteria that enhance carbohydrate digestion and may increase risk of obesity. In adulthood, the cumulative effects of antibiotic use and industrialized diets appear to reduce microbial diversity and favor microbial compositions associated with immune-induced inflammation and obesity. In contrast, factors more reflective of ancestral conditions in which humans and gut microbiota coevolved (e.g., vaginal birth, prolonged breastfeeding, non-sterile environments, and high-fiber/low-fat/low-sugar intake) appear to promote early dominance of maternally transmitted bacteria, slower maturation of carbohydrate digestion, and increased microbial diversity in adulthood. These microbial profiles in turn appear to promote healthy immune regulation and limit the presence of obesity-promoting bacteria.

As research on gut microbial development and composition has increased in recent years, the role of beneficial gut microbiota in mediating health outcomes has become a central tenet of the so-called “hygiene” or “old friends” hypothesis

(Rook and Brunet 2005; Rook 2009), and should be of vital interest to researchers in human health and evolutionary medicine. Evolutionary health researchers can promote clinical and public awareness of the various factors that influence gut microbial composition and the health outcomes they mediate, particularly at critical periods of microbial transition—at birth, during infancy, and following courses of GI distress or antibiotic administration. It is, of course, not feasible to unilaterally advocate for vaginal births, exclusive breastfeeding, and avoidance of antibiotics, as risks to health and maternal work demands often necessitate the alternatives. However, researchers can continue to promote public awareness of the relationship between hosts and their gut microbiota, the links between gut microbial integrity and health outcomes, and the varied influences of host behavior and diet on microbial populations at all stages of life.

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Part IV
Mothers and Infants: The First Social
Relationship

Chapter 12

Maternal Influences on Social and Neural Development in Macaque Monkeys

Christopher J. Machado

Keywords Emotion • Amygdala • Social brain • Infant development • *Macaca*

12.1 Introduction

Development of the neural network responsible for normal primate social behavior results from a complex interplay between one's genetic code and the combined influences of the social and physical environment. The mother–infant relationship is one very important, early component of that social environment. Although every reader of this chapter will have an implicit and subjective understanding of the importance of high-quality parental care, we still do not fully understand how such care directly influences brain development and ultimately sculpts who we become in adulthood. The need to form a more complete understanding of this topic cannot be overemphasized. Early-life stress in humans (including childhood abuse, neglect, economic hardship, nutritional deficiencies, etc.) has been linked to greater risk of mental and physical ailments (e.g., anxiety and mood disorders, impulse control deficits, psychosis, obesity, immune system dysregulation, and drug abuse) (Bellinger et al. 2008; Weaver 2009). However, it is still unclear how such early-life stress actually perturbs structural and functional development of the brain. Continued research on this topic is desperately needed to generate novel interventions or treatments that could reliably mitigate the effects of substandard or absent parental care.

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In this chapter, I will explore the connection between high-quality maternal care and the development of neural systems that support adaptive social behavior in offspring by focusing on research using a nonhuman primate animal model, the macaque monkey. Although much of the research reviewed here was conducted with rhesus macaques (*Macaca mulatta*), other species, including cynomolgus (*Macaca fascicularis*) and Japanese (*Macaca fuscata*) macaques, have also been studied both behaviorally and neurobiologically. Macaques are excellent animal models for studying the development of social behavior and its underlying neurobiological mechanisms (Capitanio and Emborg 2008; Machado and Bachevalier 2003; Nelson and Winslow 2009). Like humans, macaques live in a highly complex social system, where facial expressions and body postures are key forms of social communication. Macaque and human neuroanatomy and behavior also possess many well-documented similarities. These positive aspects inherent to macaque models do not exist in rodent models. Experiments with macaques also afford a level of experimental control that is not possible in human studies. Therefore, studies using macaques as a model species are able to ask more complex questions about, as well as make stronger comparisons to, human behavioral and brain development than those using another model system.

This chapter will provide a brief overview of normal macaque socioemotional development, focusing mainly on the first year of life. This is the critical period when young macaque monkeys are in close physical and social contact with their mother. The concomitant development of several candidate brain structures thought to be involved in social information processing (e.g., the amygdala and orbitofrontal cortex) will also be reviewed. This “normal” pattern of development will then be contrasted with the well-known behavioral sequelae that follow early maternal separation or poor maternal care in macaque monkeys. What remains relatively unknown is how a substandard early rearing environment impacts on the structural and functional development of the neural network that underlies normal socioemotional behavior. Several directions for future research that could help to fill this gap in knowledge will also be proposed.

12.2 Early Socioemotional Development of Macaque Monkeys

The normal developmental milestones of macaque monkey’s socioemotional behavior have been recently summarized in depth (Bauman and Amaral 2007; Machado and Bachevalier 2003; Suomi 2005). Therefore, this section will only provide a brief overview, with particular emphasis on the first year of life when the mother–infant bond is strongest. Although comparing relative developmental ages between humans and macaque monkeys is difficult due to different maturation rates across brain systems in both species, studies of overall brain growth (Giedd et al. 1996; Payne et al. 2010; Pfefferbaum et al. 1994) and social behavior development (Machado and Bachevalier 2003; Suomi 2005), as well as more focused investigations of the visual system (Garey and De Courten 1983) and prefrontal cortex

(Watson et al. 2006) indicate that macaques mature roughly four times faster than humans. This means that 1 week of macaque neurobehavioral development approximately corresponds to 1 month of human development. That trajectory can also be extrapolated further such that the 1-year time period discussed for macaques in this chapter corresponds roughly to the first 4–5 years of a human life.

During the first month of life, infant macaques spend approximately 70% of their time in physical contact with their mother (Brown and Dixon 2000; Hinde and Spencer-Booth 1967). Infants quickly acquire the sensorimotor skills necessary to begin short-range environmental exploration, but they still rely heavily on their mother for protection, regulation of body temperature, nutrition, and transportation during this first month (Hinde et al. 1964; Hiraiwa 1981; Mendelson 1982a, b; Suomi 1984; Suomi 1990). Given this dependency, an infant macaque's first opportunity to learn about species-typical social interactions is with its mother (Fairbanks and Hinde 2012). Grooming and physical contact initiated by the mother predominates (Hinde et al. 1964), but infant macaques also learn much about the meaning of gaze direction and vocalizations during this time. Staring directly into the eyes of another individual is a threatening gesture in macaque society (Chevalier-Skolnikoff 1973; Van Hooff 1967). Towards the end of their first month, infant macaques demonstrate knowledge of this social rule by visually inspecting faces which are looking away more than faces staring directly at them and also display lip smacking (a submissive or appeasement gesture) to staring faces more than those with averted gaze (Mendelson 1982a, b; Mendelson et al. 1982). One-month-old macaques also demonstrate a sophisticated ability to categorize vocalizations based on caller identity by reacting differently to maternal and non-maternal calls (Masataka 1986).

During the second month, interactions between mother and infant macaques move beyond mainly nursing and clinging. Infants begin to initiate grooming with their mother, but this occurs only sporadically (Hinde and Spencer-Booth 1967; Suomi 1990). Exploratory trips away from mother's "secure base" increase slowly but steadily in frequency, duration, and distance during the second month (Berman 1980; Itoigawa 1973; Nakamichi and Minami 1990; Suomi 1984, 1990; White and Hinde 1975). However, each exploratory trip ends with the infant quickly returning to its mother to reestablish physical contact. Despite allowing progressively more environmental exploration, macaque mothers rarely permit chasing or rough-and-tumble forms of play with others at this early stage. Nevertheless, infants spend considerable time watching other individuals interact and play from a distance (Hinde et al. 1964).

For macaque infants, the period between 3 and 6 months of age marks a major increase in independence as mothers begin to slowly but progressively wean them from nursing (Berman 1980; Hinde et al. 1964). Infants must begin to supplement decreased nursing with independent foraging for solid foods (Hiraiwa 1981). This increased independence creates more opportunities for infant macaques to further refine their social skills by interacting with other members of the troop on a more regular basis. An infant's vocal repertoire grows rapidly during this time, both in the complexity of utterances and the number of distinct vocalizations used to manage the behavior of others (Kawabe 1973). Infants are sought out more and more for

social interactions by other members of the troop (Hiraiwa 1981; Rowell et al. 1964; Spencer-Booth 1968). Rough-and-tumble play behavior becomes the most prominent behavioral strategy chosen by young macaques for interactions with peers, siblings, and even adults.

As independence grows and maternal supervision wanes, the repercussions of improper social interactions with conspecifics become more and more severe. Therefore, after the third month, fear progressively becomes a more common component of a young macaque's behavioral repertoire. Fearful behaviors include the fear grimace facial expression (i.e., exaggerated grin which exposes teeth), active withdrawal, and high-pitched scream vocalizations (Sackett 1966; Suomi 1984). Between 3 and 6 months of age, young macaques also develop the ability to modulate their fear reactions with regard to the magnitude of a threatening stimulus (Kalin and Shelton 1989; Kalin et al. 1991). Aggression also becomes a more frequent means to control the behavior of others between 3 and 6 months of age (Eaton et al. 1986; Suomi 1984). Although aggressive encounters increase in frequency during this time frame, young macaques progressively refine their ability to accurately judge the meaning of aggressive signals until they become yearlings (Bernstein and Ehardt 1985).

To potentially guard against fearful or aggressive encounters with others, infants between 6 and 8 months of age increase their rate of affiliative interactions (grooming, mounting, play, etc.) with individuals besides their mother. For grooming, young macaques typically seek out young childless females and peers (Rowell et al. 1964). Rudimentary forms of sexual behavior also become more common during this time, with males initiating mounts much more frequently than females, and females receiving many more mounts than males. Most of these mounts occur in the context of play or when individuals are simply sitting in proximity and only rarely, during agonistic interactions (Hanby and Brown 1974).

When a macaque reaches 9–12 months of age, several important transitions occur. They are no longer considered infants but rather juveniles. Their mother is also likely to be pregnant with her next offspring. The birth of a new sibling substantially decreases a juvenile's interactions with its mother. Rates of maternal threats and lunges directed towards their juvenile offspring increase significantly around the time of a sibling's birth. The magnitude of these changes is most severe for male offspring (Devinney et al. 2001; Hinde and Spencer-Booth 1967). This does not mean that the original mother–infant bond disintegrates completely. That relationship remains stronger for female offspring since they remain within their natal troop for their entire lives, as opposed to male offspring that emigrate to other troops at puberty (Lindberg 1971). Both male and female juvenile macaques also continue to use the mother as a secure base under stressful conditions at least until puberty. They will either seek physical contact with her or solicit her assistance during agonistic episodes with others within the troop or with members of a different troop (Suomi 1999). However, as interactions with their mother decrease after the first year, interactions with peers increase. Play continues to predominate and seems to simulate many types of social interactions that these animals will engage in later during adulthood, such as courtship, reproductive behaviors, and dominant/submissive

encounters (Ruppenthal et al. 1974). Juvenile male and female macaques also begin to show different preferences for social partners at this time. Juvenile females mostly interact with female kin and adult or similarly aged females from other families, whereas juvenile males interact more with similarly aged males, both kin and non-kin (Ruppenthal et al. 1974).

In summary, the first year of a macaque monkey's life represents a critical period for the development of socioemotional skills that are essential for adaptively forming, maintaining, and manipulating social relationships throughout the rest of its life. Developing monkeys initially learn a great deal about appropriate social interactions and the meaning of social cues (both visual and auditory) during a 2-month period of nearly constant physical contact and protection provided by their mother. Even as infants begin to venture forth and explore their social environment during the remainder of their first year, they do so under the continued supervision of their mother, likely rendering the consequences of any social behavior errors less harmful. By the time infant macaques become juveniles, the protective environment and social guidance provided by their mother has equipped them with the necessary tools to adaptively integrate themselves into the larger troop. This early pattern of socioemotional behavior development sparks a key question. Do we see similar structural and functional changes during this same time frame in brain areas that appear to be critical for normal social behavior in primates?

12.3 Development of the Social Brain

Social cognition describes a collection of perceptual, cognitive, and regulatory processes that efficiently modulate one's interactions with others (Adolphs 2010; Baron-Cohen et al. 1999; Bauman and Amaral 2007; Brothers 2002; Schumann et al. 2006). The neural network that supports such abilities is often referred to as the "social brain" (Brothers 1990; Dunbar 2002). This brief definition does not come close to capturing the complexity of a process that humans, even many great ape and monkey species (Byrne and Bates 2010), perform both consciously and automatically many times each day. Think of your most recent social interaction. Your attention needed to be focused on important verbal and nonverbal social cues. The meaning of those cues needed to be decoded with regard to context, experience, social rules, as well as your particular goals and emotional state. If you were sufficiently motivated, you likely responded to those cues at an opportune time and with appropriate magnitude. You may have also experienced a change in your physiological or emotional state. This cycle repeated itself over and over until the interaction ended.

Given the complexity of this cognitive process, the neural network supporting it must be equally complicated. Nonhuman primate studies, primarily with macaque monkeys, have implicated the temporal neocortex (particularly the superior temporal gyrus and sulcus), amygdala, orbitofrontal cortex, and anterior cingulate cortex in collectively decoding the value or meaning of social stimuli, cuing appropriate

social and emotional responses and evaluating outcomes relative to predictions (Bauman et al. 2011). Since vision is the dominant sensory modality for primates (Kirk and Kay 2004), the neural structures that contribute to visual perception and attention (e.g., superior colliculus, primary visual cortex, supplementary eye fields, and frontal eye fields) must also contribute to normal social information processing (Klein et al. 2009). Given the profound and well-documented loss of rich, context-dependent memory that follows hippocampal damage (Alvarado and Bachevalier 2005; Murray 2000; Squire et al. 2000), it is also plausible that normal social information processing requires this structure to provide access to stored information about social experiences. Despite our substantial knowledge of this complex neural network in adult primates, we still know very little about the structural and functional development of its component structures. This section will focus on the development of two brain structures that have been most often associated with normal socioemotional behavior in primates—the amygdala and orbitofrontal cortex (Babineau et al. 2011; Bauman et al. 2004a, b, 2006; Emery et al. 2001; Machado and Bachevalier 2006; Machado et al. 2008; Myers et al. 1973).

12.3.1 *The Amygdala*

Seminal overviews of macaque amygdala anatomy have been published previously (Aggleton et al. 2000; Amaral et al. 1992; Pitkanen and Amaral 1998), but a brief overview of this structure will be provided here. The primate amygdala defines a subcortical group of thirteen distinct, but highly interconnected, nuclei within the anterior medial temporal lobe (Fig. 12.1). The adult primate amygdala has extensive reciprocal connections with sensory cortical areas and interacts with many cortical and subcortical areas implicated in the initiation of motor behavior, regulation of autonomic and visceral function, as well as areas implicated in the highest forms of primate cognition. Several recent lesion (Emery et al. 2001; Machado and Bachevalier 2006; Machado et al. 2008), electrophysiological recording (Gothard et al. 2007), and functional neuroimaging studies (Hoffman et al. 2007) with macaque monkeys have indicated that the amygdala plays an essential role in modulating social behavior adaptively, especially in potentially dangerous or threatening contexts. For example, when two unfamiliar adult male rhesus monkeys are introduced, often there is an initial period of wariness and apprehension.

Fig. 12.1 (continued) of that section (in mm) from the interaural plane. The *bottom panel* shows a magnified view of the amygdala, showing major subnuclei, adjacent cortical regions, and major temporal lobe sulci. *AB* accessory basal nucleus, *AMTS* anterior medial temporal sulcus, *B* basal nucleus, *C* caudal, *CE* central nucleus, *D* dorsal, *ER* entorhinal cortex, *HIP* hippocampal formation, *L* lateral nucleus, *ME* medial nucleus, *PAC* periamygdaloid cortex, *PL* paralaminar nucleus, *PR* perirhinal cortex, *R* rostral, *RS* rhinal sulcus, *STS* superior temporal sulcus, *TE* area TE, *V* ventral. Portions of this figure were adapted from original drawings provided by Dr. Jocelyne Bachevalier, Emory University

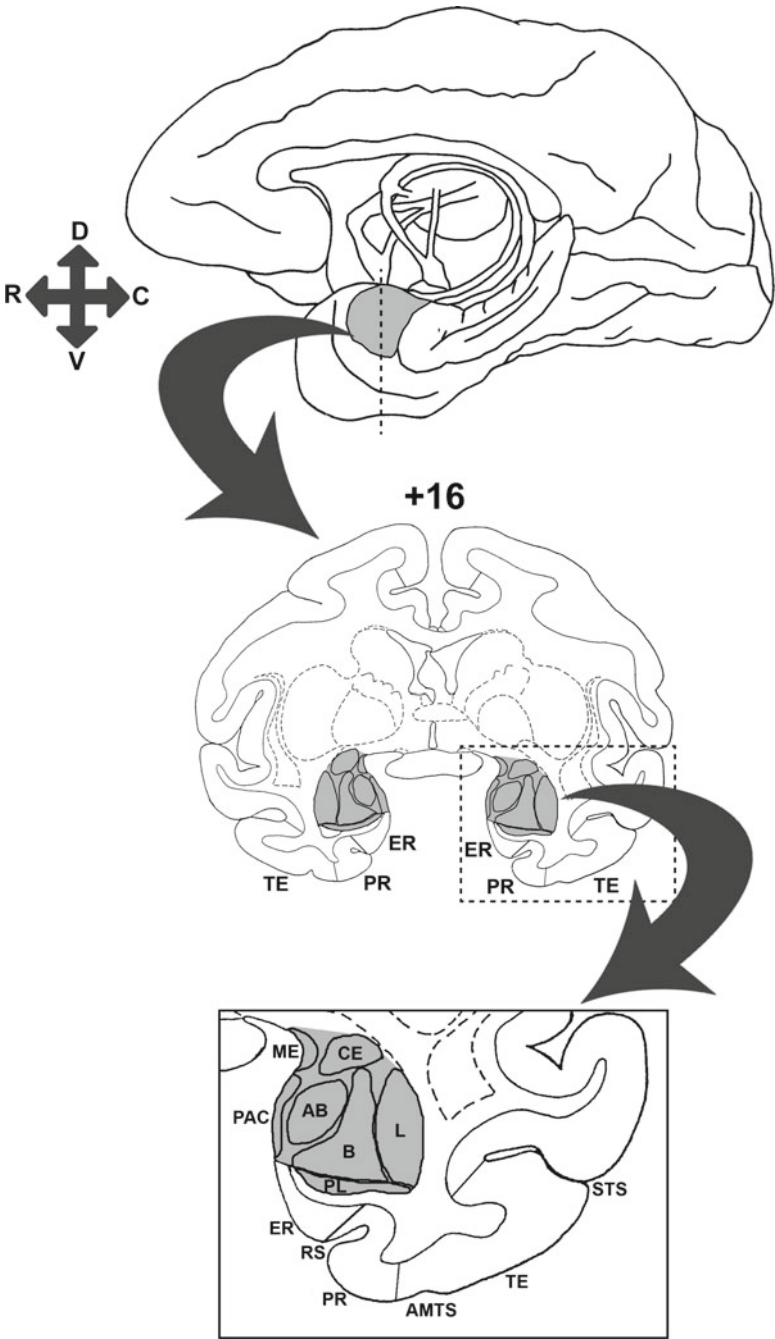


Fig. 12.1 A midsagittal drawing of the rhesus monkey brain (*top*), showing the amygdala in *gray*. The *middle panel* shows the amygdala and other adjacent cortical regions in cross section at the level indicated by the *dashed line*. The numeral above the coronal drawing represents the distance

They will actively avoid each other but observe the other animal's behavior intently, perhaps attempting to ascertain its dominance rank or intentions. This early apprehension eventually fades away, allowing the animals to approach and engage in some form of social interaction. Emery et al. (2001) showed that following bilateral lesions of the amygdala, adult male rhesus monkeys no longer exhibit this species-typical and highly adaptive pattern of wariness when they meet unfamiliar animals. By contrast, they readily engage unfamiliar animals in many social interactions that require close physical contact (e.g., grooming, mounting, and in some cases, rough-and-tumble play).

During prenatal development, amygdala neurogenesis proceeds in a smooth dorsal-to-ventral wave (Kordower et al. 1992). Neurons appear at the end of the first month of gestation (approximately 165 days in total for macaques) in the central, lateral, basolateral, and accessory basal nuclei. A gradual increase in neurons continues during the following week of gestation in all nuclei. By the middle of the second month of gestation, a major reduction in neurogenesis begins first in the central and medial nuclei and then gradually decreases in all nuclei. By the end of the second month of gestation, neurogenesis has ceased in the macaque amygdala, allowing synapse formation to begin.

For amygdala neurons to function properly, they must form synaptic contacts with other neural regions downstream (efferent connections) as well as receive projections from areas upstream (afferent connections). Most afferent and efferent connections of amygdala neurons have been established by birth, and, by the second postnatal week, amygdala efferent connections largely resemble those seen in adult monkeys (Amaral and Bennett 2000). There is, however, still some immaturity in the pattern of afferent cortical projections. Webster et al. (1991) showed that although projections from the higher visual temporal cortical area (TE) to the lateral nucleus of the amygdala are secure in their adult locations at 1 week after birth, the lateral nucleus also receives connections from the temporal cortical areas posterior to TE (i.e., area TEO) that are not found in adult brains. Because areas of the temporal cortex anterior to area TE are not fully functional until 3 months after birth (Bachevalier et al. 1991; Rodman 1994), the existence of these transient projections from TEO to the amygdala suggests that the amygdala receives more rudimentary visual information during this neonatal period than it does during adulthood. This implies that refinement of projections from the temporal cortex to the amygdala provides infant monkeys with increasingly detailed visual information as they mature. It is interesting to note that this refinement of visual input to the amygdala is occurring during the same time frame where maternal contact and protection are at their highest levels and interactions with conspecifics and the environment are at their lowest (Hinde et al. 1964). Once these connections become mature at about 3 months after birth, young macaques begin to engage in social interactions with others and show the ability to modulate their fear reactivity depending on the level of threat encountered (Kalin and Shelton 1989; Kalin et al. 1991).

Despite this pattern of fast postnatal maturation of amygdaloid afferent and efferent connections, noninvasive magnetic resonance imaging (MRI) studies have shown that the amygdala continues to grow in size throughout the first 8 months

of life before stabilizing at an adult level (Payne et al. 2010). Structural changes that influence how efficiently the amygdala communicates with other areas also show a protracted developmental time course. The speed at which electrical signals propagate from one neuron to another is increased through the progressive formation of insulation around axons, called a myelin sheath. Although myelination within the amygdala matures quickly (within the first postnatal month), myelination of efferent connections requires much more time. Gibson (1991) indicated that the stria terminalis (one of the major efferent projections of the amygdala) shows no traces of myelin until 4 weeks after birth and only a moderate level by 8 weeks. This fiber tract does not reach an adult level of myelination until more than 3 years after birth (172 weeks), once again indicating that the influence of the amygdala on other neural systems increases slowly during the first years of life.

Despite our wealth of knowledge regarding the role of the amygdala in adult macaque socioemotional behavior (Emery et al. 2001; Machado and Bachevalier 2006; Machado et al. 2008), we know very little about how this area matures structurally and functionally before adulthood. There seems to be some correspondence between the maturation of amygdaloid afferent and efferent connections with increased social interactions away from mother's secure base and adaptive modulation of fear reactivity. This is congruent with the view that the amygdala monitors sensory input and, when triggered by a particular pattern of input, restrains social behaviors that could be potentially dangerous in the current context (Emery and Amaral 2000; Machado and Bachevalier 2006; Machado et al. 2008). It remains unclear what, if any, developmental changes in amygdala structure or function coincide with the increased incidence of affiliative social behaviors (e.g., play, grooming, and mounting) that are observed after 6 months of age. We also do not know if sex differences in amygdala development influence the different social strategies implemented by males and females after weaning. This paucity of information demonstrates the need for future, systematic study of structural and functional amygdala development alongside socioemotional behavior refinement.

12.3.2 The Orbitofrontal Cortex

The nonhuman primate orbitofrontal cortex is one subcomponent of the prefrontal cortex. This region occupies the ventral surface of the frontal lobe, just above the eye orbits. The orbitofrontal cortex typically includes Brodmann areas 11, 13, and 14 (Fig. 12.2). This cortical area is heterogeneous, both in terms of cellular architecture and its pattern of intrinsic and extrinsic connections (Barbas 2007a, b; Price 2007). One prominent view is that the orbitofrontal cortex sits at the confluence of two separate, yet partially overlapping and interconnected, networks of the frontal lobe (Price 2007). A "medial network" includes all areas of the medial frontal cortex (areas 9, 10, 14, 24, 25, and 32) and the most medial sectors of the orbital surface (medial sections of areas 10, 11, and 13). This network has strong connections with the amygdala, temporal cortical structures linked to memory, striatal regions

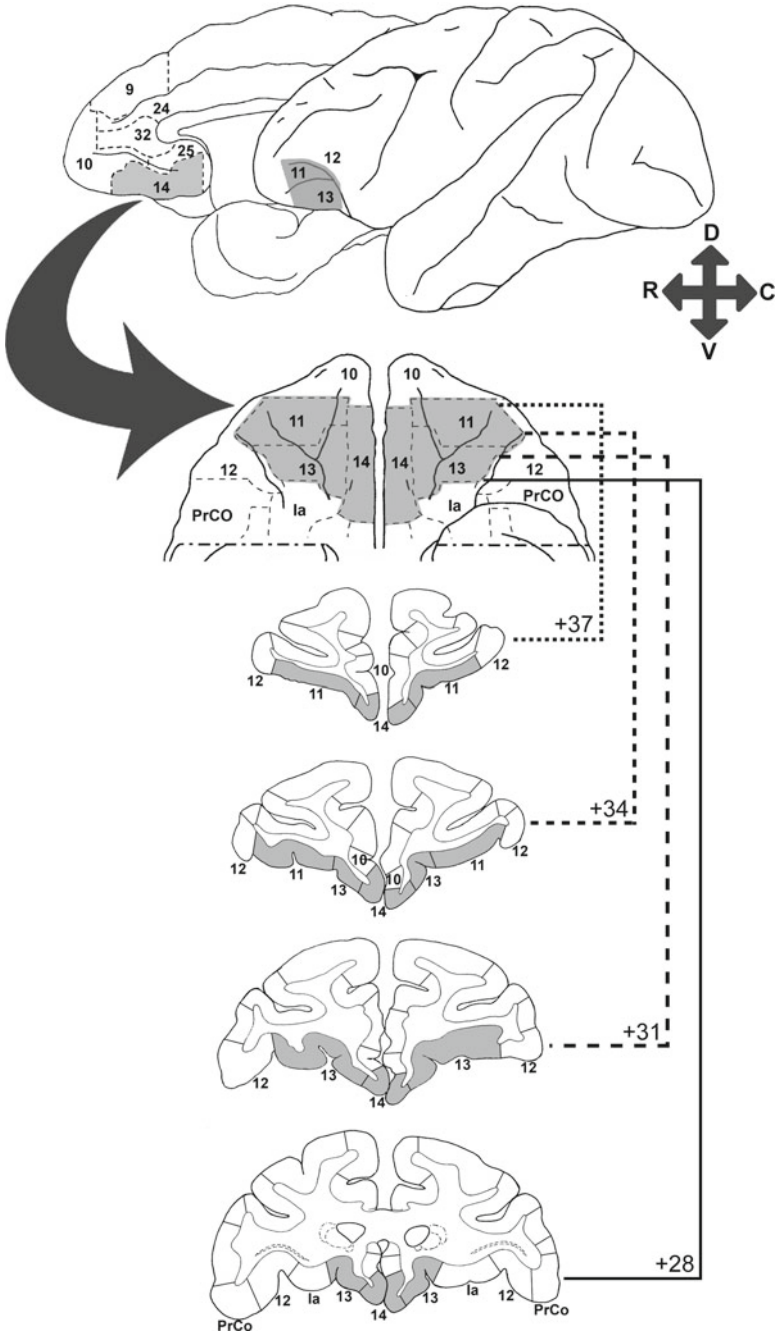


Fig. 12.2 Midsagittal and lateral drawings of the rhesus monkey brain (*top*), showing the orbitofrontal cortex in *gray*. A ventral surface view is also provided to show the individual subregions (*dashed lines*) that constitute the orbitofrontal cortex (*areas 11, 13, and 14*) as well

associated with representation of reward, and autonomic centers in the brain that influence emotional arousal. The “orbital network” includes more lateral areas on the orbital surface (lateral sections of areas 11 and 13, a majority of area 12, and the agranular insular area). This network not only predominantly receives sensory information from visual, auditory, somatosensory, and gustatory brain areas but also has connections with the amygdala via the agranular insular area. Given this anatomical organization, the orbitofrontal cortex is well positioned to integrate information regarding one’s current physiological state with external sensory stimuli and the current context to flexibly represent the reward value or meaning of environmental stimuli and predicted outcomes (Bachevalier et al. 2011), especially those of a social nature. Evidence to support this hypothesis has been provided in electrophysiological recording experiments (O’Scalaidhe et al. 1997, 1999; Rolls 2000; Schultz et al. 2000) and selective lesion studies (Babineau et al. 2011; Izquierdo et al. 2004; Machado and Bachevalier 2006, 2007a, b). For example, Rolls et al. (1989) have shown that neurons in the rhesus monkey orbitofrontal cortex respond robustly when monkeys eat a preferred food. If the monkey is allowed to eat that food without restriction to satiety, the responsiveness of those same orbitofrontal neurons decreases significantly. If rhesus monkeys are allowed to eat their favorite food to satiety and then offered a choice between that sated food and one that is less preferred, they will select the lower-preference food. Monkeys with orbitofrontal cortex damage do not show this same change in their food preference following satiation. They continue to select the higher-preference, yet sated, food when it is offered along with a lower-preference alternative (Izquierdo et al. 2004; Machado and Bachevalier 2007a, b).

Numerous reports chronicle the maturation of the dorsolateral prefrontal cortex in humans and macaque monkeys (Lewis 1997), but very few specifically describe the development of the orbitofrontal cortex. Neurodevelopmental data from the dorsolateral prefrontal cortex may not be applicable to the orbitofrontal cortex. It is not clear whether synaptogenesis and synapse elimination occur concurrently or at different rates in these two cortical regions (Rakic et al. 1986). No specific information exists regarding the prenatal genesis, migration, or differentiation of neurons in the orbitofrontal cortex. However, connections between the dorsolateral prefrontal cortex and the orbitofrontal cortex become noticeable in the third trimester of gestation in monkeys and reach adult levels approximately 3–4 weeks before birth (Schwartz and Goldman-Rakic 1991). Connections also become prominent and highly organized between the left and right orbitofrontal cortices just before birth (Goldman and Nauta 1977). Orbitofrontal afferent connections from temporal cortical areas



Fig. 12.2 (continued) as adjacent cortical fields. Finally, four coronal drawings are provided to show orbitofrontal morphology throughout its rostrocaudal extent. Numerals adjacent to each coronal drawing represent the distance of that section (in mm) from the interaural plane. *Areas 9, 10, 11, 12, 13, 14, 24, 25, and 32* cytoarchitectonic fields of the ventral and medial frontal lobe, *C* caudal, *D* dorsal, *Ia* agranular insular area, *PrCO* precentral opercular cortex, *R* rostral, *V* ventral. Portions of this figure were adapted from original drawings provided by Dr. Jocelyne Bachevalier, Emory University

appear adultlike as early as 1 week of age (Webster et al. 1994). However, efferent projections to temporal cortical regions continue to develop until the seventh week after birth (Rodman and Consuelos 1994).

Although connections within the orbitofrontal cortex, as well as those between this region and other cortical areas, all seem to reach maturity within the first 1–2 months of life, the functional efficiency (as indicated by myelination) of these fibers follows a more protracted developmental time course. According to Gibson (1991), neither the posterior nor the anterior portions of the orbitofrontal cortex show any signs of myelination until 1 and 2 weeks after birth, respectively. The posterior orbitofrontal cortex does not reach an adult level of myelination until 1 year after birth. By contrast, the anterior orbitofrontal cortex follows an even more protracted pace of myelination, reaching an adult level by 2 years after birth. This time course is much longer than that of most of the primary sensory cortices, which attain an adult level of myelination around the end of the first year.

The distribution of catecholamine innervation of the orbitofrontal cortex has been characterized for the adult macaque monkey (Levitt et al. 1984), but we also have some information regarding how such innervation develops. Dopamine innervation is present in its adult form by 3 days after birth, but developmental changes in the laminar distribution of this innervation can be seen until postnatal day 42 (Berger et al. 1990). Orbitofrontal cortex neurons containing the regulatory neuropeptide cholecystokinin (CCK) decrease drastically after the first month of life, especially in areas 11 and 14, and achieve an adult pattern of expression by 5 months after birth (Oeth and Lewis 1993). Although CCK has both excitatory and inhibitory influences upon neurons, it is usually colocalized with the inhibitory neurotransmitter γ -aminobutyric acid (GABA). This rapid postnatal decrease in CCK-containing neurons may increase the effect that GABA has on the prefrontal cortex and its protracted functional development. Modification of other neuropeptides (vasoactive intestinal polypeptide, somatostatin, and substance P) in the orbitofrontal cortex begins at approximately 4.5–5.5 months of gestation and continues until adulthood (Hayashi and Oshima 1986). Vasoactive intestinal polypeptide, somatostatin, and substance P could perhaps play a prominent role in late prenatal development of the macaque orbitofrontal cortex, but their influence might wane after birth due to extensive neuronal cell death or pruning of synapses that utilize these neuropeptides.

In summary, there is little direct information currently present in the literature regarding the structural and functional development of the orbitofrontal cortex. The available data does indicate that this cortical region undergoes major changes in its intrinsic, afferent, and efferent connections, as well as its neurochemistry and functional efficiency during the first year of a macaque's life. During this period, the animal begins to learn that the meaning of many social signals (like a fear grimace or open-mouth threat) depends upon their own affective state, the identity, rank, and intentions of the animal that initiates that signal, as well as what other individuals are present (kin, non-kin, allies, etc.). The orbitofrontal cortex is thought to be critical for this kind of evaluation (Bachevalier et al. 2011). It is also interesting to note that, like the amygdala, major structural and functional refinements seem to occur primarily during the first 3 months of life, during the period of greatest maternal

care and protection. This again highlights the importance of this period of intense mother–infant interaction in normal socioemotional and brain development. What, then, are the repercussions of diminished or absent maternal care during this early critical period for socioemotional and brain development?

12.4 How Does Substandard or Atypical Maternal Care Perturb Socioemotional and Neural Development?

An extensive literature chronicles the ramifications of absent or substandard maternal care on the development of socioemotional behavior in macaque monkeys (Winslow 2005). Such studies date back to the mid-1950s and 1960s with the seminal work of Harry Harlow and his colleagues where infant macaques were reared either in complete social isolation or with inanimate surrogates (Harlow et al. 1965). Similar studies followed but used peers or foster–mothers as social stimuli during the earliest months of life (Suomi 1997). A profoundly disturbed spectrum of socioemotional behavior emerged from these studies. When introduced into social groups, these abnormally reared monkeys showed profound social withdrawal and marked hostility towards their groupmates (McKinney et al. 1971; Sackett 1967). These animals also showed high levels of self-stimulatory behaviors and repetitive, stereotyped motor movements (Gluck and Sackett 1974; Goosen 1981). Even after repeated pairings with the same partners, animals reared without their mothers showed abnormal reactions to play solicitations, along with continued aggression and withdrawal (Chamove et al. 1973; Chamove 1984; Mitchell 1968; Mitchell and Clark 1968). Some of these deficits could be mitigated by allowing the mother-deprived monkeys to interact with younger peers that initiated social interactions in a nonthreatening manner (Suomi et al. 1972). Other studies showed that deficits in play behavior following atypical rearing persisted long term (Cummins and Suomi 1976).

These abnormal patterns of social behavior development in mother-deprived animals appear to be related to deficits in social communication, including the assessment of signals from conspecifics and the use of signals to manage or influence the behavior of others efficiently. For example, Brandt and Stevens (1971) found that isolate-reared male macaques showed less lip-smacking facial expressions (an appeasement gesture) and more yawning and tooth grinding (tension-related signals) when they could view unfamiliar conspecifics. Species-typical vocalizations are also perturbed by atypical rearing conditions. Newman and Symmes (1974) demonstrated that monkeys reared in isolation from peers emitted “coo” or contact calls that differed significantly from control monkeys in terms of pitch changes, inflections, and discontinuities in the call’s progression.

The amygdala seems to be a critical component of brain circuits that mediate responses to threat, including those in the social domain. Therefore, dysfunction of this structure leading to heightened responses to threat may partially explain the general pattern of antisocial behavior observed for non-maternally reared macaque

monkeys. In fact, when local infusions of GABA antagonists are used to disinhibit the macaque amygdala, animals show a behavioral spectrum reminiscent to that described above for isolate- or peer-reared monkeys, including decreased social contact, a loss of social play, as well as increased passivity and active withdrawal from social interactions (Malkova et al. 2003). The role of the amygdala in fear learning has also been assayed using the fear-potentiated startle paradigm (Antoniadis et al. 2007; Winslow et al. 2002). In this task, the normal whole-body startle reflex to an acoustic stimulus is measured. The animal then learns that a conditioned stimulus (CS; typically a light) predicts delivery of a mildly aversive unconditioned stimulus (US; typically an air puff to the face). Startle reflexes are then measured again both in the presence and absence of the light CS. Normal monkeys show heightened (or potentiated) startle reflexes when the acoustic probe is preceded by the light relative to when the probe is not preceded by the light. Permanent, bilateral amygdala lesions diminish the potentiated startle reflex (Antoniadis et al. 2007). Recently, two separate studies have shown that peer-reared macaques (Nelson et al. 2009), or those that experienced repeated maternal separation (Sanchez et al. 2005), exhibit significantly larger fear-potentiated startle reflexes than mother-reared counterparts. This pattern of results indicates that a lack of maternal care and protection during the first few months of life may greatly alter normal amygdala structural and functional development during an important critical period. Substandard or absent maternal care may predispose animals to abnormally high levels of agonistic and threat-related behaviors during social interactions that do not normally warrant such reactions.

The abnormal socioemotional behavior patterns displayed by isolate- or peer-reared macaque monkeys also resemble that of monkeys with selective damage to the orbitofrontal cortex. Machado and Bachevalier (2006) studied the social behavior of adult macaques before and after selective damage confined mostly to areas 11 and 13 of the orbitofrontal cortex. These lesioned animals displayed an increased frequency of threatening gestures and also received higher levels of aggression from their groupmates. The lesioned animals also showed changes in how they typically responded to both threatening and affiliative social signals received from their groupmates. Similarly, Babineau et al. (2011) recently showed that monkeys with orbitofrontal lesions display more fear grimace facial expressions than unlesioned control animals, especially when they were paired with a larger, older, and more dominant social partner. The lesioned animals also tended to avoid interacting with this same dominant male more than three other less threatening partners. These two studies show that damage or dysfunction of the orbitofrontal cortex results in behavior patterns reminiscent of those displayed by monkeys deprived of maternal interaction during an early neurodevelopmental critical period. As with the amygdala, the lack of maternal care and protection during the first few months of life may alter orbitofrontal development in such a way that animals can no longer integrate information about their internal motivational or affective state, the specific social signal, and the current context when making adaptive social decisions.

In summary, substandard or absent maternal care early in development sets off a cascade of events that result in monkeys that are socially withdrawn, abnormally

aggressive or fearful, and prone to repetitive and self-directed motor stereotypies. It is possible that this pattern of altered socioemotional behavior is mediated by structural and functional abnormalities in the amygdala and orbitofrontal cortex. A lack of maternal care seems to result in behaviors indicative of a “hyperactivated” amygdala, such that animals display elevated social avoidance and potentiated startle reflexes. Atypical early maternal care also results in behaviors that are similar to those observed following orbitofrontal damage, such as elevated aggression and fearful responses, especially with potentially dangerous social partners. However, these connections between early maternal care, neural development, and socioemotional behavior are speculative. There is, at this point, very little direct evidence to support such inferences, but that may soon change.

12.5 Directions for Future Research

We are only just beginning to understand how one’s early social environment, primarily mediated through the mother–infant bond, modulates both neural and behavioral development in macaque monkeys. It is possible that a complete lack or even diminished mother–infant interaction during the earliest stages of postnatal development may result in significant changes in the offspring’s brain as it matures. Those neurobiological alterations may set the stage for abnormal social behavior and emotional regulation later in life. For many group-living animals, including humans and macaques, the skilled use of social behavior promotes reproductive fitness through increased access to food, shelter, and potential mates, as well as greater likelihood of companionships or alliances that promote personal security. If one does not have the capacity or opportunity to learn and efficiently deploy species-specific social skills, then that individual will not reap these benefits, and their reproductive fitness will suffer.

Although we currently have a relatively clear picture of how the quality of maternal care translates to socioemotional behavior patterns of the offspring, much more work needs to be done. In particular, we still lack a clear understanding of how specific aspects of an adverse rearing environment (neglect, physical and emotional abuse, malnutrition, etc.) each influence the structural development of specific brain areas, such as the amygdala and orbitofrontal cortex, and the function of these areas while individuals actively process social information (i.e., assess the meaning of facial expressions, gaze direction, identity, and intentions of a social partner, etc.). Different kinds of stressors during development could have distinct repercussions on social cognitive skills later in life. We know that if monkeys experience abnormal maternal care early in life, they display altered forms of socioemotional behavior, but why specifically? Do they have an altered motivation to engage in social interactions? Do they lack the ability to decode the meaning of social signals? Are they deficient in the ability to use such information to consistently make adaptive behavioral choices and avoid situations that could be threatening? Do they lack the ability to regulate their affective or physiological state in a manner commensurate with the

social context? Or, does abnormal maternal care during the first months of life ultimately perturb all of these facets of socioemotional behavior? Finally, is there any way to reliably treat animals that experience early maternal deprivation and rescue normal social functioning later in life? Answers to these questions will not be attained easily but will ultimately advance our understanding of how the mother–infant bond, social brain development, refinement of social skills, and reproductive fitness are all critically linked.

Continued work with nonhuman primates will be essential for this field of study, considering the level of control such models afford and their similarities to humans. An interdisciplinary approach will also be required—one which combines extensive and reliable observations of social behavior in semi-naturalistic contexts, followed up with additional focused assessment of specific facets of social information processing (i.e., face processing, social motivation, etc.) in controlled settings. The expanded use of noninvasive functional neuroimaging to map the development of brain circuits associated with socioemotional processing will also be extremely important. An advantage of using macaque monkeys for such experiments is that the same animals can be studied across all of these experimental contexts as well as through multiple stages of development. The amount of mother–infant interaction or the type and magnitude of early-life stress (i.e., level of physical abuse, dietary abundance, or nutritional quality, etc.) can also be systematically manipulated and tightly controlled. It will also be important to disentangle the interactions between genotype and social experience in the development of socioemotional behavior. Despite these hurdles, researchers now have the necessary tools to truly determine how our earliest social relationships impact on the success or failure of social relationships throughout the rest of our lives.

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Chapter 13

Behavioral Response of Mothers and Infants to Variation in Maternal Condition: Adaptation, Compensation, and Resilience

Lynn A. Fairbanks and Katie Hinde

Keywords Mother–infant dynamics • Maternal care • Behavioral development • Juvenility • Parent–offspring conflict

13.1 Introduction

There has been a surge of interest in gestational and neonatal influences on developmental trajectories in humans and other mammals in recent years, and there is evidence that maternal nutritional ecology can affect offspring growth trajectories, metabolic processes, and vulnerability for chronic disease later in life (Bateson et al. 2004; Langley-Evans 2006; Rutherford 2009). There has been less emphasis on behavioral responses of mothers and infants to variation in maternal diet and condition during pregnancy and lactation. This chapter will focus on the effects of maternal condition on the mother–infant relationship in nonhuman primates, with consideration of long-term effects on offspring behavioral development. To understand the impact of variation in maternal investment on infant development, it is important to recognize that infants are not simply the passive recipients of variation

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in maternal care. Infant behavior and development evolved in the context of variation in maternal care, and selection has likely favored strategies for infants to get what they need for physical and social development.

The chapter begins with a discussion of parental investment and parent-offspring conflict theory (Trivers 1974; Clutton-Brock 1991), and follows with a review of the effects of habitat quality on maternal investment in nonhuman primates (Clutton-Brock 1991; Lee et al. 1991). Results from wild-living and captive populations provide support for a nonlinear relationship between maternal condition and the quality of maternal care, with females in the best and worst condition limiting investment in their current infants, in the first case to shorten the interbirth interval and in the second to preserve the mothers' health for future reproduction. Behavioral responses of mothers and infants to variation in maternal condition are illustrated here by studies of captive vervet monkeys at the Vervet Research Colony. Vervet mothers in prime condition for reproduction and mothers in marginal condition are both more likely to limit access to the nipple compared to average mothers, and in both cases, the infants respond to maternal rejection by increasing their attempts to maintain ventral contact. Diet-related weight loss also impacts maternal and infant behavior. Mothers and infants adjust their behavior in relationship to one another, with the mother responding to her own condition, and the infant trying to counteract attempts to limit maternal care.

In the next section, the focus turns to assessing long-term effects of maternal condition and maternal behavior on social and behavioral development of yearlings. Different theoretical perspectives are presented, including developmental canalization, fetal programming, resilience, and stress inoculation theories of the expected impact of early prenatal and postnatal experience on behavioral development. Results from macaques, baboons, and vervets suggest that behavioral development is largely resilient to developmental challenges within an expectable range of experience. Indeed the data in hand suggest that infants experiencing modest levels of early maternal rejection become more active promoters of their own social development and provide support for the hypothesis that the negative effects of adverse early experience are more evident under novel and challenging circumstances.

13.1.1 A Certain Amount of Mother–Infant Conflict Is the Normal Context for Development

Parental investment theory is based on the assumption that the amount of effort an individual can devote to reproduction is limited, and that parental effort that benefits one offspring will reduce the parent's ability to invest in other offspring (Trivers 1972). Natural selection will favor the evolution of life history strategies that maximize the parent's expected reproductive success across its lifetime (Clutton-Brock 1991; Stearns 1992). Nonhuman primates have evolved a strategy of substantial investment by mothers in a small number of high quality offspring. Within this general strategy, the energetic costs to the mother of gestation and lactation are expected

to vary according to the condition of the mother and her opportunities for future reproduction. Benefits of maternal effort for the infant will also change as the infant grows and develops independence.

Trivers' theory of parent-offspring conflict (Trivers 1974) focused awareness on the conflict of interest between parents and offspring in the optimal level of care for a parent to provide. A mother should attempt to optimize the allocation of her reproductive energy across present and future offspring. Because infants are more closely related to themselves than to their siblings, the optimal amount of care for an infant to receive, from the infant's perspective, would be greater than the optimal amount of care for the mother to give. This results in a certain amount of conflict over the level and timing a maternal care between mothers and their dependent infants.

Behavioral conflict during weaning is common in nonhuman primates, and has been related to the timing of conception and the interval to the birth of the next infant (Fairbanks 1993a; Maestripieri 2002). There is also evidence that monkey mothers control the timing and amount of access to the nipple in the first few months of life. This sets the stage for selection on infants to actively seek care and to develop strategies to overcome maternal resistance. Consequently, it makes evolutionary sense that infants would be resilient to perturbations in the developmental environment within a reasonable range of expected experience.

13.1.2 Habitat Quality, Maternal Condition, and Maternal Investment

Because of the complexity of the trade-offs involved, intraspecific variation in the costs of maternal care for the mother and benefits for the offspring are difficult to quantify (Clutton-Brock 1991). In a review of the relationship between habitat quality, offspring growth, and weaning age in mammals, Lee et al. (1991) noted that three different, and apparently contradictory, trends have been observed. In some studies, earlier weaning was associated with poorer food availability and higher infant mortality, while in others later weaning was related to limited food conditions. A third set of studies showed that mothers wean their infants earlier in habitats with high food abundance.

Lee et al. (1991) resolved this dilemma by postulating an inverted U-shaped function of resource availability and maternal condition with weaning age. Within a population, mothers in the best and worst condition would be characterized by relatively short periods of investment, whereas the remaining mothers would have a relatively longer period of investment. Specifically, mothers with the lowest level of resources who are unable to maintain lactation and infant growth need to terminate investment and wean their infants early, even at the cost of higher infant mortality. Enhanced food availability leads to more rapid offspring growth and allows earlier weaning with low rates of infant mortality. Mild food limitations are related to modest infant growth rates and a longer period of lactation to achieve an appropriate weaning weight.

The nonhuman primate literature provides support for aspects of the inverted U-shaped function of maternal investment in relation to maternal condition. Macaque and baboon mothers who are less fit for reproduction by virtue of being too young, too old, or underweight are more likely to abandon their infants and have higher rates of infant mortality (Schino and Troisi 2005; Schlabritz-Loutsevitch et al. 2008). Young and low weight marmoset and rhesus mothers produce less milk than experienced mothers and their infants grow at a slower rate (Tardif et al. 2001; Hinde et al. 2009). Among both captive and wild-living Old World monkeys, high ranking females, often in the best condition for reproduction, have been found to experience higher rates of fertility and reproductive success (Drickamer 1974; Dunbar and Dunbar 1977; Wilson et al. 1978; Whitten 1983; Garcia et al. 2006). These reproductive outcomes may be facilitated by weaning their infants earlier than do lower ranking females. For example, high ranking Chacma baboons at Moremi National Wildlife Reserve weaned their infants and resumed cycling earlier than lower ranking females (Johnson 2003). At Amboseli National Park, high ranking baboon mothers were more rejecting and spent less time carrying their infants compared to lower ranking mothers (Altmann 1980; Altmann and Samuels 1992). Maternal rejection was also more common among high ranking rhesus mothers on Cayo Santiago, and these high rates of rejection during the mother's first estrous increased the probability of conception (Berman 1992; Berman et al. 1993).

Field studies of the effects of habitat quality on maternal investment have shown that under extremely poor conditions, such as drought, females are likely to terminate pregnancy early and rates of infant mortality are high (e.g., lemurs: Gould et al. 1999; baboons: Beehner et al. 2006). Stable differences in the density and quality of food between habitats are often related to maternal investment in the opposite direction, however, with higher rates of rejection and earlier weaning in better quality habitats. Comparison of vervet mothers in two field habitats suggested that maternal behavior was keyed to the ability to shorten the interbirth interval by controlling access to the nipple (Hauser and Fairbanks 1988). Maternal rejection of infant contact was more frequent in the higher food quality swamp habitat where females had the opportunity to reproduce annually. In a seasonal environment, interbirth intervals are ecologically constrained, and females in the poorer food quality woodland habitat had a 2-year median interval between births. In that habitat, mothers could not benefit in lifetime reproductive success by limiting their infant's access to the nipple in the first 6 months of life. Maternal rejection was higher when control over nipple access allowed her to shorten the interbirth interval without markedly reducing the infant's chances for survival (Hauser and Fairbanks 1988). Comparison of maternal investment in baboons living in different habitats also reached the same conclusion (Lycett et al. 1998). Mountain baboons have adapted to a relatively harsh and food-poor environment by delaying weaning and extending the interbirth interval compared to baboons observed at east African field sites, with lower rates of conflict over access to the nipple. Reported rates on weaning conflict are higher at sites with more abundant food supplies that allow shorter interbirth intervals.

13.1.3 Maternal Care Is a U-Shaped Function of Maternal Condition

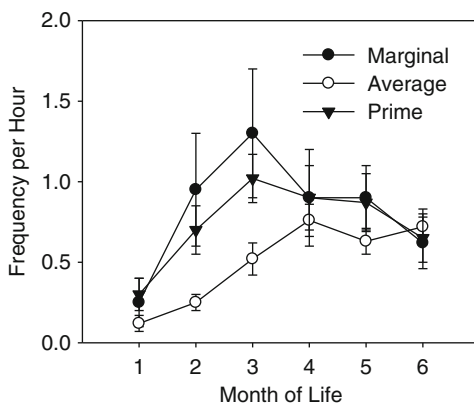
Prior to 1995, there was separate support in the nonhuman literature for limitation of maternal care for mothers in the worst and best circumstances, but no single study had demonstrated that maternal care was a U-shaped function of maternal condition. Then, we presented an analysis that considered both hypotheses simultaneously using data from 160 mother–infant dyads from social groups of vervet monkeys at the Vervet Research Colony (Fairbanks and McGuire 1995). The Vervet Research Colony is a captive colony that was established in Los Angeles in 1975 with vervet monkeys (*Chlorocebus aethiops sabaesus*) from St. Kitts, Eastern Caribbean. The original founders and their descendants lived in large outdoor enclosures in stable matrilineal social groups. In order to compare mothers across the full range of circumstances, we categorized adult females into three groups based on their condition for reproduction. The Marginal group included very young, old, and underweight mothers, factors that were related to reduced fertility and infant survival in the captive colony (Fairbanks and McGuire 1984). The Prime group included high ranking mothers of prime reproductive age, factors that were associated with increased fertility in the colony. The remaining females were placed in the Average group. Mother–infant dyads were observed throughout the first 6 months of the infant’s life. We predicted that maternal rejection and the quality of maternal care would be a U-shaped function of maternal condition, i.e., that mothers in both the Marginal and Prime groups would limit access to the nipple compared to the Average mothers. The results of this study are summarized in Table 13.1.

Observations in the first month of the infant’s life showed that Marginal mothers spent more time out of contact with their infants and had significantly higher rates of infant mortality in the first few months of life compared to mothers from the

Table 13.1 Summary of effects of maternal condition on vervet mothers and infants (Fairbanks and McGuire 1995)

	Marginal	Average	Prime
Criteria	Very young (<4 years) Old (>14 years) Underweight (<4 g)	All others	High ranking Prime age (5–14)
Time in contact—month 1	Less time in contact	Average	Average
Early infant mortality	Higher than average	Average	Average
Maternal behavior— surviving infants	More rejecting	Less rejecting	More rejecting
Infant response—surviving infants	Greater effort to maintain contact	Lesser effort to maintain contact	Greater effort to maintain contact
Contact time—months 1–6	Less time in ventral contact	More time in ventral contact	Less time in ventral contact
Interbirth interval	Longer than average	Average	Shorter than average

Fig. 13.1 Frequency per hour of maternal rejection by maternal condition and infant month of life. Redrawn from Fairbanks and McGuire (1995)



Average and Prime groups. This supported the hypothesis that mothers in the worst condition for reproduction would be more likely to terminate investment early, even at the cost of losing their infants.

Observation of the 127 surviving infants from birth to 6 months indicated that both Marginal mothers and Prime mothers rejected their infants significantly more often than Average mothers. For mothers in the Average group, rejection rose to a peak in months 4–6 when the mothers were coming into estrous and preparing to conceive again (Fig. 13.1). For the Marginal and Prime mothers, higher rates of rejection were observed as early as the second month of age, with a peak in the third month.

Infants responded to the limitation of maternal care by Marginal and Prime mothers by increasing their attempts to regain ventral contact. The Contact Index developed by Robert Hinde (Hinde and Atkinson 1970) measures the relative role of mother and infant in initiating and maintaining ventral contact. Infants of both Marginal and Prime mothers scored significantly higher on this index compared to infants of Average mothers, indicating that they were more responsible for maintaining contact than infants of Average mothers. In this study, the infants did not succeed completely in overcoming their mother's rejecting behavior, and infants of Marginal and Prime mothers had significantly lower rates of ventral contact with their mothers compared to infants of Average mothers.

The Prime mothers in this study were able to translate the increased control over nipple access into future reproduction, as evidenced by a significantly shorter mean interbirth interval to the next birth compared to the Average mothers. Marginal mothers took longer to recover, and did not show a fertility increase related to infant mortality or to the reduction in care to their surviving infants. The results of this study are consistent with the hypothesis that mothers in poor condition for reproduction limited maternal care to restore their own health, sometimes at the expense of infant mortality, while mothers in the best condition for reproduction used rejection to shorten the interbirth interval without risking higher mortality for their infants.

13.1.4 Verification That Maternal Care Is a U-Shaped Function of Maternal Condition

Since the time of our original study, support for the hypothesis that maternal care is a U-shaped function of maternal condition has also been reported by Fite et al. (2005) for marmoset mothers. Marmoset mothers who were challenged by overlapping lactation and gestation reduced their carrying time for current infants compared to mothers who did not conceive during the postpartum estrous. In another comparison, mothers with experienced alloparents available to help with infant carrying also reduced their infant carrying time and increased rejection. The authors concluded that mothers are “flexible opportunists” who maximize their reproductive success by reducing investment under the worst and best of conditions.

Further evidence of a U-shaped function between maternal condition and the quality of maternal care is provided here by a replication of the behavioral components of the original study at the vervet colony, using new data on mother–infant behavior for 205 infants born in 2000–2003. This replication allows us to validate the original findings and to characterize the early experience of infants who then could be followed as juveniles (see Sect. 13.3.3). The mothers were grouped according to the decision rules for age, weight, and rank that defined the Marginal, Average, and Prime mothers in Fairbanks and McGuire (1995). The Marginal group included mothers who were very young, old, or low in weight in body weight (Table 13.1). The Prime group included high ranking females of prime age for reproduction. The data available for the replication sample was limited to months 2–3 of the infant’s life, a time when individual differences in maternal rejection are most evident. The results from the replication study were consistent with the 1995 study and demonstrated that maternal rejection is a U-shaped function of maternal condition (Fig. 13.2a).

To understand the reaction of the infant to variation in maternal behavioral care, we measured the rate of infant distress calls and found that frequency per hour of distress calls was also a U-shaped function of maternal condition (Fig. 13.2b). Infants of both Marginal mothers and Prime mothers had higher rates of distress cries compared to infants of Average mothers. Based on the 1995 study, we predicted that infants would respond to the higher levels of maternal rejection in the Marginal and Prime groups by increasing their attempts to gain ventral contact. As expected, there was a significant quadratic effect of maternal condition on the infant’s role in contact (Fig. 13.2c). The contribution of the infant to regaining contact was higher for infants of Marginal mothers and Prime mothers than for infants of Average mothers.

The new sample replicated the central findings from the original study that maternal rejection of infant contact is a U-shaped function of maternal condition, and that infants responded to higher levels of maternal rejection by increasing their own efforts to regain ventral contact. These results provide further support for the general hypothesis that mothers are allocating maternal care to maximize their own lifetime reproductive success, and that infants are adapted to respond to expectable variation in maternal care to preserve their own self interest.

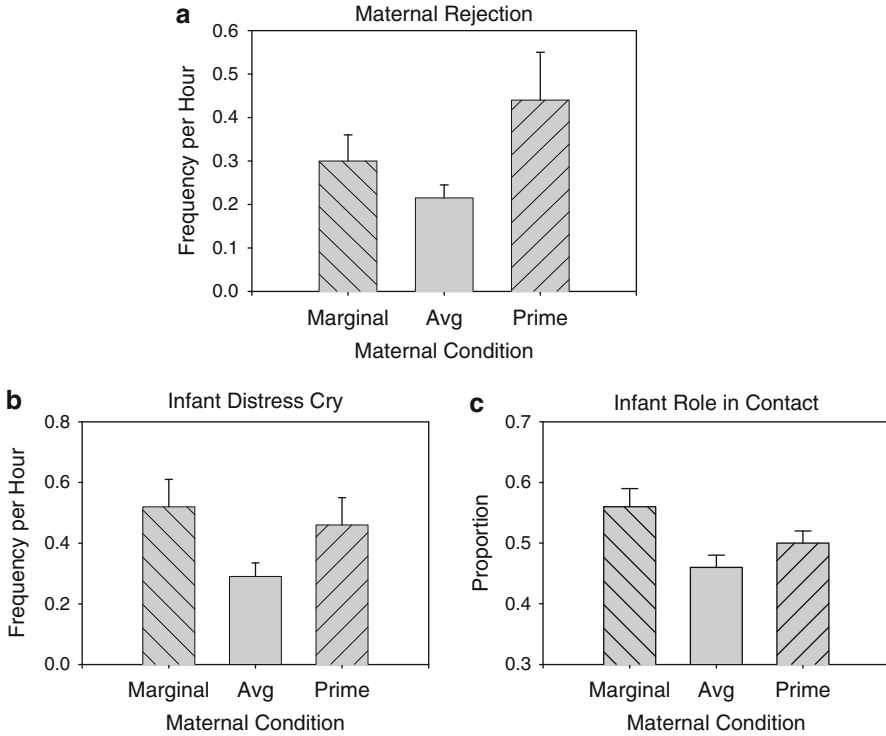


Fig. 13.2 Replication of effects of maternal condition on maternal and infant behavior: (a) maternal rejection. The significant quadratic term ($F=4.30$, $df=2,201$, $p=0.04$) supports the hypothesis that maternal rejection is a U-shaped function of maternal condition. Sample size: Marginal=44, Average=116, Prime=44; (b) infant distress cry (Quadratic term: $F=6.62$, $df=2,201$, $p=0.01$); and (c) infant role in contact (Quadratic term $F=6.89$, $df=1,201$, $p=0.009$)

13.1.5 Dietary Restriction, Weight Loss, Pregnancy, and Lactation

In the captive studies of vervets and marmosets described above, food was freely available and differences in maternal condition were based on factors related to age, size, rank, social support, and overlapping gestation and lactation. Experimental manipulation of diet affords further insights into maternal reproductive trade-offs. Moderate caloric restriction has been shown to promote general health and increase longevity in nonhuman primates (Colman et al. 2009), but during pregnancy and lactation, maternal nutrient restriction has complex and often negative effects on the offspring. For example, energy restriction in pregnancy can precipitate spontaneous abortion and preterm birth in common marmosets (Tardif et al. 2004, 2012). Nutrient restriction of baboon mothers during pregnancy altered the functioning of the placenta and led to changes in fetal brain development (Li et al. 2007; Antonow-Schlorke

et al. 2011), and restriction during lactation reduced milk production (Roberts et al. 1985). Among humans, results from the Dutch famine in the winter of 1944–1945 revealed that pregnant women who experienced the famine during the third trimester had infants that were significantly underweight for their gestational age (Roseboom et al. 2006). These results demonstrate that physiological investment is sensitive to maternal diet and energy balance, but how might nutrient restriction impact maternal behavioral care?

13.1.6 Effects of Diet Quality on Maternal Behavior in Vervets

A recent study from the vervet colony demonstrates the effects of diet variation and maternal weight loss on the behavior of mothers and infants. The diet at the colony was changed from the standard commercial laboratory chow diet to a new high-fiber formulation in 2004 to promote health and provide a more natural level of fiber in the diet. The high-fiber diet was lower in available energy, and also lower in carbohydrates and higher in protein than the standard diet. Food was not restricted but the palatability and the composition of the high-fiber diet led to a 10% spontaneous weight loss for adult females in the colony (Fairbanks et al. 2010). Because we expected maternal behavior to be sensitive to maternal condition and resource availability, data on mother–infant interactions for 280 infants born from 2000 through 2006 were assessed for effects of the diet change.

Mothers of infants born in 2000–2003 were fed the standard diet during gestation and lactation (standard diet group). This is the sample of mothers and infants used for the replication study described in Sect. 13.2.4. The new diet was phased in early in the summer of 2004, so the mothers of infants born that year experienced gestation on the standard diet and transitioned to the new diet during lactation (transitional diet group). The diet change precipitated moderate weight loss so the transitional mothers were in negative energy balance during lactation. Mothers of infants born in 2005–2006 had already experienced weight loss and were on the high-fiber diet throughout gestation and lactation (high-fiber diet group).

There were no differences in neonatal mortality for infants on the new diet, and other than the spontaneous weight loss, there were no apparent effects of the diet change on adult female morbidity or mortality. The new diet did have a significant effect on maternal behavior and that effect was linked to the mother's weight at conception. The mothers who went through gestation and lactation on the high-fiber diet had double the rate of rejecting ventral contact compared to mothers in the standard and transitional diet groups (Fig. 13.3a). Within the high-fiber diet group, there was an inverse relationship between the mother's weight at conception and her degree of maternal rejection: the lower the mother's weight at conception, the higher her degree of rejection (Fairbanks et al. 2010).

As with the maternal condition study described above, the infants in the diet study did not just passively accept the reduction of care by their mothers. There was a significant effect of diet on the infant's contribution to maintaining ventral contact.

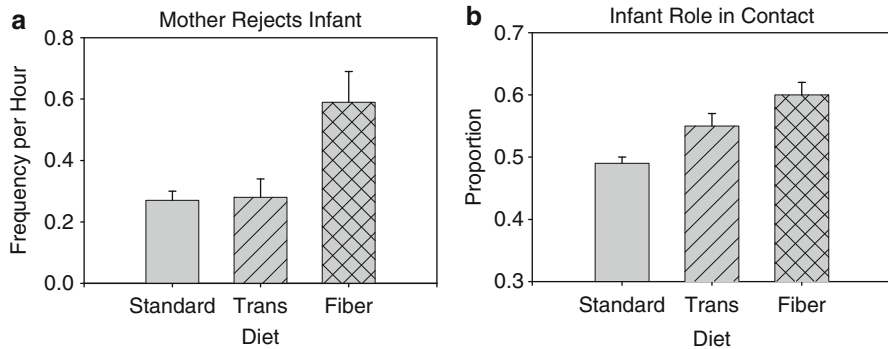


Fig. 13.3 Effects of standard, transitional (Trans), and high-fiber (Fiber) diets on (a) maternal rejection, and (b) infant role in contact (Fairbanks et al. 2010)

Both the absolute and the relative rates of contact initiations made by the infant increased following the diet change, with the highest levels for infants in the high-fiber diet group (Fig. 13.3b). The increased role of the infants in making contact counteracted the mother's actions and resulted in a slight but not statistically significant reduction in the percent time infants spent in ventral contact with their mothers on the high-fiber diet.

The results of this study showed that maternal behavior is sensitive to negative energy balance, even in the high-to-moderate weight range. Other studies have shown that the metabolic cost of lactation, as reflected in maternal energy balance, is critically important for resumption of reproductive function in humans and baboons, possibly to a greater extent than is nursing frequency (Valeggia and Ellison 2009; Rosetta et al. 2011). This is because the regulation of the hypothalamic-pituitary-ovarian axis is exquisitely sensitive to energy balance (Valeggia and Ellison 2009). However, we can predict that the physiological cues of energy balance that affect reproductive state also influence maternal behavioral care during lactation. Importantly the vervet study also showed the active part played by infants in counteracting reductions in maternal care within the normal range of expected experience.

13.2 Are There Long-Term Effects of Maternal Condition and Maternal Behavior on Offspring Behavioral Development?

13.2.1 Adverse Early Experiences: Divergent Theories

There is a long history of research on the effects of adverse early life experiences on behavioral development in nonhuman primates (see Stevens et al. 2009; Parker and Maestripieri 2011 for recent reviews). Early studies focused on the effects of permanently separating infants from their mothers shortly after birth, and it is clear from this work that the absence of a mother has profound and long-lasting effects on physiological

Table 13.2 Predictions from different hypotheses about the long-term effects of early experiences with Marginal or Prime mothers on yearling behavior, compared to Average mothers

Hypothesis	General predictions	Marginal	Prime
Deficit	Emotional dysregulation, deficiencies in social competence, increased reactivity to novelty	More anxiety Less social approach Less time near Less play Less novelty seeking	Slightly more anxiety Slightly less play Less novelty seeking
Fetal/lactational programming	Adaptations to reduced expectations for nutrition and social support	Less activity Less social approach Less play Less novelty seeking	Few or no differences
Canalization	Return to normal developmental trajectory	No differences	No differences
Resilience	Deficits in social and emotional functioning are alleviated by positive social support	More anxiety Less activity Less social approach Less time near Less play Less novelty seeking	No differences
Stress Inoculation	Moderate early life challenges increase ability to handle stress in later life	More social approach More play More novelty seeking	More social approach More play More novelty seeking

regulation and social development. There is evidence that multiple shorter separations of young infants from their mothers produce acute distress and may have long-term consequences on later responses to stressful circumstances (Spencer-Booth and Hinde 1971; Stevens et al. 2009). There is also evidence that experimentally altering the level of effort for the mother to acquire food in the variable foraging demand paradigm can have long-term consequences on offspring behavior and neurophysiology (Andrews and Rosenblum 1994; Coplan et al. 1996; Rosenblum et al. 2001). Spontaneously occurring individual differences in maternal style have also been noted, and a few studies have looked for long-term consequences for offspring behavioral development (Fairbanks 1996; Schino et al. 2001; Maestripieri et al. 2006).

Various different hypotheses and theoretical approaches have been used to predict and explain individual response to early adversity and the long-term effects on developmental trajectories (Table 13.2). Most studies of extreme alteration of the infant's early environment have focused on *deficits* in functioning. Deviations from the ideal early experience are expected to impair normal development and lead to negative long-term outcomes in a linear dose–response fashion. The more adverse the early experience, the worse the outcome is expected to be. This has been the prevailing hypothesis for most studies of adverse early experience in humans and nonhuman primates (Suomi 1997; Sameroff and Rosenblum 2006).

Developmental theories arising from biology have taken a more adaptationist approach. Waddington (1942, 1957) noted that individuals of the same species tended to develop similar adult phenotypes in spite of environmental differences. His concept of *developmental canalization* pointed to the role of natural selection in

favoring genetic mechanisms that would return an individual to a species-typical developmental trajectory after an environmental perturbation. An example of developmental canalization is accelerated “catch-up” growth following periods of illness or food restriction (Kay’s and Hindmarsh 2006).

Fetal programming is an alternate adaptationist view of the effects of early experience on development (Barker et al. 2002). The early nutritional environment is proposed to match fetal and neonatal growth rates and metabolism to the available nutrition in ways that promote infant survival. Thus, infants of underweight mothers who are developing in a food-poor gestational and lactational environment can increase their chances of survival by slowing their growth rates (Belogolovkin et al. 2009). These adaptations may result in a trade-off of increased early survival with reduction in later health and fitness (Bateson et al. 2004; Langley-Evans 2006). From a behavioral perspective, a large body of literature reveals that social stress, such as population crowding, experienced by pregnant females organizes offspring behavior postnatally (Kaiser and Sachser 2005; Sachser et al. 2011).

Psychologists have been interested in the concept of *resilience* in understanding the effects of early adversity on human development (Masten and Obradovic 2001; Rutter 2006). While stressful early experiences may increase risk for emotional disorders, one of the noteworthy features of response to early adversity in humans is the variability of individual outcomes. Masten (2001) argues that resilience is a common phenomenon that arises from adaptive processes, such as forming connections to competent and caring adults in the family and community. Genetic factors, personal attributes, and positive coping experiences have also been implicated as protective factors that promote resilience in the face of adversity (Rutter 1985, 2006).

A variant of the resilience concept is the *stress inoculation* hypothesis. A number of studies of humans and nonhuman primates have reported that early exposure to mildly stressful experiences can enhance the ability to handle future stressors (Garnezy et al. 1984; Lyons et al. 2009). For example, Parker et al. (2006, 2007) showed that brief mother–infant separations can enhance arousal regulation and increase later exploratory behavior if the separations are conducted at the age that squirrel monkey infants are normally gaining independence from the mother. Examining life stress across a continuum from none to mild to more severe showed that psychological assessments of distress and functional impairment in humans were related to cumulative lifetime adversity in a U-shaped function (Seery et al. 2010). High adversity scores were associated with poorer outcomes, but individuals who had experienced some adversity scored better on measures of mental health and well-being than individuals who reported no stressful life events.

13.2.2 Nonhuman Primate Studies of the Relationship of Maternal Rejection and Offspring Behavioral Development

Adjusting to variation in the physical and nutritional condition of the mother is a common problem for primate infants in the natural world. Mothers would be

expected to differ in body weight, experience, and other factors that influence their ability to invest in offspring. Annual differences in the quality of food available for the mother to eat during gestation and lactation would also be part of the environment of evolutionary adaptedness. Mothers have evolved mechanisms to adjust fertility and investment in offspring according to their own physical and ecological circumstances. Thus, it is reasonable to expect that primate infants would have evolved mechanisms to promote healthy development when faced with reductions in maternal investment within the expectable range.

Data that are available on behavior of nonhuman infants who experienced higher levels of early maternal rejection within the normal range are generally consistent with the hypotheses of canalization, resilience, and stress inoculation. Surviving infants of relatively rejecting mothers tend to initiate more contacts with others and develop independence at an earlier age (Fairbanks 1996; Bardi and Huffman 2002).

Only a few studies have followed nonhuman primate infants after the first year of life to assess the long-term effects of early maternal rejection on individual differences in behavior of juvenile or adult offspring. Behavioral observations of rhesus monkeys of high and low rejecting mothers in the second year of life showed that offspring of rejecting mothers had lower rates of solitary play, but no differences were found in measures of aggression, avoidance, grooming, scratching, or social play (Maestripieri et al. 2006). The authors concluded that the exposure to maternal rejection in the first 6 months of life was generally not a good predictor of offspring behavior in the second year of life. Schino et al. (2001) found no effects of early maternal rejection on affiliative behaviors recorded in the home group for juvenile and adult Japanese macaques, but there was a difference in how individuals responded to potential aggression. Monkeys who had experienced relatively high rates of maternal rejection as infants were less likely to show a fear reaction when being approached by other monkeys and were less likely to display post-conflict scratching, an indicator of anxiety after an aggressive encounter. These results are consistent with the resilience and stress inoculation hypotheses of the effects of early adversity on later behavior.

13.2.3 Long-Term Effects of Maternal Condition on Behavior of Juvenile Vervets

13.2.3.1 Predictions

The replication of the maternal condition study provided the opportunity to look at the long-term effects of maternal condition and maternal behavior on behavioral development of yearlings at the vervet colony. Most of the infants observed in 2000–2003 were observed as yearlings for behavior in the home group, including measures of anxiety (scratching and self-directed behavior), aggression, locomotor activity, affiliative approach, social play, and time near others.

Predictions about the impact of maternal condition on yearling behavior vary among the differing hypotheses described in Sect. 13.3.1 (Table 13.2). A straight deficit approach would predict impairment of adaptive behaviors for the offspring of Marginal mothers who experienced higher rates of maternal rejection, and possible nutritional deficiencies in gestation and lactation, compared to average mothers. Thus, infants of marginal mothers might be expected to show more anxiety-related behavior, engage in less social play and social affiliative, and be more fearful and inhibited in response to novelty. Offspring of Prime mothers who experienced higher rates of maternal rejection and more distress in early life might also be expected to show modest deficits in the same areas. The fetal programming hypothesis would predict differences for offspring of Marginal mothers related to set points for slower growth and reduced nutritional needs. This might be reflected in delays in physical development, lower activity levels, and reduced confidence in social encounters.

In contrast, the canalization model would predict no differences between offspring of the three maternal condition groups as yearlings recover and return to species-typical developmental trajectories. The resilience hypothesis would predict few or no deficits for offspring of Prime mothers who experienced high rates of maternal rejection in the context of the social and physical benefits of high matrilineal rank. Deficiencies in social competence, anxiety, and emotional regulation might be expected for yearlings of Marginal mothers who do not have the compensating benefits of high rank. Finally, the stress inoculation hypothesis might predict that infants who had successfully dealt with rejecting mothers by actively seeking contact would continue to be active and effective agents in meeting their social and developmental needs, and would be resistant to the stress of the novelty test situation, leading them to be higher in novelty seeking compared to yearlings from the average group. We explore these predictions below.

13.2.3.2 Yearling Results: Home Group Behavior

Sex differences in behavior begin to emerge late in the first year of life and are pronounced in juvenile vervets (Fairbanks 1993b). As expected, yearling males in this sample engaged in social play more than juvenile females, and females had higher rates of affiliative approach. To accommodate these sex differences in behavior and developmental goals, the analyses of the effects of maternal condition on yearling behavior were conducted separately for males and females. For yearling males, there were no effects of early maternal condition on locomotion, social approach, anxiety indicators, aggression, or percent time near others, but there was a significant effect on social play. Males born to Marginal mothers had the highest rates of yearling play, while males born to Prime mothers had the lowest rates (Fig. 13.4a). For females, there were effects of maternal condition on two measures of yearling behavior (Fig. 13.4b, c). There was a significant quadratic relationship between maternal condition and the rate of initiating social approaches. Daughters of

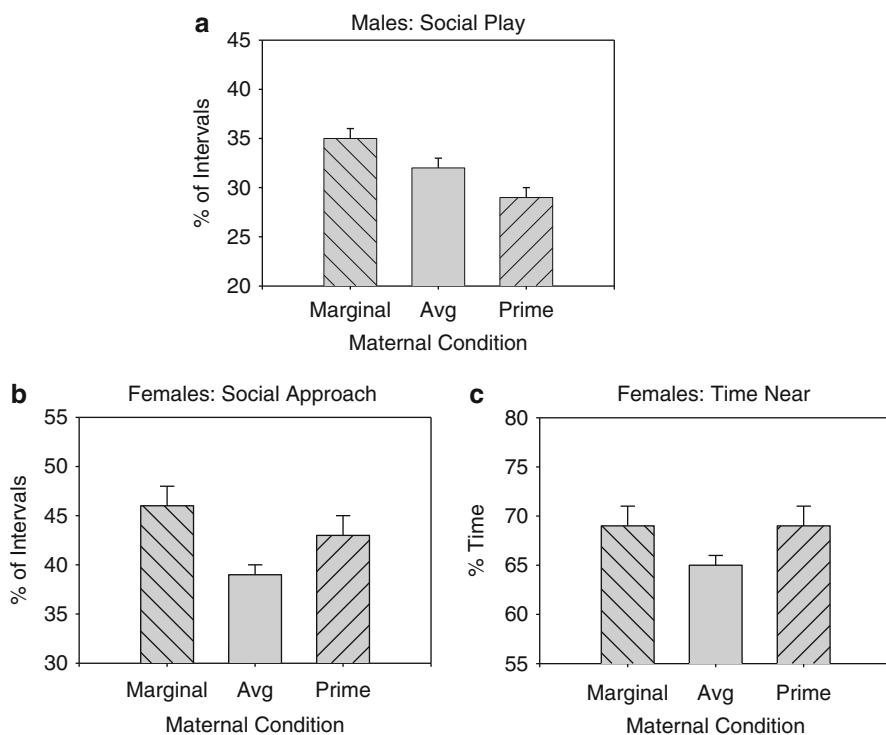
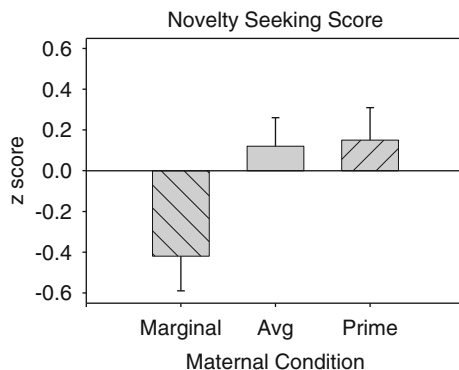


Fig. 13.4 Yearling behavior by early maternal condition: (a) Yearling sons of Marginal females had the highest rate of social play (linear $F=9.32$, $df=2,72$, $p=0.003$); (b) Yearling daughters of Marginal and Prime mothers had higher rates of social approach compared to yearling daughters of Average mothers (Quadratic $F=6.73$, $df=2,69$, $p=0.12$); and (c) Yearling daughters of Marginal and Prime mothers spent more time near other group members (Quadratic $F=4.20$, $df=2,69$, $p=0.04$) compared to yearling daughters of Average mothers

Marginal mothers had the highest rates of initiating social approaches and daughters of Average mothers had the lowest rates. There was also a significant quadratic effect of maternal condition on time spent near others, with daughters of Average mothers having the lowest rates.

These results suggest that offspring of Marginal mothers continued to compensate for disadvantages they experienced during gestation and lactation by engaging in higher rates of social play for males and higher rates of affiliation for females. This pattern is consistent with the hypothesis that development is canalized and buffered against perturbations in early experience within the expectable range. It is also consistent with the psychological concepts of stress inoculation and resilience in the face of early hardship. The behaviors that showed a difference, social play for males and affiliation for females, are particularly important for the development of adult behavioral competence (Fairbanks 1993b).

Fig. 13.5 Yearling offspring of Marginal mothers had lower Novelty Seeking scores in the Home Group Novelty test compared to offspring of Average and Prime mothers (linear $F=4.42$, $df=2,106$, $p=0.04$)



13.2.3.3 Yearling Behavior in the Novelty Challenge

Long-term effects of early life challenges frequently do not show up in behavior in familiar settings, but are more evident when individuals are confronted with novel and challenging situations. Since 2003, all animals at the Vervet Research Colony have been tested once a year on the Home Group Novelty test (Bailey et al. 2007; Fairbanks and Jorgensen 2011). During this test, a novel and potentially threatening object is placed inside or adjacent to the home cage, and responses of group members are recorded for a 30-min test period. Group members typically respond with interest and arousal, and occasional alarm calls. The 1 m area is a small fraction of the home enclosure and there is no need for the subjects to respond, but most animals in a group eventually approach the object at some point during the 30-min test. The Novelty Seeking score reflects the rapidity of approach and the amount of ongoing interest in the novel object. We interpret this score as a measure of curiosity and novelty seeking in a free-choice context. Performance on this test has recently been related to physiological and environmental indicators of stress, with higher cortisol levels and a higher levels of environmental stress associated with lower Novelty Seeking scores (Laudenslager et al. 2011; Fairbanks et al. 2011). Subjects born in 2002–2003 ($N=109$) were tested as yearlings in the Home Group Novelty test. Novelty Seeking scores were standardized by year to account for mean differences between the stimuli used in each year. There were no differences in scores for males and females, so both sexes are analyzed together.

Offspring of Marginal mothers had significantly lower Novelty Seeking scores compared to offspring of Average mothers and Prime mothers (Fig. 13.5), and there was a strong linear effect among maternal condition groups for novelty seeking behavior. The results of this analysis provide evidence that marginal maternal condition has an inhibitory effect on yearling confidence and curiosity in novel situations. This analysis also allows us to separate any direct effects of maternal rejection from the context in which they occur. Offspring of Prime mothers experienced higher rates of early maternal rejection in the protected context of growing up in a high ranking matriline. That is, in sharp contrast to offspring of

Marginal mothers who experienced higher rates of maternal rejection in a context that may also have involved deficiencies in nutrients available during gestation and lactation (Rutherford 2012; Hinde 2012). The Marginal group included “teen-age” mothers who were still growing and trying to establish their position in the social hierarchy, and older mothers who may have been suffering from age-related illnesses and the reduced energy levels associated with aging. Thus, the offspring of Marginal mothers were developing in a world that was less secure socially as well as physically. The results of the novelty challenge test are consistent with the deficit and fetal programming hypotheses for the effects of marginal maternal condition during gestation and lactation on juvenile response to novel and challenging conditions. They support the canalization and resilience hypotheses for the effects of early maternal rejection on juvenile response to novelty challenge for offspring of mothers in prime condition.

13.3 Directions for Future Research

The research presented here has barely touched the surface of the effects of diet and maternal condition on the mother–infant relationship and offspring behavioral development.

Most of the studies on primate maternal effects on offspring development are epidemiological, and there are many uncontrolled individual and contextual variables that could affect the outcomes of interest (Maestripieri 2009). There is a need for more controlled experimentation to specify factors and determine cause–effect relationships, and there is also a need for longitudinal research in naturalistic settings to assess long-term outcomes of early differences on behavioral development. For example, in one controlled study, Antonow-Schlorke et al. (2011) found significant effects of moderate caloric restriction during gestation on infant brain microanatomy, but the effects of these differences on postnatal cognition and behavior are currently unknown. The results and theories discussed here illustrate the importance of the protracted time frame and the social context in assessing relationships between early experience and later behavior.

A more complete picture of the effects of diet and maternal condition on the mother–infant relationship requires an understanding of the physiological and neurobiological mediators between maternal condition and maternal behavior. As an example, gene knockout research in rodents has demonstrated that the central activity of oxytocin and prolactin affects maternal behavior (Leckman and Herman 2002), but in the periphery these same hormones are instrumental in milk synthesis and let-down during nursing (Akers 2002). Similarly pathways that are frequently associated with behavior (e.g., HPA axis) have important interactions with the metabolic pathways that are sensitive to diet and nutrition (Nyberg 2012; Hinde 2012), but these interactions and the consequences for behavior remain to be systematically studied in primates. Many of the chapters in this volume focus on the importance of the placenta and milk quality as physiological mediators of the effects of

maternal condition on infant physical development, and a few address offspring behavioral outcomes (e.g., Hinde 2012). Further exploration of placental and lactational effects on infant and juvenile behavioral development would augment the behavioral studies described here. There is clearly a lot more research needed to understand the mechanisms and consequences of variation in maternal condition for mothers and offspring.

13.4 Conclusions

Research with nonhuman primates brings an appreciation of the complex interplay and trade-offs between costs and benefits for the mother and the infant in determining the extent of postnatal maternal care and the timing of weaning. Data from the field and from captive primate colonies support the hypothesis that maternal investment is highly sensitive to maternal condition. Compared to average mothers, females in the best condition for reproduction can increase their lifetime reproduction by controlling nursing access without jeopardizing their current infants' survival. In contrast, females in the worst condition for reproduction may have to limit investment to protect their own health and future reproductive opportunities, even at the cost of increased infant mortality. This results in a U-shaped function between maternal condition and the quality of maternal care, a finding that has now been verified in several studies. Results from vervets and other nonhuman primate species have also demonstrated that mothers will respond to a change in their condition for reproduction by modifying maternal investment. Caloric restriction and even a healthy diet-induced weight loss can lead mothers to increase rejection and limit access to the nipple.

An important conclusion of the research presented here is that offspring are not simply passive recipients of maternal care decisions. In most cases, infants actively thwart their mothers' attempts to reduce investment and control access to the nipple. Infants of rejecting mothers increase their attempts to regain and maintain ventral contact, and often succeed in achieving levels of contact that are comparable to infants of less rejecting mothers. Young monkeys continue to respond to variation in maternal condition and early maternal rejection, even after weaning. In vervets, there was evidence for fetal programming, compensation, and resilience in different behavioral domains. Offspring of marginal mothers were more cautious when presented with a novelty challenge compared to their age–sex peers, but they also took a more active part in initiating affiliative interactions in the familiar home group setting. Importantly, maternal condition and the level of early maternal rejection did not predict yearling measures of anxiety, activity, or aggressiveness in the home group. Much work remains to be done to gain a better understanding of the long-term effects of variation in maternal condition, diet, and behavior on primate behavioral development, but the research in this chapter illustrates the value of considering offspring capacities for adaptation, compensation, and resilience in response to variation in early experience within the normal context of development.

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Chapter 14

The Role of Mothers in the Development of Complex Skills in Chimpanzees

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Keywords Social learning • Foraging behavior • Infant development • *Pan* • Tool-use

14.1 Introduction

The significance of the maternal relationship for normal infant development in primates has been recognized since the 1960s (Harlow et al. 1965). Compared to other mammals, primates experience long periods of prereproductive dependency. During this time, they acquire an astonishing array of skills, including how to avoid predators, how to navigate complex social situations, and how to find and process food.

Studies in a variety of primates and other mammals have demonstrated that young individuals learn much of what they know about foraging from observing and sampling what their mother eats (primates, Rapaport and Brown 2008; elephants, Lee and Moss 1999; felids, Kitchener 1999). In a recent review, Rapaport and Brown (2008) summarize and describe the potential role of social learning in the development of foraging across the primate order. For prosimians, very little is known regarding the role of social- versus individual-based learning in the ontogeny of foraging, owing to a relative lack of study of these taxa. Among New World primates, the most intriguing example is that of the complex stone tool-use exhibited by wild capuchin monkeys while foraging on nuts. Through intensive observation of known individuals over the course of development of the behavior, researchers have documented careful attentiveness of youngsters to proficient adults, the developmental

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trajectory of the behavior, and different foraging traditions displayed by different capuchin populations (reviewed in Ottoni and Izar 2008). Among the apes, there is now a rich dataset on the importance of social learning in the development of tool-use skills in chimpanzees, which will be discussed below. In orangutans, Jaeggi et al. (2009) report that immature individuals had a nearly identical diet to their mothers' despite considerable variation among those mothers. All of these studies demonstrate the key role that a primate mother plays as a model for her young as they develop foraging behaviors.

In the case of chimpanzees, the mother–infant relationship is of paramount importance due to their relatively long period of nutritional and social dependency and their relative lack of paternal care (Goodall 1967, 1986, but see Lehmann et al. 2006). Chimpanzees live in “communities” (Goodall 1968) or “unit groups” (Nishida 1968) that range in size from 20 to 150 individuals. These communities are multimale, are promiscuous, and have a male dominance hierarchy in which males form the stable core of the community and defend a group territory (Goodall 1986). Chimpanzee society is termed “fission–fusion” as members of a community can join or leave traveling parties at any time (Goodall 1986; Wrangham 1979). An individual's presence in a party is determined by a combination of factors which may include food availability, sexual state of females, and social relationships with other individuals. Neighboring chimpanzee communities are highly territorial and intercommunity interactions can have fatal results (Goodall 1986; Wilson and Wrangham 2003). Chimpanzees are also slow to reproduce in the wild, having their first offspring at 13 years of age, on average, with a three to five year interbirth interval (Goodall 1986; Nishida et al. 2003). Single offspring are the most common result of pregnancy, although some sets of twins have been reported (Goodall 1986; Nishida et al. 2003). Offspring are nutritionally dependent on their mother through infancy until weaning between the ages of 3 and 5, but remain behaviorally dependent (i.e., continually traveling and socializing with) through the juvenile years, until at least the age of 8 (Pusey 1990). Only after the age of 10 years do most chimpanzees start to spend the majority of time away from their mother (Pusey 1983, 1990), and it is not uncommon for adult chimpanzees (those over 12) to spend a significant amount of time with their mothers.

Chimpanzees spend almost half of their waking hours feeding, and much of the rest of the time moving between food sources (Wrangham and Smuts 1980). Chimpanzees are omnivorous, but feed predominantly on seasonally ripe fruit; where measured, fruit makes up between 60% and 85% of feeding time (Potts et al. 2011). However, hundreds of food species have been identified from long-term study sites and these include leaves, pith, insects, mammals, honey, nuts, and many others items (e.g., 200 species at Bossou, Guinea—Humle 2011; over 200 species from Mahale, Tanzania—Nishida et al. 1983). Consequently, it is imperative that a young chimpanzee learn how, where, and when to eat the various foods in its environment, which they learn primarily by observing their mother (Goodall 1968; Corp and Byrne 2002). Some items in the chimpanzee diet require the use of tools to access the edible parts, and in fact, chimpanzees are exceptional among nonhuman primates with regards to the number and variety of tool-assisted skills present in their behavioral repertoire (Goodall 1986; Whiten et al. 1999). Tools are often used

during feeding to gather insects or access nuts with hard shells. While these are not critical portions of the chimpanzee diet, they are highly valued, and chimpanzees may spend a substantial percentage of their time feeding on these items during certain seasons (e.g., up to 14% of observation time spent eating termites during the seasonal peak—Lonsdorf 2006).

The mechanisms by which these tool-assisted skills are acquired and learned remain an important area of research. In the last decade, research on social learning has exploded (Whiten and Mesoudi 2008). The most basic and inclusive definition of social learning is that “individual B learns some or part of the behavior from individual A,” which is presumed to draw on more complicated cognitive processes than individual trial-and-error learning (Whiten and Ham 1992). Social learning has been further analyzed and dissected into several different types which are regularly debated (see Byrne and Russon 1998; Whiten 2000), but for the sake of simplicity, three general categories are largely agreed upon: (1) *stimulus enhancement*, in which A draws B’s attention to the location or object to which the behavior is directed and B then learns the goal and form of the behavior on her own; (2) *goal emulation*, in which B learns from A the goal of a particular behavior, but does not reproduce the exact form of A’s behavior; or (3) *imitation*, in which B learns some part of the form of the behavior from A (Whiten and Ham 1992). In addition, social learning is argued to be key to the development and maintenance of animal “traditions” or “culture,” although the existence of culture in nonhumans remains a matter of great debate (see McGrew 2010 for a recent review).

In humans, the role of the mother or alloparents in social learning is often the role of “teacher.” Various definitions of teaching have been proposed, but a useful operational definition for nonhuman animals was described by Caro and Hauser (1992):

An individual actor A can be said to teach if it modifies its behavior only in the presence of a naive observer, B, at some cost or at least without obtaining an immediate benefit for itself. A’s behavior thereby encourages or punishes B’s behavior, or provides B with experience, or sets an example for B. As a result, B acquires knowledge or learns a skill earlier in life or more rapidly or efficiently than it might otherwise do, or that it would not learn at all.

The frequent and widespread occurrence of active teaching is thought to be a driving force in the evolution and maintenance of cultural diversity in humans (Boyd and Richerson 1996). Given that chimpanzees are arguably the most adept tool-using nonhuman animal and are also purported to show group-specific behavioral diversity akin to culture, one might assume that the role of the mother in developing such skills should also be that of “teacher.” In fact, active teaching is quite rare in chimpanzees and, indeed, across the animal kingdom (see Hoppitt et al. 2008; Byrne and Rapaport 2011 for recent reviews of animal teaching as defined by Caro and Hauser). Much research in the area of social learning has utilized experiments in captivity since carrying out longitudinal developmental studies in the wild is typically precluded by time and cost. However, as more long-term field studies progress, we are able to follow individual development with greater precision, and new findings are coming to light. In this chapter, I will review the current state of knowledge of the mother’s role in the development of complex tool-assisted skills in her offspring in wild chimpanzees.

14.2 Field Studies on Tool-Use Development

Several field studies of chimpanzees have now focused on how infants and juveniles develop complex, tool-assisted foraging techniques. These include studies of nut-cracking (Boesch 1991; Biro et al. 2003), termite-fishing (Lonsdorf 2005; Sanz and Morgan *in press*), and ant-dipping (Humble et al. 2009), all of which are described below and present strong evidence that social learning plays a key role in the development of these behaviors. Although the role of the specific maternal characteristics and/or behaviors is more difficult to assess directly in an observational field study, these studies have begun to elucidate the role of the chimpanzee mother in the transmission of tool-use acquisition.

14.2.1 Nut-Cracking

In West Africa, chimpanzees at two long-term study sites are known to engage in a tool-assisted foraging behavior known as nut-cracking (Tai Forest, Ivory Coast—Boesch and Boesch 1981; Boesch and Boesch-Achermann 2000; Bossou, Guinea—Sugiyama and Koman 1979, reviewed in Biro et al. 2003). Nut-cracking consists of positioning a hard-shelled nut on an “anvil” stone or substrate, striking it with a “hammer” stone, and then extracting the nut out of the broken shell and eating it (see Fig. 14.1). It is one of the more complicated tool-use behaviors observed in wild chimpanzees since the use and manipulation of two tools is required. The age at which youngsters can successfully open a nut is 3.5 years at Bossou for cracking open oil-palm nuts, *Elaeis guineensis* (Inoue-Nakamura and Matsuzawa 1997), and between 5 and 6 years at Tai for Coula nuts, *Coula edulis* (Boesch and Boesch 1984). Adult-comparable efficiency, in which individuals can open nuts with no more than a couple of blows with the hammer, is not achieved until between 8 and 14 years at Bossou (Biro et al. 2003) and when fully adult at Tai Forest (Boesch and Boesch 1984).

Boesch (1991) observed 19 mother–infant pairs in the Tai Forest and described the three ways that mothers may influence their youngsters’ development of nut-cracking skills. The first was termed “stimulating”—that is, leaving hammers or nuts near the anvil stone. Boesch reported that mothers are significantly more likely to leave their hammers at an anvil (and risk losing it to other chimpanzees) once their offspring reach an age (typically 3 years old) at which they become interested in the nuts and tools. In addition, while nonmothers never left nuts on or near the anvil, mothers often did. The second way that mothers affected youngsters’ development was termed “facilitating”—that is, actively providing nuts and stones to offspring. Boesch (1991) tallied 272 instances of mothers providing stones to offspring and 316 instances of mothers providing nuts in over 4,000 min of observation. However, two important points should be mentioned. Boesch used the term “provide,” which suggests that mothers actively handed over stones and nuts to their offspring. However, in the description of these events, it seems clear that the mothers simply tolerated the taking of their materials. For example, “Ella let her son consecutively take four hammers from her” and “During one nut-cracking session, Ella’s 5-year-old son took

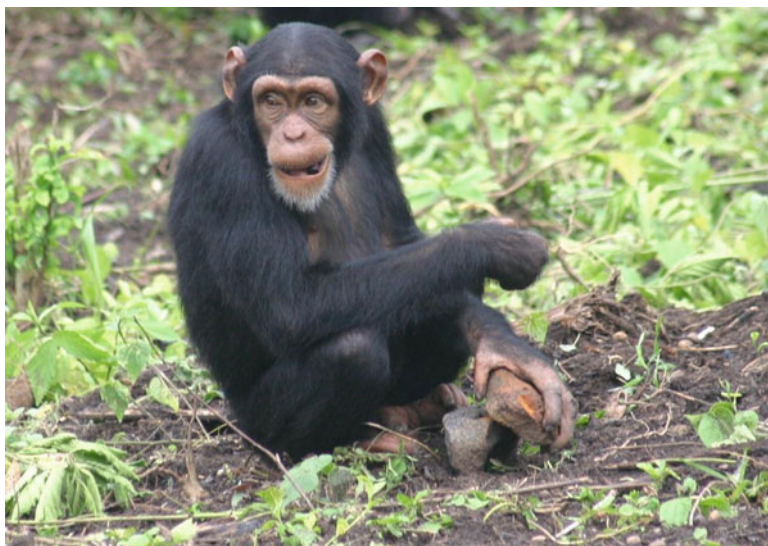


Fig. 14.1 A chimpanzee uses stone tools to crack open nuts at Bossou, Guinea. Photo courtesy Tatyana Humle

from her 43 of the 47 nuts he opened” (Boesch 1991). Furthermore, a full 75% (205/272) of the instances of hammer facilitation were performed by a single mother, while almost 45% (144/316) of the instances of nut facilitation were performed by another, suggesting that such actions were not routine among mothers. Finally, Boesch (1991) described in great detail two instances of what appear to be a mother actively teaching her offspring to nut-crack. In one case, a mother interrupted an offspring’s clumsy attempts and repositioned a nut in a more appropriate position on the anvil stone. In another case, a mother approached an offspring that was struggling to open a nut due to an improper grip on the hammer in relation to the anvil. The mother took the tool and slowly rotated it into a better position, cracked open several nuts, then returned the tool to her offspring. Her offspring subsequently adopted her mother’s grip and successfully opened nuts. These types of adjustments by the experienced individual are akin to “scaffolding,” which is used in the child development literature to denote instruction that successively increments the complexity of the task until the learner is capable of the full form of the task (e.g., Young 1993).

Inoue-Nakamura and Matsuzawa (1997) conducted a field experiment with the wild chimpanzees at Bossou, Guinea, to directly examine the ontogeny of nut-cracking skills. Stones and nuts were provisioned in a natural clearing where the chimpanzees gathered, which allowed for close and detailed observation of the frequency and type of interactions with nuts, stones, and other chimpanzees. Over four consecutive years, observers gathered 4,674 min of observation on three youngsters and charted the ontogeny of the skill. As at Tai, the mother was the primary source for information about the skill. If infants were in physical contact with other chimpanzees during nut-cracking, it was predominantly their mothers: 100% at the age of 0.5 years, 98% at the age of 1.5 years, 88% at the age of 2.5 years, and 90% at the age of 3.5 years. In addition,



Fig. 14.2 A young chimpanzee interacts with his mother while she fishes for termites at Gombe National Park, Tanzania. Photo courtesy Joshua Leonard

mothers were the primary targets of observation by their offspring, but this observational focus declined with age as the young started to observe other models. The percent of total time that youngsters' observations focused on their mother was 100%, 71%, 42%, and 14% for the 0.5-, 1.5-, 2.5-, and 3.5-year age groups, respectively (Inoue-Nakamura and Matsuzawa 1997). The other individuals observed included, in order of frequency, other adult females, siblings, other adolescents, and adult males. However, in contrast to Boesch's observations described above, researchers at Bossou did not observe a single instance of active facilitation over the course of the study. The role of the mother was "characterized by the lack of any feedback to infant chimpanzees' attempts at nut-cracking behaviors" (Inoue-Nakamura and Matsuzawa 1997). Biro et al. (2003) expanded on this and explained that during infancy, mother's showed high levels of tolerance to infant explorations, allowing them to take nuts and interact with her stones, but did not provide social feedback or change her behavior due to the presence of the infant.

14.2.2 *Termite-Fishing*

The chimpanzees of Gombe National Park, Tanzania, display an extractive tool-assisted foraging behavior known as termite-fishing (see Fig. 14.2). This behavior requires fashioning an appropriate tool out of the surrounding vegetation, inserting the tool into a mound built by termites, and extracting the termites that attack and

Table 14.1 Age (in years) by which critical elements of termite-fishing are acquired by all young chimpanzees and range of earliest and latest appearance of the behavior

Behavior	Age by which all have acquired the behavior	Range of earliest and latest appearance of the behavior
Identify hole	1.5	0.5–1.5
Manipulate tool	1.5	1.5
Make tool	3.5	1.5–3.5
Insert tool into hole	4.5	2.5–4.5
Extract termites	5.5	2.5–5.5

cling to the tool (Goodall 1964). Goodall (1986) presented anecdotal reports of individual differences in termite-fishing competency and rate of performing the behavior among the adult chimpanzees of Gombe National Park. Lonsdorf (Lonsdorf et al. 2004; Lonsdorf 2005, 2006) performed a four-year field study on 5 mothers and 14 offspring in order to determine whether and how maternal characteristics affected the speed of acquisition and eventual proficiency of their offspring. The maternal characteristics examined included the following: (1) mother's proficiency, as measured by termites gathered per tool insertion; (2) mother's time spent fishing, which can be viewed as the primary learning opportunity for a young chimpanzee; (3) mother's sociality, which represents the opportunity that offspring have to observe and learn from other individuals; and (4) mother's social interactions with offspring at the termite mound.

Offspring speed of acquisition of termite-fishing was measured in terms of the number of critical elements (CE) of the task acquired by a certain age category (see Table 14.1). For termite-fishing, the critical elements were (1) identify hole on the mound, (2) make tool, (3) manipulate tool, (4) insert tool into hole, and (5) extract termites. All chimpanzees studied were able to successfully complete these five elements and acquire termites between 5 and 6 years of age. Lonsdorf (2006) investigated the effects of mother's characteristics separately for each year prior to and coinciding with the year in which her offspring were assessed for acquisition to understand the influence of previous and current learning opportunities. Mother's social group size at the termite mound was divided into the following categories: (1) "alone"—with dependent offspring only, (2) "family"—with members of her maternal family, e.g., dependent and nondependent offspring, (3) "small group"—with fewer than three other maternally unrelated adult individuals, and (4) "large group"—with three or more other unrelated adults. No maternal characteristics were found to be significant predictors for the numbers of critical elements acquired for age category 1–2 years. However, by age category 2–3 years, maternal characteristics proved to be very important. The strongest positive correlates of the number of critical elements acquired were (1) mother's time spent fishing in a small group at age 1.5 and (2) mother's time spent fishing alone in the coinciding year (age 2.5). For age 3–4 years, the strongest correlates were (1) mother's overall time spent alone or with family at age 2.5 and (2) mother's overall time spent alone or with family in the coinciding year (age 3.5). By age 4.5, most offspring had acquired the critical elements, so maternal characteristics were no longer significant by this age.

The significant correlates for number of critical elements acquired by age 2.5 seem inconsistent: mother's time spent fishing in a small group at age 1.5 and mother's time spent fishing alone at age 2.5. So, in order to acquire the critical elements of the skill in the timely manner, is it better to have a mother who fishes in a small group or a mother who fishes alone? One possible explanation is that, at age 1.5, young chimpanzees at a termite mound spent more time watching others termite-fish than performing any other behavior (Lonsdorf 2005). By age 2.5, these infants had outgrown simply watching and now spent more time performing active elements like investigating the mound and manipulating tools. Perhaps having other individuals present to observe in the primary "watching" age (1.5) is beneficial, but once offspring spend more time actually performing elements of the skill (age 2.5), the presence of other individuals creates competition for tools or termite holes and reduces opportunities for learning.

Lonsdorf (2006) found no direct correlation between any of the abovementioned maternal characteristics and offspring proficiency (termites/dip). Instead, the key predictors of offspring proficiency were offspring age and sex, with older individuals and females being the most proficient (Lonsdorf 2005). However, since the offspring being measured were not yet adults, it is quite possible that if these individuals were resampled as adults, a stronger correlation would be found. Such comparisons between mother and offspring skills level at adulthood have not yet been conducted for wild chimpanzees.

To more fully understand the role of the mother in termite-fishing development, and whether maternal behavior may favor female offspring, Lonsdorf (2006) also directly analyzed the social interactions observed at the termite mound during fishing sessions. Offspring exhibited a number of behaviors that were scored when interacting with another at the termite mound, which in turn elicited maternal responses (Table 14.2). Offspring behaviors were further categorized as "passive," such as "watching," or "active," which included all other behaviors that involved directly interacting with another individual or with their materials. The behavior of the recipient was then categorized as "neutral," e.g., allowing the offspring to watch, or "negative," e.g., shoving a watching offspring away. The vast majority of interactions (92%) occurred within the maternal family, with mothers, siblings, or adult maternal relatives. Across all individuals at each age, offspring interacted with their mothers in 67% of all social interactions, and mothers were overwhelmingly tolerant of their offspring. Almost all offsprings' actions (whether active or passive) were tolerated by their mothers, and importantly, mothers tolerated male and female offspring equally. For sons, mothers responded neutrally to 85% of active actions and 99% of passive actions. For daughters, mothers responded neutrally to 86% of active actions and 99% of passive actions.

As with the results from nut-cracking at Bossou described above, Lonsdorf (2006) never observed instances of a mother actively facilitating her offspring's learning. Mothers were oriented completely to the task of termite-fishing and rarely even made eye contact with their offspring. A mother never offered a termite to her offspring, never handed her offspring a tool, and never molded the offspring's behavior while fishing. Chimpanzee offspring were simply allowed to observe and occasionally "steal" a tool or a termite, sometimes resulting in a negative reaction from their mothers. Alternatively, offspring would go to a hole immediately after

Table 14.2 Infant behaviors and mother responses during termite-fishing

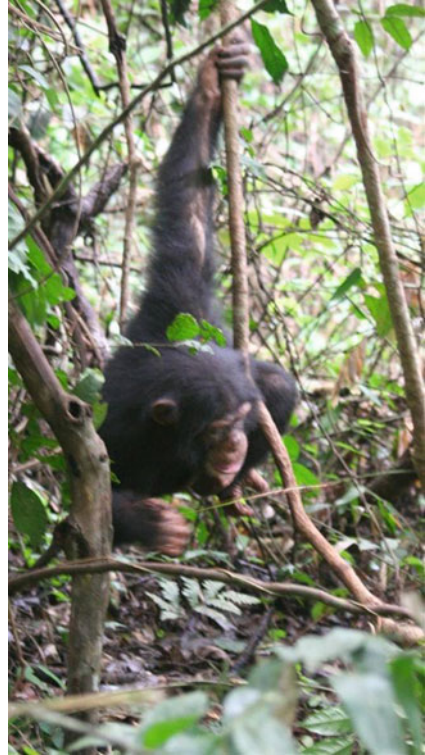
Offspring behaviour	Category	Description
Watch	Passive	Watch another termite-fish (face oriented to demonstrator for >3 s)
Reach	Active	Reach to another's hand, mouth, or tool while the other is termite-fishing. Individual may touch the tool, but does not take possession of it
Steal	Active	Steal another's tool out of their hand. Individual takes possession of the tool
Mound-inv-oth	Active	Investigate mound where another is working, includes sniffing, poking, and looking directly into a hole
Both-oth	Active	Manipulate tool at same mound hole where another is fishing
Term-int-oth	Active	Interacting with another's termites by taking with either hands or mouth
Mother response	Category	Description
Allow	Neutral	Allow whatever the offspring is doing
Shove	Negative	Push focal away
Move	Negative	Move self away from focal
Avoid	Negative	Avoid behavior of focal by changing body position

their mother's departure from the area and use her discarded tools. Similar to the reports of nut-cracking at Bossou, the role of the mother in the development of termite-fishing at Gombe is very passive.

A more recent study of termite-fishing in chimpanzees has been underway in the Goulougo Triangle, in the Nouabale-Ndoki National Park of Republic of Congo. Here, the tool behavior displayed by chimpanzees to extract termites is more complicated than at Gombe, in that it requires the use of multiple tools or a "tool-set" (Sanz and Morgan 2010). For subterranean mounds, chimpanzees first use a stout puncturing tool to open an access hole into the termite nest, then a slender fishing probe to extract the termites. For aboveground termite mounds, a perforating twig is used to gain access to a fishing hole, and then the slender probe is again used to fish for termites (Sanz et al. 2004). Visits to termite-fishing sites have been recorded by direct observation and remote video recording since 1999. As at Gombe, mothers with dependent offspring were the most common group to visit a termite mound (37% of visits, $n=388$ termite-fishing sessions), followed by lone individuals (32%); larger, mixed-sex groups were more rare (12%). Similar to the other abovementioned studies, youngsters were permitted to observe from a close distance (Sanz and Morgan *in press*). Sanz and Morgan (*in press*) also tallied the number of times tools were transferred between individuals, which happened 33 times out of 388 termite-fishing sessions. Comparable data do not yet exist for other sites. These transfers were usually, but not always, in response to begging by the offspring, and mothers were more likely to share tools with infants and juveniles rather than adolescents.

Future detailed comparisons of termite-fishing behavior between the two sites will be important to distinguish whether there are fundamental differences in the social interactions surrounding termite-fishing at Gombe and Goulougo. Of specific interest is whether the increased complexity of the tool-set at Goulougo results in

Fig. 14.3 A chimpanzee ant-dipping at Bossou, Guinea. Photo courtesy Tatyana Humle



more maternal facilitation when compared to Gombe. Such comparative studies at multiple sites would help to elucidate any potential differences and the range of variation of the maternal role in tool-use skill development.

14.2.3 Ant-Dipping

Another recent addition to this body of work is a study of wild chimpanzee ant-dipping conducted at Bossou, Guinea, by Humle and colleagues (2009). Bossou chimpanzees use tools to forage on five different species of *Dorylus* ants (otherwise known as army ants) which form conspicuous nests and trails on the forest floor. Ant-dipping requires manufacture of a tool from the surrounding vegetation. The chimpanzee then holds the tool between the index and the middle finger, inserts it into the nest or lays it across the trail, and rocks it back and forth to disturb the ants. The ants then attack by swarming up the tool and are subsequently ingested by the chimpanzee via either direct mouthing off of the tool or a sweeping motion of the hand into the mouth (see Fig. 14.3). Ant-dipping is quite similar to termite-fishing (described above); however, ant-dipping is considered much more dangerous. The swarm of army ants

can run right up the tool and onto the chimpanzee to inflict painful bites, while termites cling to the tool with their mandibles and can be eaten one by one with a minimal risk of injury. At Bossou, chimpanzees dip at ant nests, where offspring are at a higher risk for ant bites, and at ant trails, which are lower risk.

Over a 9 year period from 1997 to 2006, ant-dipping observations were collected on 13 offspring (10 years or younger) and 7 mothers (Humle et al. 2009). Here again, the mother was the key source of information for infants (5 years or younger), who only ant-dipped when their mothers did. Older offspring who had been weaned (>5 years old) ant-dipped in 62% of the same sessions as their mothers. Similar to termite-fishing, mothers with young offspring (≤ 5 years) ant-dipped more frequently alone with their dependent offspring, while mothers with offspring ages 6–10 more often had larger group sizes. Finally, infants watched mothers preferentially (mean = 92% of time spent observing individuals), while weaned youngsters did not (mean = 35%).

For termite-fishing (see above), maternal differences in time spent fishing were less significant for predicting offspring acquisition than was sex of the offspring. However, for ant-dipping, maternal differences were significant: offspring of more frequent dippers acquired the skill faster and were more proficient. No sex difference was found in this case (Humle et al. 2009). Intriguingly, chimpanzee mothers with young offspring (5 years old or younger) ant-dipped significantly more at trails than at nests, which provided a less risky learning situation for both mothers and offspring. Mothers may have preferred dipping at trails rather than nests while carrying a clinging infant simply because it was easier—the difficulties of managing a long tool, aggressive ants, and an active baby cannot be overlooked. However, whether intentional or not, this preference for dipping at trails also facilitates offspring learning by providing them with a safer environment in which to explore and learn this behavior.

14.3 Discussion

The field studies presented above provide strong evidence that social learning plays a role in the development of tool-assisted foraging skills in wild chimpanzees and that the mother is the primary model for observation in all tasks studied. What is less easy to distinguish in observational studies is which precise social learning mechanisms are at work on the part of the “learner” (but see Lonsdorf et al. 2004), and thus many social learning experiments are conducted in more controlled captive settings (e.g., Hirata and Celli 2003; Whiten 2010). Lonsdorf (2005) attempted to address the social learning processes likely involved in termite-fishing following the broad categorization outlined by Whiten and Ham (1992) and described above. *Stimulus enhancement* describes the process by which young chimpanzee offspring learn from their mother that the termite mound is the object to which attention should be directed. Once the mother starts to termite-fish, offspring learn that the goal of the behavior is to capture termites (*goal emulation*).

Due to technique matching between mothers and female offspring (but not male offspring), Lonsdorf (2005) proposed that female offspring also learn something about the form of the behavior (*imitation*), while male offspring develop their own method of achieving this goal. For both sexes, individual trial-and-error learning follows, as the offspring learns how to withdraw the tool without dislodging the prey. This part of the behavior must be learned individually, as it takes place inside the termite mound and cannot be seen.

In this chapter, I have attempted to describe what is known about the other side of the learning equation, that is, to understand the role of the chimpanzee mother as a “teacher.” Since Boesch’s (1991) landmark observation of active teaching during the course of nut-cracking in the wild chimpanzees of the Tai Forest, several other studies have now conducted detailed observations of the maternal role in the development of offspring tool-use skills. Boesch found evidence for all of Caro and Hauser’s (1992) criteria of teaching in animals. Mothers left hammers at an anvil stone more often when offspring were present, suggesting maternal recognition of her offspring’s lack of skill and adjustment of her behavior. Mothers allowed infants to take stones and nuts, which is an immediate cost to them. Finally, on two occasions two different mothers were seen to directly mold and shape the behavior of their offspring, thereby improving their proficiency. In 1997, Inoue-Nakamura and Matsuzawa (1997) presented another detailed assessment of nut-cracking development, but did not observe any social feedback, behavioral shaping, or behavioral changes on the part of the mother. Matsuzawa and colleagues (Matsuzawa et al. 2001) characterized how youngsters learn these skills as “education by master-apprenticeship.” They described the process as follows: no active teaching occurs between master and apprentice, that is, there is no shaping or molding of apprentice behavior by the master. Instead, the apprentice acquires the skill through repeated observations of the master, and the master, in turn, exhibits high levels of tolerance for the close proximity of the apprentice. In the case of nut-cracking, this tolerance allows young chimpanzees to observe very closely, manipulate stones, and manipulate and consume nuts.

Similar to the case of nut-cracking, Lonsdorf (2006) also found no active instruction by mothers during termite-fishing sessions at Gombe National Park, Tanzania. Mothers were extremely tolerant to close observation and even to disruptive behaviors on the part of the offspring, such as the taking of tools or termites. Nevertheless, mothers did not actively mold or shape the youngsters’ behaviors, offer tools, or appear to intentionally adjust their behavior in a way that would facilitate offspring learning. It was not possible to test whether mothers behaved differently when in the presence of the naïve observer (i.e., her offspring) because mothers and an offspring were always present together. However, in a detailed investigation of tool transfers from mother to offspring, Sanz and Morgan (*in press*) found that mothers did transfer tools more often to infants and juveniles than adolescents, perhaps suggesting recognition on the part of the mother of the offspring’s knowledge state and a behavioral adjustment based on that recognition. Similarly, Humle et al. (2009) presented evidence that mothers more frequently chose safer situations in which to ant-dip when they were with young offspring, than when they were with older offspring.

However, it remains to be seen whether this is an active assessment on behalf of the mother to facilitate learning or whether it is simply the easiest situation for her. Regardless, it is intuitive that ant-dipping in a less risky environment facilitates offspring acquisition.

In a recent review, Byrne and Rapaport (2011) recommend a reevaluation of Caro and Hauser's (1992) definition and criteria for teaching for nonhuman animals. They argue that Caro and Hauser's approach of reducing the study of teaching in animals to function (which is what we can observe) rather than intention on the part of the teacher (which cannot be observed and can be quite difficult to rigorously demonstrate) risks simplifying the study of information transfer to a level which is no longer helpful to the understanding of the evolution of human teaching and cultures. Chimpanzees are an ideal species to study such issues given their genetic closeness to humans; wild chimpanzees are particularly relevant given their demonstrated behavioral variability that is often argued to represent the "roots" of human cultures. However, the evidence thus far suggests that intentional molding and shaping of a naïve individual's behavior to improve their skills is extremely rare across wild chimpanzee populations and tasks. Future comparisons with regards to maternal behavior across field sites with slightly different complexities in tasks, such as termite-fishing at Gombe and at Goulougo, may shed more light on this in the future. Similarly, a series of naturalistic studies that modified aspects of task complexity could examine whether complexity and maternal facilitation correlate. However, the logistical difficulties of gaining access to large numbers of young chimpanzees cannot be overlooked nor can the ethical concerns inherent in initiating field experiments that might alter natural behavior. As such, these experiments may be better suited for captive populations, where youngsters are also rare due to tightly controlled breeding programs.

In captive apes, instances of active teaching in animals have been observed in sign language-trained apes who have themselves been actively taught by humans (Fouts and Fouts 1989), suggesting that future captive experiments focusing on transmission of teaching itself may be fruitful. One could envision an extension of the traditional social learning approaches that investigate task transmission, in which one population has a "knowledgeable" individual that has had the task demonstrated, while the other does not (reviewed in Whiten and Mesoudi 2008). To investigate teaching transmission, one target animal could be actively molded (i.e., taught) by a human experimenter to complete the task, and in another, the task is simply demonstrated without active molding, shaping, or otherwise scaffolding. The behavior of the knowledgeable individual towards offspring and/or other group members could then be analyzed for differences in facilitation. Of course, safety concerns would have to be considered, so apes may not be the ideal candidate animal for such a study.

In summary, while there is no doubt that the chimpanzee mother is critical to her offspring's acquisition of complex skills, there remain intriguing differences in the magnitude of that role between humans and our closest living relative. Future comparative and experimental work will hopefully begin to narrow in on the conditions under which the maternal role is more or less important and whether mothers modify their behavior accordingly.

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Part V
The Expanding Social Network

Chapter 15

Reproductive Strategies and Infant Care in the Malagasy Primates

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Keywords Alloparental care • Malagasy primates • Lemurs • Infants • Investment • Meta-analysis

15.1 Introduction

The old African proverb, “It takes a village to raise a child,” may extend well beyond the collective effort attributed to human child rearing strategies. In fact, allomaternal care is taxonomically widespread, particularly among mammalian taxa (e.g., rodents: Gubernick and Alberts 1987; Solomon and Getz 1997; chiroptera: O’Farrell and Studier 1973; canids: Moehlman and Hofer 1997; cetaceans: Gero et al. 2009; and primates: Hrdy 1976; Chism 2000). Allomaternal care includes infant care provided by the father (paternal care, Fernandez-Duque et al. 2009) or by conspecifics other than the parents (alloparental care, Wilson 1975). While well represented by a

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diversity of taxa, allomaternal care is not common among mammals (e.g., 9–10% of taxa display paternal care; Kleiman and Malcolm 1981; Huck and Fernandez-Duque 2012). However, allomaternal care has been recently noted to occur at relatively high frequencies in the Order Primates, particularly among many haplorhine (e.g., monkey and ape) species (Tardif 1997; Chism 2000; Ross and MacLarnon 2000; Hrdy 2009). While studies have examined the causes and consequences of allomaternal care among haplorhines, to our knowledge, there has yet to be a comprehensive analysis of allomaternal care across the entire primate order (e.g., including the primates of Madagascar, hereafter referred to as lemurs). This is in large part because studies of lemur allomaternal care have lagged behind those of their primate cousins. The most recent attempt at a synthesis of primate allomaternal care found that it was a haplorhine-biased phenomenon, finding no evidence of lemurs participating in allomaternal care-related behaviors (Ross 2003), and thus precluding any analysis of allomaternal care within that taxon. However, recent increases in attention to and sampling effort of lemur care behaviors have revealed that allomaternal care is more common in lemurs than originally thought (Mitchell 1969; Klopfer 1974; Pereira et al. 1987; Wright 1990; Patel 2007; Hrdy 2010; Rowe and Myers 2011; Tecot and Hrdy, unpublished data). Moreover, a number of studies in recent years have added to our understanding of this postnatal care strategy in lemurs, making it possible to include these species in broader taxonomic comparisons of primate reproductive strategies. In light of these recent discoveries, we aim to (1) describe the different types of allomaternal care observed in primates, including a discussion of how each type of care is expressed in monkeys and apes, and a summary of what is currently known for lemurs; (2) discuss the benefits of allomaternal caretaking and whether such behaviors benefit lemur mothers; and (3) outline important gaps in our knowledge of lemur allomaternal care, suggesting future avenues of research.

15.2 Primate Allomaternal Care

Investment in infants can take many forms (Ross 2003). In most mammalian species, mothers are their infants' primary care-providers; however, in some taxa, maternal care is supplemented by allomaternal care (Hrdy 1976; see Lewis and Pusey 1997 for review). Within the Order Primates, this phenomenon is taxonomically widespread (Hrdy 2009), though the form and frequency of allomaternal care among taxa are highly variable (Chism 2000; Ross and MacLarnon 2000). The variation in primate caregiving behaviors by mothers and/or allomaternal caregivers can be organized into nine categories that represent unique combinations of nesting, parking, carrying orally, carrying on fur, and allomaternal caring (Ross 2003). The variation in primate allomaternal care itself can be organized into three major categories: infant transport (Goldizen 1987a; b), babysitting (Stanford 1992), and energy transfer (i.e., food provisioning, Feistner and Price 1991; allomaternal nursing, Packer et al. 1992; Williams et al. 1994; Perry 1995) (see "Glossary" for definitions).

15.2.1 *Infant Transport*

Carrying infants long distances while foraging is rare among eutherian mammals, yet quite common among primates (Ross 2001). While some primates park their infants, the vast majority carries their infants (orally or with the infant clinging to the fur) or uses a combination of parking and carrying (Ross 2001). Infant transport is energetically expensive and may put the carrier at a disadvantage, particularly when foraging and avoiding predators (Schradin and Anzenberger 2001). For example, when carrying infants, maternal yellow baboons (*Papio cynocephalus*) are estimated to expend 5% more energy in the first month of carrying (Altmann and Samuels 1992), and leaping abilities in common marmosets (*Callithrix jacchus*) are compromised (Schradin and Anzenberger 2001). While individuals reduce their travel time when carrying infants, potentially balancing the additional energy required to carry (Tardif 1997), such adjustments may reduce necessary foraging time (Goldizen 1987a). Species whose infants ride dorsally or ventrally have smaller home ranges, and they begin reproduction at older ages, resulting in lower reproductive rates (Ross 2001). Thus, help with infant transport can be of great energetic benefit to mothers, particularly in energetically difficult habitats.

While carrying is ubiquitous across the Primate Order, taxa vary quite dramatically in the timing and intensity of nonmaternal infant transport. In siamangs (*Symphylangus syndactylus*), for example, females are exclusive care-providers during the infant's first year of life. It is only during the second year that adult males and older juveniles contribute to infant carrying (Chivers 1974; Lappan 2008), which can vary dramatically between individuals and group types (i.e., monogamous versus polyandrous) (Lappan 2008). In contrast, both titi monkeys (*Callicebus*) and owl monkeys (*Aotus*) are characterized by extensive and obligate paternal carrying (Fernandez-Duque et al. 2009). Soon after birth, males assume the role of primary care-provider, carrying infants for up to 90% of their total time carried (Dixon and Fleming 1981; Fragaszy et al. 1982; Wright 1984). Of course, infant transport can also extend beyond parental care, as is the case in the small new world monkeys, marmosets and tamarins (callitrichines) (Goldizen 1987a; b). In this taxon, all group members, including the mother, father, siblings, and other nonrelatives, share in infant transport (Bales et al. 2000; Tardif et al. 2002; Zahed et al. 2007). In fact, group members often compete for the opportunity to carry dependent infants (Fernandez-Duque et al. 2009).

Alternatively, as briefly stated above, some primates park and/or nest their offspring while foraging nearby (Ross 2001). In many cases, parking behaviors are biased toward litter-bearing taxa such as the cheirogaleids and *Varecia*; however, there are some non-litter bearing exceptions (e.g., lorises; Nekaris and Bearder 2011). While this strategy may help to reduce the energetic constraints on mothers by freeing females to travel and forage more efficiently away from infants, it also comes with added costs, including increased infant vulnerability to predators while mothers are away (see van Schaik and Kappeler 1997). One means by which parking/nesting mothers may reduce these costs is via allomaternal babysitting, whereby individuals other than the mother guard crèched infants in their mothers' absence.

15.2.2 *Babysitting and Infant Guarding*

Babysitting has been described in a number of primate taxa, but is particularly prevalent in old world monkeys (i.e., cercopithecines and colobines; Stanford 1992; Chism 2000). The costs to babysitters have not been investigated extensively in primates. However, in the meerkat (*Suricata suricatta*), a non-primate mammal with a cooperative breeding system, young are parked in burrows during the first month of life (Carlson et al. 2006) and parents rarely stay with them; babysitters are critical to this system, and lose weight in proportion to time spent babysitting (Clutton-Brock et al. 1998), indicating that the cost to babysitters can be great. Babysitting may also carry risks for mothers, as kidnaping and infant mistreatment (also known as “aunting to death”; Hrdy 1976; Hrdy 1977; Quiatt 1979; Altmann 1980; Silk 1980; Maestripieri 1994) have been observed in primates. But babysitting can be considered adaptive for a number of reasons (e.g., practice mothering by immature females: Lancaster 1971; Hrdy 1976; Quiatt 1979; increased likelihood of adoption: McKenna 1981; improved infant socialization: Hrdy 1976; McKenna 1981). The most commonly cited advantage conferred to mothers is that allomaternal care allows mothers to reduce their own energetic investment while simultaneously allowing the opportunity to maximize foraging efficiency (Vogel 1984; see also Poirier 1970; Lancaster 1971; Jolly 1972). Although initially examined from the perspective of the female helpers, these “aunting” behaviors are also common among males. Adult male baboons will commonly babysit “friends” infants, and have been demonstrated to assist and protect infants during potential infanticidal attacks (Palombit et al. 1997; Smuts 1998).

15.2.3 *Energy Transfer*

The most extreme form of allomaternal care involves energy transfer, which includes allomaternal nursing (nonmaternal nursing of infant, Packer et al. 1992), a rare phenomenon among mammals (Packer et al. 1992), and food provisioning (Brown et al. 2004). For mothers, the energetic cost of infant transport is second only to lactation (Altmann and Samuels 1992), which far exceeds the costs of transport (Kirkwood and Underwood 1984; Tardif 1997) and can significantly increase female mortality rates (Packer et al. 1992). Thus, allomaternal nursing can be extremely costly to the caregiver if she nurses more than she would otherwise, and it can confer significant advantages to the mother whose energetic contribution may be lowered (König 2006). If allomaternal nursing is accompanied by babysitting, mothers may also benefit from increased time away from their infants, enabling them to spend more time foraging (facilitated by trading-off with other reproductive females, i.e., reciprocal allomaternal nursing). While reciprocal allomaternal nursing may not directly reduce the energetic burden to mothers or costs to helpers, reciprocal nursing may benefit all participating mothers by increasing foraging time relative to what they

might otherwise experience in the absence of allomaternal contributions. Several hypotheses for why this behavior occurs have been discussed by Eberle and Kappeler (2006), and range from misdirected care due to an inability to discriminate offspring, to brood parasitism whereby non-offspring steal milk, to kin selection where allomaternal caregivers nurse only related infants. Food provisioning, the other form of energy transfer, occurs when infants approach individuals with food, so on some level the infant determines whether and from whom they receive provisions (Brown et al. 2004). In callitrichines this caregiving activity is performed by all group members (Feistner and McGrew 1989; Feistner and Price 1991), and may be a means by which dependence upon milk is reduced at an earlier stage while enabling infants to maintain growth rates, and allowing females to enter into estrus quickly (Garber and Leigh 1997). This behavior may also be necessary due to the complexity of extractive foraging (Brown et al. 2004).

Although relatively rare, some form of energy transfer has been observed in a handful of taxa in the form of either allomaternal nursing (e.g., squirrel monkeys: Williams et al. 1994; capuchins: Fragaszy et al. 2004; Baldovino and Di Bitetti 2008) or food provisioning (e.g., callitrichines: Huck et al. 2004; owl monkeys: Wright 1984; Wolovich et al. 2007; titi monkeys: Wright 1984; 1990). Energy transfer appears to be phylogenetically biased (Jaeggi and van Schaik 2011). For example, food provisioning is absent in Old World monkeys and present in one tarsier species (spectral tarsier, Gursky 2000), five ape species, and 21 New World species (including 13 callitrichines) (Brown et al. 2004). To our knowledge, only callitrichine infants rely entirely upon provisioning prior to independent feeding, and energy transfer is regularly observed only in this subfamily (see Feistner and Price 1991; Bales et al. 2000).

15.3 Benefits of Allomaternal Care

Allomaternal care is usually assumed to be adaptive, in that it is thought to benefit some or all of the individuals involved (Emlen 1991; Ligon and Stacey 1991; Mumme 1997; Tardif 1997; see Ross and MacLarnon 2000 Table 1 for a list of adaptive and nonadaptive causes of allomaternal care). However, as noted above, allomaternal care can also confer serious costs. Infants may be kidnapped or injured due to mishandling (Hrdy 1976; Quiatt 1979), they may receive reduced opportunities to nurse, and mothers may suffer reduced time foraging if vigilance is required when other individuals (such as inexperienced caretakers) handle infants (Chism 2000). Allomaternal caregivers are either nonbreeding individuals with delayed natal dispersal or reproductive suppression who sacrifice reproduction to care for offspring that are not theirs, or reproductive individuals who expend energy on offspring other than their own (Solomon and French 1997). Thus, with so many potential costs, the benefits of allomaternal care must be great in order for it to persist.

Traditionally, the evolution of allomaternal care has been addressed from the perspective of the helper (reviews in Hrdy 1976; Emlen 1991; Tardif 1997), with

Table 15.1 Lemur maternal and allomaternal care behavior

Care category	Care behavior ^a	Scientific name
1	Carry on fur	<i>Avahi laniger</i> <i>Eulemur fulvus</i> and sister taxa <i>Indri indri</i> <i>Prolemur simus</i> <i>Propithecus edwardsi</i>
2 ^b	Carry on fur, park	<i>Hapalemur aureus</i>
3 ^b	Carry on fur, carry orally, park, allomaternal care	<i>Hapalemur griseus</i>
4	Carry on fur, allomaternal care	<i>Eulemur collaris</i> <i>Eulemur macaco (flavifrons)</i> <i>Eulemur mongoz</i> <i>Eulemur rubriventer</i> <i>Lemur catta</i> <i>Propithecus candidus</i> <i>Propithecus coquereli</i> <i>Propithecus diadema</i> <i>Propithecus tattersalli</i> <i>Propithecus verreauxi</i>
5	Carry orally, park	<i>Lepilemur ruficaudatus</i>
6 ^b	Carry orally, nest, allomaternal care	<i>Microcebus griseorufus</i> <i>Microcebus murinus</i>
7 ^b	Carry orally, park, nest, allomaternal care	<i>Cheirogaleus medius</i> <i>Varecia rubra</i> <i>Varecia variegata</i>

^aCharacteristics of infant contact behaviors following Ross (2003), with numerically adjusted care categories. “Carry on fur” (infant clinging) and “carry orally” (carrying in the mouth) describe how individuals transport infants; “nest” indicates that infants are parked in nests or other protected shelters, and “park” indicates that infants are parked on tree branches or in vegetation; “allomaternal care” indicates that individuals other than the mother carry, babysit, or feed infants (only this category indicates the presence of care from individuals other than the mother). See “Glossary” for more information

^bPreviously undescribed categories

studies ranging from the proximate or physiological factors that affect alloparental care (e.g., Ziegler 2000; Ziegler et al. 2000; Numen and Insel 2003; Tecot 2007), to the functional roles of social and environmental factors and constraints (e.g., habitat saturation: Emlen 1984; queuing for breeding opportunities: Kokko and Johnstone 1999), as well as the possible adaptive explanations for the evolution and maintenance of nonparental care (e.g., learning to mother: Lancaster 1971; Hrdy 1977). It is much less common that allomaternal care is addressed from the perspective of the mother and/or infants (Mitani and Watts 1997; but see Bales et al. 2000; Ross and MacLarnon 1995; 2000; Ross 2003), though the benefits obtained are potentially great. For example, mothers receiving extensive help have been shown to benefit by shorter interbirth intervals (Fairbanks 1990), larger litters or faster infant growth (Leutenegger 1980; Goldizen 1987a; Wright 1990), and improved feeding time

(Stanford 1992), all of which may translate into higher lifetime reproductive success (Lemon and Barth 1992; Russell et al. 2002). Comparative analyses of allomaternal care in haplorhine primates controlling for phylogeny and body size found similar results to single-species investigations, in that allomaternal care is correlated with increased growth rates and decreased interbirth intervals overall (Mitani and Watts 1997; Ross and MacLarnon 1995; 2000). Moreover, infants can benefit from improved predator protection, thermoregulation, and improved competition later in life (König 1997).

15.4 Malagasy Primate Reproductive Strategies

Lemurs are glaringly absent from reviews of primate allomaternal care. While it is possible that this is in part due to lower frequencies of allomaternal care behavior in the taxon, it is certainly due to there being comparatively fewer studies. Several studies have focused on the unique reproductive strategies of Malagasy primates (e.g., Jolly 1984; Young et al. 1990; Pereira 1991; Richard and Dewar 1991; Whitten and Brockman 2001) and how these strategies reflect adaptations to an energetically poor and unpredictable environment (see below in “Malagasy Primates: An Unusual Case?”). Surprisingly, however, most such studies have focused primarily on these species’ strict breeding seasonality, particularly its timing and duration, the effects of photoperiod, and the associated physiological changes. More recently, some researchers have investigated pre-mating strategies such as changes in food intake and weight gain prior to conception (e.g., Lewis and Kappeler 2005). While these studies have made large strides in understanding lemur reproductive energetics, we know very little about postnatal strategies beyond milk quality (Buss et al. 1976; Tilden and Oftedal 1995; Hinde and Milligan 2011) and growth rates (e.g., Pereira 1993; Ravosa et al. 1993; Kappeler 1996; Godfrey et al. 2004), such as investment in infant care (but see Ross 2003), and thus how these strategies influence infant development, survivorship, and ultimately reproductive success.

To fill this gap in our understanding, we summarize the current state of knowledge of infant care in Malagasy primates, with emphasis on evidence of allomaternal care, its distribution, and expression. We first describe the types of infant care strategies used by lemur mothers and others (following Ross 2003) and then focus on one of those strategies: allomaternal care. Of those species in which allomaternal care was present, we describe the type of allomaternal care observed. Although some authors report the presence of allomaternal care in species on the basis of infant socialization through grooming, holding, or play by caregivers (e.g., Gould 1992; Bastian and Brockman 2007; Patel 2007), here we define allomaternal care as nursing, carrying, or babysitting/guarding infants by non-mothers, as these behaviors are exclusively performed by mothers in the majority of taxa, and thus it is notable when others perform such potentially costly behaviors (see Mitani and Watts 1997). Because few studies have quantified allomaternal care in lemurs, we were unable to use Ross’s (2003) definition of allomaternal care (when an individual other than the mother

carries or protects the infant for more than 5% of the time). Based on published accounts or personal communications with researchers, we categorized care behaviors as present or absent (using similar methods to Mitani and Watts 1997), and only included taxa for which allomaternal care has been explicitly stated as being present or absent (with one exception, noted below). We used data on wild populations whenever possible, and supplemented these data with information from captive populations as indicated.

15.5 Infant Care in Malagasy Primates

Our review of the literature yielded data for 23 lemurs including taxa from four of the five lemur families (excluding Daubentoniidae). While our results include an additional eight taxa relative to those in Ross (2003), we could not confirm allomaternal care designations for two taxa included in her review (*Mirza*, *Cheirogaleus major*) in which allomaternal care was reportedly absent, a result that could be due to the fact that we did not consider allomaternal care absent unless it was explicitly noted as being absent in the literature or in personal communications (with the exception of one species, *Indri*, in which reports on maternal care were used to determine the absence of allomaternal care). We found that lemurs adopt seven combinations of infant caregiving behaviors, four of which include allomaternal care (Table 15.1). Three of these seven strategies were previously described by Ross (2003); four are described here for the first time (Table 15.1). Six additional strategies described by Ross (2003) were not present in lemurs, though one of those strategies was not assigned to any primate taxa in her review (“carry orally-carry on fur”), thus leaving five strategies present in haplorhine primates for which we found no evidence in lemurs. This result is in part due to new information included in our review. For example, four of the five strategies that we found to be absent in lemurs were reported by Ross (2003) to only occur in lemurs and other strepsirrhines. In her review, *Hapalemur griseus* was described as using a strategy of “carrying orally-carrying clinging to the fur-nesting-parking,” whereas we identified *H. griseus* as having a strategy of “carrying orally-carrying clinging to the fur-parking-allomaternal care.” One strategy reported to occur in the pygmy marmoset (*Cebuella pygmaea*) and humans (“carrying on fur-parking-allomaternal care”) was not found in any lemur species.

Our findings are *contra* Ross (2003), in which allomaternal care was described as being absent in all lemur species, and in which allomaternal care was only present in primates who carried their infants clinging to the fur. Based on our results, allomaternal care was present in 16 of 23 species for which we could find explicit reports of either its presence or absence, and behaviors fell within each of the three major allomaternal care categories (Table 15.2).

Table 15.2 Allomaternal care behaviors and evidence of mishandling and abuse by caregivers observed in each species in the analysis

Scientific name	Allomaternal care	Infant transport	Babysit	Nurse	Details	Frequency of allomaternal care behaviors	Care-associated mishandling observed (or possible)? ^a	References
<i>Avahi laniger</i>	-	-	-	-	Only maternal care observed	Absent	No data	Ganzhorn et al. (1985)
<i>Cheirogaleus medius</i>	+	-	+	-	Paternal babysitting. Begins immediately after birth. Considered necessary for infant survival	Regular	No	Fietz (1999), (2003), P. Lahann, personal communication
<i>Eulemur collaris</i>	+	+	-	+	Carrying and nursing by an infant's grandmother	Unknown	No	Kesch (2009)
<i>Eulemur fulvus</i> and sister taxa	-	-	-	-	Only maternal care observed	Absent	No (kidnaping by female, infanticide by adult group male)	Barthold et al. (2009), Jolly et al. (2000), S. Johnson personal communication
<i>Eulemur macaco (flavifrons)</i>	+	+	-	-	Infant carrying by adult males, juvenile males, and siblings beginning at 5 weeks. Observed in one of two birth seasons. Allomaternal carrying 5% of the time. 67% by adult males	Regular	No (infanticide by extra-troop males, troop females)	Andrews (1998), Volampeno et al. (2011)

(continued)

Table 15.2 (continued)

Scientific name	Allomaternal care	Infant transport	Babysit	Nurse	Details	Frequency of allomaternal care behaviors	Care-associated mishandling observed (or possible)? ^a	References
<i>Eulemur mongoz</i>	+	+	-	-	Infant carrying by father. Between weeks 2-5 on several occasions	Occasional- Regular	Unknown (infant wound, unknown source)	Curtis and Zaramody (1998), (1999)
<i>Eulemur rubriventer</i>	+	+	-	-	Infant carrying by father and siblings but not in all groups. Allomaternal carrying frequent with twins. Elevated cortisol levels in fathers and siblings follow mid-gestation maternal elevations	Occasional- Regular	No	Overdorff (1991), Overdorff and Tecot (2006), Tecot (2007), (2008), unpublished data
<i>Haplemur aureus</i>	-	-	-	-	Only maternal care observed	Absent	No data	Tan (2000)
<i>Haplemur griseus</i>	+	+	-	-	Infant carrying by fathers and siblings after 3 weeks in captivity. Fathers carried 20%, siblings 5%. Passive paternal food sharing and predation defense	Occasional	No	Wright (1990), Grassi (2001), Grassi, personal communication

<i>Indri indri</i>	-	-	-	-	Only maternal care observed	No data (designation based on reports of maternal care but no reports of allomaternal care)	No data	Pollock (1975)
<i>Lemur catta</i>	+	+	-	+	Infant carrying by other mothers and male and female juveniles. Nursing from females who lost own infants and mothers with infants. Reciprocal nursing between allomothers at 4-6 weeks. Adoption of dependent young after mother's death	Regular	Yes ("mothers often...kidnap infants" (Sussman 1977); infant wounding and killing by immigrant males, dominant females (during attack on mother), extra-troop individuals, and troop adult males)	Sussman (1977), Gould (1992), (2011), Jolly et al. (2000), A. Jolly, personal communication, T. O'Mara, personal communication, S.Meredith, personal communication, Merti-Millhollen, personal communication
<i>Lepilemur ruficaudatus</i>	-	-	-	-	Only maternal care observed	Absent	No data	Hilgartner et al. (2008)
<i>Microcebus griseorufus</i>	+	-	?	+	Allomaternal nursing inferred	Unknown	No	Génin (2008)

(continued)

Table 15.2 (continued)

Scientific name	Allomaternal care	Infant transport	Babysit	Nurse	Details	Frequency of allomaternal care behaviors	Care-associated mishandling observed (or possible)? ^a	References
<i>Microcebus murinus</i>	+	+	+	+	Allomaternal nursing common among relatives. Adoption of related, dependent young after mother's death. Group nesting. Babysitting observed in Ampijoroa. Related females carry in captivity	Occasional- Regular	No	Martin (1972), Eberle and Kappeler (2006), E. Zimmerman, personal communication
<i>Prolenur simus</i>	-	-	-	-	Only maternal care observed	Absent	No data.	Tan (2000)
<i>Propithecus candidus</i>	+	-	-	+	Infant carrying by nursing allo-mother at 6 weeks and by adult male. Allomaternal nursing observed during months 4 and 5. Infant carrying by juvenile males	Occasional	Yes (2-year-old male took infant from male babysitter, returned without infant)	Patel (2007), personal communication
<i>Propithecus coquereli</i>	+	-	-	-		Unknown	No (transfers between juveniles and infants rough: pulling, jerking, squirming, crying)	Bastian and Brockman (2007)

<i>Propithecus diadema</i>	-	-	-	-	Infant carrying by a nonmaternal dominant female	Rare	No data	Grieser (1992)
<i>Propithecus edwardsi</i>	-	-	-	-	Only maternal care observed	No data (based on ~24 years of consistent research)	No (infanticide by immigrant males)	Wright (1995), personal communication, Erhart and Overdorff (1998)
<i>Propithecus tattersalli</i>	+	+	-	-	Infant carrying by nonmaternal females. In one group occurred for "very large amounts of time." However, "in most groups infant care was completely handled by the mother."	Rare	No (one several-month-old infant left briefly with main male who "practically sat on the infant" (Meyers 1993). Infant emitted distress calls)	Meyers (1993)
<i>Propithecus verreauxi</i>	+	-	+	-	Infant carrying (2% of time)	Rare	No (kidnaping observed, H Rasamimanana, RJ Lewis, personal communication)	H. Rasamimanana, personal communication, R.J. Lewis, personal communication

(continued)

Table 15.2 (continued)

Scientific name	Allomaternal care	Infant transport	Babysit	Nurse	Details	Frequency of allomaternal care behaviors	Care-associated mishandling observed (or possible)? ^a	References
<i>Varecia nubra</i>	+	-	+	+	Infant carrying by non-maternal females ($n \geq 1$). Infant guarding by adult males and females. All males in study ($n = 3$) guarded infants. Allomaternal nursing observed ($n = 2$). Inferred adoption by an adult female. All reproductive males observed	Regular	No	Vasey (2007)
<i>Varecia variegata</i>	+	-	+	+	Allomaternal nursing inferred. Infant guarding by adults of both sexes and a male sibling. Group nesting ("kindergartens")	Regular	No	Morland (1990); White et al. (1992); Baden 2011; Baden et al. 2011; Baden et al. in revision; Balko, unpublished data

^aRefers to any mention of mishandling within the context of allomaternal care, found in allomaternal care references. Other instances of mishandling outside of the allomaternal care context are noted parenthetically

15.5.1 Infant Transport

The ancestral primate pattern of infant care during travel is proposed to be non-riding (i.e., oral transport or parking of infants) (Kappeler 1998; Ross 2001). Transport by extant Malagasy primates takes two forms: the “ancestral” pattern, whereby infants are carried orally, and the “derived” pattern with the infant clinging to the fur. Ross (2001) proposed that transport of clinging infants evolved at least four times in the lemurs and their close relatives (e.g., galagos, lorises, and tarsiers). The transport of clinging infants occurs in the Lemnidae and Indridae; infant parking and/or oral carrying occurs in *Phaner*, *Varecia*, *Daubentonia*, *Lepilemur*, and the Cheirogaleidae (e.g., *Microcebus* and *Cheirogaleus*; references within Ross 2001; Schülke 2005); and parking during the first 2–4 weeks, followed by carrying orally, and then carrying by clinging occurs in *Hapalemur* (Wright 1990; Tan 2000; C. Grassi, personal communication). In all cases, allomaternal carrying occurs.

Similar to *Callicebus* and *Aotus* (Dixon and Fleming 1981; Fragaszy et al. 1982; Wright 1984), frequent carrying by adult male and/or juvenile helpers has been reported in *Hapalemur griseus* in captivity (Wright 1990) and several *Eulemur* species in the wild or captivity (Curtis and Zaramody 1999; Tecot 2008; Duke Lemur Center Records), particularly when twins are present (Tecot, personal observation). *E. mongoz* adult males frequently carry pair-mates’ infants before infants begin exploring independently, between their second and fifth weeks of life (Curtis and Zaramody 1999). *E. rubriventer* pair-mates carry infants any time after four days of life in captivity, and 20 days in the wild, and males and females do not differ in the amount of time spent caring for infants until day 55, when the infant either travels independently or is carried exclusively by the male (Overdorff 1991). While juvenile *E. rubriventer* carry infants as well (Tecot 2008), detailed data are lacking. Overdorff (1991) suggested that faster infant development in *E. rubriventer* compared with *E. rufifrons* (a species belonging to the brown lemur species complex) could be related to allomaternal care, as no allomaternal care has been observed in *E. rufifrons* (Overdorff 1996a).

While *Hapalemur* and *Eulemur* species with extensive allomaternal carrying tend to live in small, pair-bonded groups (e.g., Curtis and Zaramody 1999; Grassi 2001; Overdorff and Tecot 2006), males of non-pair-bonded species have also been reported to carry (and hold, groom, and play with) infants on occasion. *Propithecus coquereli* juvenile males (Bastian and Brockman 2007) and fathers (Grieser 1992) carried infants in captivity, and a juvenile male *Lemur catta* (Gould 1992), a male *P. candidus* (Patel 2007), and resident dominant male *P. verreauxi* (see Bastian and Brockman 2007) were observed briefly carrying infants in the wild. Non-maternal adult females have been observed carrying infants as well, although this behavior occurs only occasionally in the wild (*E. coronatus*: Kesch 2009; *Lemur catta*: Gould 1992; *P. diadema*: Grieser 1992; *P. tattersalli*: Meyers 1993; *P. candidus*: Patel 2007; *Varecia rubra*: Vasey 2007). In *L. catta*, infants may initiate such behavior, though it may be unwelcome by the designated carrier, as indicated by the carrier’s acrobatics and nips seemingly meant to remove the infant from its back (T. O’Mara, personal

communication). Such occasional infant transport by caregivers may not be important in terms of an evolved reproductive strategy to increase maternal reproductive success or inclusive fitness in these species, though it may be employed when environmental or social circumstances require. The benefits of allomaternal carrying have not been investigated in any of these species.

15.5.2 *Babysitting and Infant Guarding*

Babysitting and infant guarding are primarily found in nesting species that park their infants, particularly in *Varecia* (Morland 1990; Vasey 2007; Baden 2011; Baden et al. 2011; Baden et al. [in revision](#)) and some cheirogaleids (*Cheirogaleus medius*: Fietz 1999; *Microcebus murinus*: Eberle and Kappeler 2006; E. Zimmerman, personal communication), but perhaps also in some non-nesting *Propithecus* species (e.g., *P. coquereli*: Grieser 1992; Bastian and Brockman 2007) and *Lemur catta* (L. Gould, personal communication). As nesting species tend to have relatively large litters of rapidly growing, altricial (nonclinging) offspring (e.g., Table 15.3; Kappeler 1998; but see Ross 2001), mothers are required to leave their offspring at the nest, with or without babysitters, because they cannot transport the entire litter at once. Babysitting can therefore reduce the risk of infant mortality by such events as predation and accidental falls, and in the exceptional case of *Varecia*, perhaps infanticide (see van Schaik and Kappeler 1997). Babysitting may also reduce energetic stress on mothers spending time protecting vulnerable infants from predation or other mortality risks. For example, pair-living fat-tailed dwarf lemurs (*Cheirogaleus medius*) rely on fat stores for seasonal hibernation. Fietz and Dausmann (2003) found that reproductive females had lower fat stores and body condition than nonreproductive females, which is not unexpected after reproduction. However, there was also a trend for males who shared babysitting duties to have lower fat stores and body condition than nonreproductive males, suggesting that this care behavior is costly, but that it also benefits the mother by reducing the energetic burden that would otherwise be solely her responsibility (Fietz and Dausmann 2003). Another recent study found that such energetic benefits to mothers could result in higher infant survival. Maternal ruffed lemurs (*Varecia variegata*) suffered a significant reduction in feeding time following the birth of offspring (Baden 2011; Baden et al. 2011; Baden et al. [in revision](#)), a burden that was later mitigated by the onset of co-nesting and babysitting. Following the onset of communal nesting, an infant care strategy involving crèches of multiple litters parked together into a single nest, communal nesters fed significantly more and experienced higher infant survival than did singly nesting females (Baden 2011; Baden et al. 2011; Baden et al. [in revision](#)). In both *C. medius* and *Varecia* species, males, nonreproductive females, and other mothers took turns at babysitting their offspring (Morland 1990; Fietz 1999; Vasey 2007; Baden 2009; Baden 2011; Baden et al. 2011; Baden et al. [in revision](#)). In both taxa, females without allomaternal care were significantly less successful at raising their young.

Table 15.3 Lemur diet, interbirth interval (IBI), litter size, fetal growth rate, and postnatal growth rate

Scientific name	Common name	Diet ^a	IBI (mos)	Litter size	Fetal		Mean group size ^f	Mean home range size (ha) ^f	References
					growth rate	Postnatal growth rate			
<i>Avahi laniger</i>	Eastern Woolly Lemur	Foliv	12	1	0.187	3.16	Adult pair and offspring	1–2	Tattersall (1982) ^{c,e} , Godfrey et al. (2009) ^{d,e} , Jones et al. (2009) ^{b,c} , Catlett et al. (2010) ^e , Mittermeier et al. (2010) ^{c,e}
<i>Cheirogaleus medius</i>	Fat-tailed dwarf lemur	Omni	18	2.5	0.594	3.75	Adult pair and offspring	4	Tattersall (1982) ^c , Kappeler (1996) ^d , Fietz (1999) ^c , (2003) ^{b,c} , Lindenfors (2002) ^d , Jones et al. (2009) ^{b,c}
<i>Eulemur collaris</i>	Collared brown lemur	Frug	12	1.1	0.688	–	3–7	–	Rasmussen (1985) ^c , Mittermeier et al. (2010) ^b , Donati, personal communication ^b , Duke Lemur Center Records ^d
<i>E. fulvus</i> and sister taxa	Brown lemur species complex	Frug	15	1.1	0.708	9.45	Range 6–12	Range 1–>20, up to 100 seasonally (Ranomafana Nat'l. Park)	Boskoff (1978) ^{c,e} , Tattersall (1982) ^{c,e} , Harvey and Clutton-Brock (1985) ^e , Rasmussen (1985) ^{c,e} , Duke Lemur Center Records in Wright (1990) ^e , Kappeler (1996) ^d , Overdorff et al. (1999) ^b , Lindenfors (2002) ^d , Kappeler and Pereira (2003) ^e , Godfrey et al. (2004) ^e , Brockman and van Schaik (2005) ^e , Jones et al. (2009) ^{b,c}

(continued)

Table 15.3 (continued)

Scientific name	Common name	Diet ^a	IBI (mos)	Litter size	Fetal growth rate	Postnatal growth rate	Mean group size ^f	Mean home range size (ha) ^f	References
<i>E. macaco (flavifrons)</i>	Black lemur	Frug	12	1	0.588	6.76	10 (range 5–14)	3.5–7	Harrington (1978) ^e , Tattersall (1982) ^{g,e} , Harvey and Clutton-Brock (1985) ^e , Harvey et al. (1987) ^e , Kappeler (1996) ^d , Godfrey et al. (2004) ^e , Lindenfors (2002) ^d , Kappeler and Pereira (2003) ^e , Jones et al. (2009) ^{h,e} , Catlett et al. (2010) ^e , Mittermeier et al. (2010) ^{g,e} , Volampeno et al. (2011) ^{h,e}
<i>E. mongoz</i>	Mongoose lemur	Frug	12	1	0.399	4.19	Range 3–8	2.8	Tattersall (1982) ^{g,e} , Duke Lemur Center Records in Wright (1990) ^e , Kappeler 1996 ^d , Curtis (1997) ^{h,e} , Curtis and Zaramody (1999) ^{g,e} , Lindenfors (2002) ^d , Ross (2003) ^e , Godfrey et al. (2004) ^e , Jones et al. (2009) ^e
<i>E. rubriventer</i>	Red-bellied lemur	Frug	15	1.5	1.086	6.84	Adult pair and offspring	19	Kappeler (1996) ^d , Tecot and Overdorff (2005) ^e , Tecot (2010) ^{h,e}

<i>Hapalemur aureus</i>	Golden bamboo lemur	Foliv	12	1	–	–	Range 2–6	26–80	Tan (2000) ^{c,e} , (2006) ^b
<i>H. griseus</i>	Gentle bamboo lemur	Foliv	13	1.5	0.504	4.372	Range 1–9	0.6–26	Tattersall (1982) ^{c,e} , Harvey and Clutton-Brock (1985) ^f , Duke Lemur Center Records in Wright (1990) ^e , Kappeler (1996) ^d , Tan (2000) ^{f,c,e} , Lindenfors (2002) ^d , Kappeler and Pereira (2003) ^e , Ross (2003) ^e , Godfrey et al. (2004) ^e , Jones et al. (2009) ^{b,c} , Grassi, unpublished data ^e
<i>Indri indri</i>	Indri	Foliv	30	1	0.875	–	Adult pair and offspring	34–40	Pollock (1977) ^{b,c} , Powzyk (1997) ^e , Lindenfors (2002) ^d
<i>Lemur catta</i>	Ring-tailed lemur	Frug	15	1	0.616	8.235	11.5 and 16 (at two sites), range 3–27	6–35	Jolly (1966) ^b , Tattersall (1982) ^{b,c,e} , Sussman 1991 ^{b,c} , Kappeler (1996) ^d , Lindenfors (2002) ^d , Godfrey et al. (2004) ^f , Jones et al. (2009) ^{b,c}
<i>Lepilemur ruficaudatus</i>	Red-tailed sportive lemur	Foliv	12	1	0.163	2.63	Solitary or male–female pairs	0.8	Martin (1972) ^e , Tattersall (1982) ^{c,e} , Godfrey et al. (2004) ^{d,e} , Hilgarter et al. (2008) ^{b,c,e} , Jones et al. (2009) ^e , Mittermeier et al. (2010) ^{f,c,e}
<i>Microcebus griseorufus</i>	Gray-brown mouse lemur	Omni	14	2	–	–	–	–	Génin (2008) ^{b,c}

(continued)

Table 15.3 (continued)

Scientific name	Common name	Diet ^a	IBI (mos)	Litter size	Fetal growth rate	Postnatal growth rate	Mean group size ^f	Mean home range size (ha) ^f	References
<i>M. murinus</i>	Gray mouse lemur	Omni	12	2.5	0.195	1.92	Sleeps in groups of 1–15	0.22–3.2 (males); 0.24–1.8 (females)	Petter-Rousseaux (1964) ^b , Tattersall (1982) ^f , Harvey and Clutton-Brock (1985) ^b , Kappeler (1996) ^d , Lindenfors (2002) ^d , Jones et al. (2009) ^{b,c} , Mittermeier et al. (2010) ^e
<i>Prollemur simus</i>	Greater bamboo lemur	Foliv	12	1	–	–	Range 4–12	62	Tan (2000) ^b (2006)
<i>Propithecus candidus</i>	Silky sifaka	Foliv	20	1	–	–	4.3, Range 3–7	–	Patel (2007) ^{b,e}
<i>P. coquereli</i>	Coquerel's sifaka	Foliv	12	1	0.718	5.94	Range 3–10	4–8	Richard (1976) ^{c,e} , Tattersall (1982) ^{c,e} , Kappeler and Pereira (2003) ^{b,d,e} , Godfrey et al. (2004) ^{d,e} , Jones et al. (2009) ^{b,c,d}
<i>P. diadema</i>	Diademèd sifaka	Foliv	25	1	0.846	5.05	4.83, Range 3–8	33–42	Tattersall (1982) ^{c,e} , Powzyk (1997) ^{c,e} , Godfrey et al. (2004) ^{d,e} , Jones et al. (2009) ^{b,c,d}
<i>P. edwardsi</i>	Milne-Edwards' sifaka	Foliv	19	1	0.922	6.305	5.3, Range 2–9	400	Wright (1995) ^e , Pochron et al. (2004) ^b , Arrigo-Nelson (2006) ^{c,e} , Morelli et al. (2009) ^b , King et al. (2011) ^{d,e}
<i>P. tattersalli</i>	Golden-crowned sifaka	Foliv		1	0.582	4.21	5, Range 3–10	9–12	Tattersall (1982) ^e , Meyers and Wright (1993) ^{c,e} , Kappeler and Pereira (2003) ^{d,e} , Godfrey et al. (2004) ^{d,e} , Jones et al. (2009) ^d

<i>P. verreauxi</i>	Verreaux's sifaka	Foliv	18	1	0.686	5.07	6, Range 2–14	3–10	Richard (1978) ^b , Tattersall (1982) ^{y,c} , Harvey and Clutton-Brock (1985) ^y , Kappeler (1996) ^d , Lindenfors (2002) ^d , Richard et al. (2002) ^{b,c,e} , Kappeler and Pereira (2003) ^e , Godfrey et al. (2004) ^e , Lewis and Kappeler (2005) ^e , Jones et al. (2009) ^{b,c} , Vasey (2007) ^{b,c} , Zehr et al. (2011) ^d
<i>Varecia nuba</i>	Red ruffed lemur	Frug	12	2.1	2.157	–	2–6, 18–31	25–58	Tattersall (1982) ^{y,c} , Harvey and Clutton-Brock (1985) ^y , Harvey et al. (1987) ^y , Morland (1990) ^{y,c} , (1991) ^{y,c} , White et al. (1992) ^{e,e} , Kappeler (1996) ^d , Balko (1998) ^{y,c} , (2011) ^y , Lindenfors (2002) ^d , Kappeler and Pereira (2003) ^e , Godfrey et al. (2004) ^y , Jones et al. (2009) ^{b,c} , Baden (2011) ^{y,c}
<i>V. variegata</i>	Black-and-white ruffed lemur	Frug	12	2.2	2.14	50.09	Range 2–6 and 8–16	30–150	

Values represent the midpoints when more than one source was available

^aFoliv = folivore, Omni = omnivore, Frug = frugivore. Diet data from Muldoon and Goodman (2010)

^bReferences for interbirth interval (IBI)

^cReferences for litter size

^dReferences for fetal growth rate or variables used to calculate fetal growth rate (litter mass and gestation length)

^eReferences for postnatal growth rate or variables used to calculate postnatal growth rate (litter mass at weaning, litter mass at birth, age at weaning)

^fSee references in Gould et al. (2000) for mean group size and mean home range size

15.5.3 Allomaternal Nursing

Allomaternal nursing differs from the other categories of non-maternal infant care in that, as far as we know, it does not appear to be a strategy used consistently by any lemur species with the exception of one, or possibly two (see below). The rarity of this behavior in lemurs may be due in part to the relatively large number of species that are singular breeders, in which only one female breeds at a time (e.g., several *Eulemur* species, *Avahi*, *Cheirogaleus*, *Indri*, *Hapalemur aureus*, and occasionally *H. griseus* and *Propithecus* species) (Mittermeier et al. 2010), and thus opportunities for allomaternal nursing do not exist. In a clever study employing the use of infrared cameras in nests, litter-bearing (1–3 infants per birth) *Microcebus murinus* were observed nursing others' infants (9 of 12 females, 16.7% of their nursing time when other mothers were not present), though they exclusively carried their own offspring, and thus could likely discriminate kin (Eberle and Kappeler 2006). Wright (1990) noted that although small body size or high infant/maternal weight ratios are associated with extensive paternal care, this relationship is lacking in *Cheirogaleus* and *Microcebus*, the smallest Malagasy primate species. It might then be expected that future research with these genera will discover that allomaternal nursing occurs in more cheirogaleid species than presently known. Other plural breeding species (where several females breed per group) in which allomaternal nursing has been witnessed include *E. collaris* (Kesch 2009), *Lemur catta* (Klopfer 1974; Gould 1992; 2011; A. Jolly, T. O'Mara, S. Meredith, personal communication), *P. candidus* (Patel 2007), *Varecia rubra* (Vasey 2007), and *M. griseorufus* (inferred, Génin 2008) in the wild, and *V. variegata* in captivity (Pereira et al. 1987). Some of the best descriptions available are from recent work with *L. catta*, in which almost 55% (12 of 22) of all infants were nursed by allo-mothers (T. O'Mara, personal communication). The frequency of allomaternal nursing varied depending on the infant's age (peaking toward the end of weaning), and ranged from 10% to 90% of all nursing bouts (T. O'Mara, personal communication). Future work on the differential treatment of infants who are orphaned versus those who are not (S. Meredith, personal communication), and on the relatedness of helpers and mothers should help determine ultimate explanations for this behavior. Food sharing by caregivers, beyond passive tolerance of infants tasting foods, occurs in relatively few primate species (Brown et al. 2004), and has not been observed in any Malagasy primate.

15.6 Allomaternal Care and Life History Traits

To determine the benefits of allomaternal care in primates, we can look at the distribution of allomaternal care and life history traits such as growth rates and interbirth intervals. Cross-taxonomic analyses of life history traits and infant care in haplorhines (Mitani and Watts 1997; Ross and MacLarnon 2000), and haplorhines and strepsirhines (Ross 2003), found that increased levels of primate allomaternal

care correlated with faster growth rate, younger age at weaning, and shorter interbirth interval. These studies suggest that allomaternal care benefits the mother by reducing the intensity and duration of her energetic contribution to infant rearing (e.g., carrying, babysitting, nursing) and increases her potential reproductive output. It is important to note that previous research treated all Malagasy primate species as non-allomaternal caregivers. Therefore, it is uncertain whether these benefits of allomaternal care also exist within Malagasy primates.

We recently tested the hypothesis that, like haplorhines, lemur mothers benefit from allomaternal care (Tecot et al., [in revision](#)). Based on earlier studies, we predicted that the presence and type of allomaternal care are associated with faster fetal and postnatal growth rates, as well as shorter interbirth intervals, when controlling for diet and body mass (Mitani and Watts 1997; Ross and MacLarnon 2000; Ross 2003). Using data collected from the literature and from personal communication with lemur researchers and the Duke Lemur Center (DLC) (Table 15.3), we scored five predictor variables as absent or present. The predictor variables were: (1) allomaternal care, (2) allomaternal nurse, (3) carry by caregiver, (4) nest, and (5) park. We conducted phylogenetic generalized least squares models (Pagel 1999). Controlling for body mass and dietary niche (as defined by Muldoon and Goodman 2010), we tested the relationship between our five predictor variables and three dependent variables: (1) postnatal growth rate, (2) fetal growth rate, and (3) interbirth interval (see Tecot et al., [in revision](#)).

Counter to our expectations, our hypothesis was not supported; contrary to what has been found in haplorhines (Mitani and Watts 1997; Ross and MacLarnon 2000), the presence of allomaternal care does not translate into more rapid infant growth, nor does it yield reduced interbirth intervals in lemurs (Tecot et al., [in revision](#)). This result may, in part, be due to Malagasy primates' adaptations to their unique ecology, as discussed in detail below. Unlike haplorhines, weaning in lemurs is timed with resource abundance (Wright 1999). Thus, increasing growth rates and decreasing the age at weaning may not be appropriate reproductive strategies, as weaning must coincide with sufficient resources for a mother recovering from lactation or an infant largely inexperienced in supporting itself nutritionally. Furthermore, faster growth rates and earlier weaning may not, in fact, increase reproductive rates at all, since lemurs tend to be highly seasonal breeders (Wright 1999; Tecot 2010). It is true however that interbirth intervals can range from 1 to 3 years (Table 15.3). Thus, one might expect mothers to benefit by reproducing in consecutive years, thereby shortening interbirth intervals, yet we did not find a relationship between allomaternal care and interbirth interval for lemurs overall (Tecot et al., [in revision](#)). Thus, the benefit to species that express allomaternal care behaviors remains to be determined.

Interestingly, while allomaternal care itself is unrelated to increased infant growth in lemurs, infant parking and nesting were associated with faster life histories. Parking and nesting were positively related to fetal and postnatal growth rates (*contra* Kappeler 1998), and nesting was further positively related to shorter interbirth intervals, when accounting for body mass and diet (Tecot et al. [in revision](#)). Ross (2003) found a similar relationship between nesting and postnatal growth

rates, suggesting that parking and nesting may impact female reproductive energetics. Higher fetal growth rates have been argued to indicate higher maternal investment (Godfrey et al. 2004); thus our results indicate that parkers and nesters may actually invest more heavily (or efficiently) in offspring than mothers who carry their young. Since approximately half of the parking species included in our analysis also build nests, it was difficult to disentangle the individual effects that each of these behaviors has on infant growth. If, however, nesting can be used as a proxy for babysitting, as is the case in some taxa (e.g., *Varecia*: Morland 1990; Vasey 2007; Baden 2011; Baden et al. 2011; Baden et al. *in revision*), then this particular type of infant care may indeed reduce maternal energy expenditure in species with the highest maternal investment. These infants may also reach maturity faster. Although offspring of haplorhine species with allomaternal care and faster growth rates do not reach maturity sooner, likely due to the constraints of brain growth (Ross 2003), offspring of litter-bearing taxa may. Mothers of litters tend to have higher quality milk compensating for parking offspring for long periods without access to their mother's milk, and as a result infants tend to mature faster (wean and breed earlier) (Tilden and Oftedal 1995; 1997).

We currently lack data on babysitting in some nesters and parkers. Nevertheless, if nesting and parking are associated with babysitting or guarding, it remains to be determined whether allomaternal care, or just general relief from the energetic burden of transporting an infant, drives these relationships. There is some evidence that mothers who park and nest directly benefit from receiving help with their infants. In *Varecia variegata*, a taxon known for its exceptionally high prenatal and postnatal energetic investment (see references in Vasey 2007), energy intake post-parturition as measured by time spent feeding was higher in communal nesters compared with single nesters (Baden 2011; Baden et al. 2011; Baden et al. *in revision*). Furthermore, communally nested infants had higher survival rates (Baden 2011; Baden et al. 2011; Baden et al. *in revision*), indicating that infants directly benefit from allomaternal care, not just via inclusive fitness, as has been suggested for primates overall (Ross 2003), and not just from parking or nesting per se. Thus, nesting (and possibly babysitting) may be one strategy that saves the mother energy that she can then invest in future reproductive opportunities, and allows her to reproduce quickly with high prenatal and postnatal growth rates and relatively short interbirth intervals.

15.7 Comparisons with Haplorhines

We can observe gross phylogenetic patterns in the distribution of caregiving behaviors in lemurs: allomaternal nursing and parking or nesting occurs in fast-growing (Leigh and Terranova 1998), litter-bearing species (e.g., *Varecia* spp., *Microcebus* spp.), and allomaternal carrying occurs in slow-growing (Leigh and Terranova 1998), frequently twinning or pairbonded species (e.g., *Eulemur* spp.). In her comparison of caregiving behaviors and life history traits, Ross (2003) found that the positive relationship between allomaternal care and litter weight in species where

infants cling to fur was largely due to the high frequencies of allomaternal care and twinning in callitrichines. She noted that the presence of paternal care and the absence of twinning in Goeldi's monkeys support Dunbar's (1995) suggestion that twinning secondarily evolved after paternal care. The distribution of allomaternal care in form and frequency in lemur taxa support this hypothesis (as far as we can tell from the published literature and personal observations). *Eulemur* demonstrate the most habitual use of allomaternal carrying and perhaps allomaternal care, and frequently twin (though more data from more species are needed to confirm this assertion) (Tecot 2010). Fathers and siblings often carry offspring in several *Eulemur* species, though this behavior is not always employed in all groups (e.g., *E. macaco*: Volampeno et al. 2011; *E. rubriventer*: Overdorff 1991; Tecot, personal observation). *Varecia* may also fall within this framework, though infants are transported orally. *Varecia* bear litters and there is some indication that babysitters at the nest may be fathers (Baden 2009). However, litter-bearing species do appear to have very different strategies than twinning species, and *Varecia* in particular show a combination of caregiving behaviors (carry orally, park, nest, allomaternal care [babysitting]) not observed in any other primate species (Table 15.1). In particular, parking and nesting enable at least some independent movement on the mother's part, regardless of allomaternal care received. Nevertheless, in lemur species with relatively high variance in litter mass, a relationship between allomaternal care and litter mass may exist, and remains to be tested.

As predicted by inclusive fitness theory (Hamilton 1964; Trivers 1972), allomaternal care in vertebrates (excluding primates) is largely restricted to family groups, and where kin and nonkin are present, individuals preferentially help kin (Emlen 1997). Within primates, allomaternal care by males tends to be strongest in species where paternity is certain (Ross and MacLarnon 2000). Interactions between parents may stimulate male care of offspring (Storey et al. 2006). For example, changes in maternal hormones during gestation may be honest cues received by her pairmate that she is pregnant. Upon receiving this cue, male hormone levels (e.g., prolactin and cortisol) respond and may in effect prepare him for providing infant care (Ziegler et al. 2004). Within the genus *Eulemur*, the distribution of allomaternal care may be consistent with haplorhine trends. For instance, of all *Eulemur* species in this study, the brown lemur species complex (*E. fulvus* and sister taxa) live in the largest groups, consisting of multiple males and females (Richard 1987; Overdorff et al. 1999), and *E. mongoz* and *E. rubriventer* live in small pairbonded family groups (Curtis and Zaramody 1999; Overdorff and Tecot 2006). To date, allomaternal care has not been reported in the brown lemur species complex, whereas carrying by adult males (*E. mongoz*, *E. rubriventer*) and juveniles (*E. rubriventer*) is common in the pairbonded species (Curtis and Zaramody 1999; Overdorff 1996a; Overdorff and Tecot 2006; Tecot 2008). These patterns are also consistent with the hypothesis that paternal behaviors (but not necessarily allomaternal care) are more likely in smaller groups of a given species (Eaglen and Boskoff 1978; Bastian and Brockman 2007). Future work within *Eulemur* species measuring allomaternal care, group size, and paternity certainty would allow us to begin to test these hypotheses.

15.8 Malagasy Primates: An Unusual Case?

While allomaternal care is present in some form in each lemur taxon, its expression does not conform to the pattern evident in haplorhines, whereby allomaternal care is positively correlated with female reproductive output. We propose that this strategy may not equally benefit Malagasy primates because reproductive rates in this taxon appear to be less flexible. Further, the combination of rapid infant growth rates (Leigh and Terranova 1998), perhaps already at maximal, sustainable velocity, and concomitant shortened duration of infant dependence in lemurs compared with haplorhines, may reduce the need for allomaternal care at all. Alternatively, it is possible that we need to test a different set of predictions altogether in order to understand the distribution of allomaternal care in lemurs. Ross and MacLarnon (2000) tested several ecological hypotheses in haplorhines to investigate whether energetic stress might select for allomaternal care, none of which were supported. In contrast, Malagasy primates live in unique and challenging environments that are said to differ from those of other primate habitats (Wright et al. 2005; Dewar and Richard 2007) and are thought to have shaped them in ways that distinguish them from even their closest primate relatives. For example, the relationships between diet (folivory vs. frugivory), infant development, and maternal investment in Malagasy primates differ from haplorhines in that folivores (leaf eaters), rather than frugivores (fruit eaters), have higher maternal investment, develop more slowly, and reach reproductive maturity later (Godfrey et al. 2004). We might therefore expect to see relationships between allomaternal care and ecological factors, particularly those that impact energetic stress, such as the abundance and predictability of resources (Tecot *in press*).

Although many mammals time reproductive events with dynamic ecological processes such as temperature, rainfall, and food production (Negus and Berger 1972; Bronson and Heideman 1994; Brockman and van Schaik 2005), Madagascar's environmental challenges demand that the island's fauna adapt unusual strategies for coping with seasonal yet unpredictable environments (Tecot 2010). While other primate species may live in equally difficult habitats, lemurs as a whole exhibit a distinctive suite of traits that sets them apart from other primates (Wright 1999). For example, lemurs possess adaptations to seasonality such as strict seasonal breeding (Janson and Verdolin 2005) with short estrus periods cued by photoperiodicity (van Horn 1975; Rasmussen 1985; Pereira 1993), typically occurring once per year and resulting in high birth synchrony (Jolly 1967; Rasmussen 1985; Pereira 1991; Sauther 1998). Moreover, lemurs also exhibit adaptations to unpredictability that confer flexibility, as also observed in other primates. Recent evidence suggests that several species adopt a strategy whereby they time reproduction with the best environmental conditions in response to exogenous cues such as photoperiod, but there is some flexibility in the system. Some species may respond to endogenous cues such as fat stores (e.g., Lewis and Kappeler 2005), which enables them to make reproductive decisions based on internal and external states (Brockman and van Schaik 2005). Finally, Malagasy primates display adaptations

to energy-poor environments. For instance, small group size allows individuals to exploit scarce, small resource patches (Ganzhorn et al. 1999), with little intra-group competition (Wright 1995; Overdorff 1996a; b), and for longer periods of time (Wright 1999). *Cheirogaleus* and *Microcebus* spp. in particular further reduce energy expenditure by entering torpor in the winter (see Geiser and Ruf 1995; Petter-Rousseaux 1980; Wright and Martin 1995; Schmid and Kappeler 1998; Sørge et al. 2003; Dausmann et al. 2004). While torpor can be considered an adaptation to seasonal environments, it is generally understood to be an adaptation to enable energy conservation in harsh environments (Schmid and Stephenson 2003). As a whole, these suites of traits observed in Malagasy primates, as well as others not discussed here, maximize energy intake and minimize energy expenditure (Wright 1999), preventing physiological stress and promoting reproduction in a harsh and unpredictable environment (Tilden and Oftedal 1995; Pereira et al. 1999; Tecot 2008; Tecot in press).

15.9 Avenues for Future Research

Ross (2003) points out that meta-analyses of allomaternal care across the order are difficult because of the paucity of high quality, detailed data from strepsirrhine taxa, including, for example, quantifications of allomaternal care behaviors such as those employed by Ross and MacLarnon (2000). While broader taxonomic studies were able to categorize presence and absence relative to a threshold of percent allomaternal care (e.g., 5%, Ross and MacLarnon 2000), such methods precluded the inclusion of any lemur taxa as allomaternal caregivers. Differences between Ross's (2003) review and ours may be due to these differences in criteria for the presence of allomaternal care, leading to the exclusion of all accounts of allomaternal care in lemurs during her study. Differences between studies may also be due to the fact that such information is not often the subject of study, is only addressed in discussions, and is thus easily missed or left unquantified. Finally, our results may differ because of the availability of more recent data on lemur allomaternal care. While our method may overestimate the presence of allomaternal care in the species included in our analysis, we believe that the reality likely falls somewhere between Ross's (2003) study (no allomaternal care in lemurs) and ours. The absence of a relationship between growth rates and allomaternal care within lemur species in our study may be due to this inability to analyze percent allomaternal care. More conservative assessments of allomaternal care within these species might yield different results, and as a first step, we suggest that comparisons of relative time spent caring for infants by the mother and allomaternal caregivers be made. Until these data are available, we feel that it is premature to speculate as to the potential differences between haplorhine and lemur allomaternal care, if in fact they exist.

Lemur researchers do not often conduct field research with the goal of studying allomaternal care because allomaternal care is largely unexpected in these species (and non-haplorhine primates as a whole), and does not occur at high rates (to our knowledge). Moreover, our knowledge of life history traits in wild species is slim, as many species are rarely, if at all studied, and comparatively few long-term studies exist (see Wright et al. 2012). With more and more long-term studies initiated every year, we are hopeful that these data will soon be available, and current sample sizes will be boosted. We can then begin to ask questions such as whether allomaternal helpers are related and thus satisfy requirements for kin selection (Hamilton 1964; van Schaik and Paul 1996; see Buchan et al. 2003 for agonistic interventions by fathers on behalf of juveniles), or if helpers are unrelated and might help as a way to strengthen social ties (see Mumme 1997 and Ross and MacLarnon 2000). Are infants, mothers, or helpers responsible for transferring infants between caregivers and is this transfer met with resistance (Poirier 1968; Lessnau et al. 1993)? Can caregiving be a mechanism of “agonistic buffering” (Deag and Crook 1971), reducing aggression between adults? Are helpers juvenile and nulliparous females who might be learning to mother (Lancaster 1971; Hrdy 1977)? What are the costs to helpers? For example, do helpers delay dispersal (Koenig et al. 1992) or experience lower reproductive rates (as observed in siamangs, *Symphalangus syndactylus*, Lappan 2008)? However, in the meantime, we encourage researchers to report even anecdotal accounts of allomaternal care, as well as exclusive maternal care when they do not observe allomaternal care (e.g., Tan 2000). Studies of allomaternal care can be better developed with an understanding of which species express these behaviors, and many more species can be included in comparative analyses to provide a broader perspective, and help determine the selective pressures for non-maternal infant care in primates.

Finally, we suggest that future research should focus on ecological explanations for the presence of allomaternal care in Malagasy primates. Specifically, how do the type and frequency of allomaternal care vary with diet, day range, and food availability (or competition)? For instance, day range is known to affect life history traits across primates (e.g., Pontzer and Kamilar 2009). Yet, because there is such great variation in habitat quality (largely due to habitat degradation), certain data such as day range can be highly variable within species. While site-specific variation can be a cause for difficulty in broad-scale analyses, it is our belief that such variation can be especially informative. With more site-specific data, particularly for species in which allomaternal care exists but is not ever-present, investigations of these proximate relationships can lead us to ultimate explanations of the evolution of allomaternal care in Malagasy primates.

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Glossary

Allomaternal care Costly behaviors directed toward infants, which are provided by individuals other than the mother. This can include care by the genetic father, siblings, and other distantly related or unrelated group members.

Allomaternal nursing The behavior of females nursing offspring that are not genetically their own.

Carrying on fur Also known as infant riding; the infant clings to its mother's fur during movement between locations.

Carrying orally Care-providers transport young in their mouths, such as when moving between nests. Oral carrying typically occurs when infants are altricial and cannot cling to their mother's fur.

Cheirogaleidae A family within the infraorder Lemuriformes including the genera *Allocebus*, *Cheirogaleus*, *Microcebus*, *Mirza*, and *Phaner*.

Crècheing A shared nest or centralized location where the young of several mothers are cared for in a communal fashion (i.e., by one or many individuals other than the mother).

Daubentonidae A family within the infraorder Lemuriformes including the genus *Daubentonia*.

Energy transfer When group members provision infants with food resources to the energetic benefit of the infant. Includes food sharing and allomaternal nursing.

Food sharing Transfer of food resources from group members to infants, often due to infant solicitation.

Haplorhini A suborder of primates including catarrhines (Old World monkeys and apes), platyrrhines (New World monkeys), and tarsiers.

Helper Infant care-provider other than the mother.

Indriidae A family within the infraorder Lemuriformes including the genera *Avahi*, *Indri*, and *Propithecus*.

Infant guarding or "babysitting" When group members other than the mother remain with an infant while its mother is away. This can involve predator protection, protection against infanticide, and general supervision.

Infant transport When a care-provider moves an infant between locations (transport can be over short or long distances) and includes carrying on fur (i.e., infant clings) and/or oral carrying, as in cases where infants cannot cling.

Infant mistreatment/"Aunting to death" Exploitative cases of allomaternal care which result in the mishandling, injury, and sometimes death of infants receiving care.

Lemuridae A family within the infraorder Lemuriformes including the genera *Eulemur*, *Haplemur*, *Lemur*, *Prolemur*, and *Varecia*.

Lemuriformes An infraorder of strepsirhini primates endemic to the island of Madagascar.

Lepilemuridae A family within the infraorder Lemuriformes including the genus *Lepilemur*.

Nesting When infants are left in actual nests that have been constructed from leaves, lianas, and other materials. Often occurs when infants are altricial and cannot cling, and is common among litter-bearing taxa.

Parking When infants are left hidden in a tree-hole, amongst lianas and tree tangles, or clinging to a branch while family members feed and forage. Often occurs when infants are altricial and cannot cling.

Strepsirrhini A suborder of primates including lemurs, lorises, and galagos.

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Chapter 16

When Dads Help: Male Behavioral Care During Primate Infant Development

Maren Huck and Eduardo Fernandez-Duque

Keywords *Aotus* • Carrying • Dispersal • Development • Male care • Mating effort • Night monkeys • Owl monkeys • Paternal care

16.1 Introduction

In contrast to birds, male mammals rarely help to raise the offspring. Of all mammals, only among rodents, carnivores, and primates, males are sometimes intensively engaged in providing infant care (Kleiman and Malcolm 1981).¹ Male caretaking of infants has long been recognized in nonhuman primates (Itani 1959). Given that infant care behavior can have a positive effect on the infant's development, growth, well-being, or survival, why are male mammals not more frequently involved in

¹ Quantitative measures of male care in mammals, although occasionally cited, are problematic. Since Kleiman and Malcolm reviewed the then available data in 1981 much more and new information has become available, which sometimes lead to reclassifications, for example, of mating systems. Due to the lack of field data, their review mainly included data from captivity, which are not necessarily representative for patterns observed in the wild. Furthermore, the definitions of male care can vary substantially and thus the calculated proportions for different taxa.

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“building babies”? The Theory of Parental Investment originally provided an elegant explanation (Bateman 1948; Maynard Smith 1977; Parker et al. 1972; Trivers 1972) that has been recently modified with interesting implications (Houston and McNamara 2002, 2005; Kokko and Jennions 2008; Wade and Shuster 2002, 2005). Males may not necessarily have to trade-off mating opportunities and parental care, as suggested by classic theoretical formulations, but may instead benefit by direct involvement in infant care (Geary 2005).

We begin the chapter defining a few relevant terms and introducing the theory and hypotheses that have historically addressed the evolution of paternal care. We then review empirical findings on male care among primate taxa, before focusing, in the final section, on our own work on paternal care in South American owl monkeys (*Aotus* spp.). We conclude the chapter with some suggestions for future studies.

16.2 Parental Care Revisited

16.2.1 *Parental Investment and Male Care*

Male care, paternal care, and paternal investment are frequently, but incorrectly, used interchangeably (Sheldon 2002). First, we refer to “male care” instead of “paternal care” because genetic paternity is rarely known for most primate studies. Second, we make a distinction between “care” as a suite of behaviors that the male directs to the infant and “investment” which entails an increase or decrease in the present or future reproductive success of the male (Clutton-Brock and Vincent 1991; Trivers 1972). The investment made by the male can be in the form of direct care (e.g., transporting or feeding the infant) or indirect care. The latter might, for example, take the form of antipredator vigilance that frees time for the mother to forage or rest. Direct male care is a behavior directed to the infant that has a positive effect on its development, growth, well-being, or survival. It might consist in carrying, grooming, playing, food sharing, feeding, cleaning, retrieving, huddling, babysitting, or defending.

16.2.2 *The Theory of Parental Investment*

According to the classic formulation of the Theory of Parental Investment (Maynard Smith 1977; Parker et al. 1972; Trivers 1972), physiological sex differences in mammals have selected for females to provide significant infant care and males to compete for access to infant care providing females. This explanation is particularly relevant for mammalian females who make high energy and time contributions to gestation and lactation. Due to these high energetic demands, it is predicted that in most species the reproductive success of females will be mainly constrained by food intake, whereas male reproductive success will be primarily limited by access to

females. Several other factors favor the “typical” mammalian sex roles: strong intra-sexual selection on males, loss of paternity because of female promiscuity, or male mortality due to competition may all generate a female-biased adult sex ratio (Kokko and Jennions 2008). Any of these three factors will make it more beneficial for males to desert females since they all result in a higher proportion of females than males (i.e., a female-biased ratio). It follows from this that male care should be a rare phenomenon among mammals, and in fact it is.

In the last decade, however, several modifications to the theory have been proposed (Houston and McNamara 2002, 2005; Kokko and Jennions 2008; Wade and Shuster 2002, 2005) including the reevaluation of factors traditionally considered to favor the “typical” mammalian sex roles (Kokko and Jennions 2008). For example, the classic argument that females should invest more because they have invested more since the beginning (e.g., larger gametes) evokes the “Concorde Fallacy,” because it is not expected that optimal decisions are based on past investment, but instead on future payoffs (Dawkins and Carlisle 1976). With regards to males, a traditional assumption has been that a male-biased operational sex ratio will always lead to intra-male competition. In other words, it has been predicted that when there are more reproducing males than reproducing females in the population, this will quasi-automatically produce a trade-off between parental care and mating effort. But this is not necessarily true, since some of the earlier models neglected the “Fisher condition,” the fact that in sexually reproducing species each offspring has exactly one parent of each sex (Houston et al. 2005; Kokko and Jennions 2008). When the “Fisher condition” is properly considered, the theory predicts that when the operational sex ratio is male-biased (i.e., more reproductively active males than females at a given time), there will be more male competition which will result in increased parental investment by males. Finally, recent models have also shown that the operational sex ratio and the adult sex ratio might influence the evolution of patterns of parental care. If caring behavior is associated with increased mortality of the caregiving adult, this will change the operational sex ratio. The caring sex will be rarer due to the increased mortality and as a consequence the mating success of the less-caring sex will be diminished. This, in turn, will lead to more similar care behavior of both sexes (Kokko and Jennions 2008). An earlier analysis suggesting that caregiving is associated with lower mortality (Allman et al. 1998) was conducted on mortality data from captive individuals which may limit the generalizability of the findings. Furthermore, in particular with regards to monogamous species where male care is prevalent, this analysis suffered from lack of correction for phylogenetic effects, and an unjustified reliance on statistical significance and data of dubious origins.

16.2.3 Why Is Providing Care Beneficial to Males?

A male may derive benefits from infant care behavior in at least three ways: direct benefits through enhanced infant survival, reduction of the female’s reproductive burden, or as a mating strategy to enhance future mating success (Geary 2005).

First, providing care may enhance the survival or fitness of his own genetic offspring or highly related individuals like younger siblings or nephews and nieces (“genetic advantage” hypothesis, Table 16.1) (Charpentier et al. 2008; Gubernick and Teferi 2000; Kingma et al. 2010; Moreno et al. 1999; Wuensch 1985). Second, the male’s assistance may alleviate the reproductive burden of the female (“maternal relief” hypothesis) to an extent that she will be able to produce infants of better condition, or at a higher rate (Achenbach and Snowdon 2002; Austad and Rabenold 1986; Kingma et al. 2010; Morcillo et al. 2003; Price 1992a, b; Sánchez et al. 1999; Stallcup and Woolfenden 1978). Even if a female is able to successfully rear an offspring without male care, she may be energetically depleted and may not be able to reproduce again as quickly as she would with male assistance. In primates, allo-maternal care is correlated with relatively fast infant growth rates (Mitani and Watts 1997). Finally, providing infant care might also be a strategy to increase mating opportunities (“mating strategy” hypothesis) (e.g., Härdling and Kaitala 2004; Keddy Hector et al. 1989; Price 1990; Smuts and Gubernick 1992, but see Tardif and Bales 1997). In other words, males who provide infant care will receive benefits from the female, such as matings, in exchange for their caregiving behavior (Smuts and Gubernick 1992).

There are some predictions derived from these three hypotheses that might offer some insight into the mechanisms and evolution of parental care. The most basic adaptive explanation would be that *only* direct genetic benefits for the male are responsible for paternal care. In contrast, according to the “maternal relief” and “mating strategy” hypotheses, the benefits to the male should be independent of genetic relatedness to the current infant, and providing care would also benefit males who may be caring for non-offspring (Anderson 1992). If males only cared for their own genetic offspring, one would predict that the replacement of the biological father by another intruding male (“stepfather”) should have a negative impact on infant survival. We would also predict that subadults disperse at younger ages following the replacement of the biological father, given that the stepfather should be less tolerant of potential food and mate competitors. On the other hand, if male care served as “maternal relief” or as a “mating strategy,” we would predict that a stepfather should care for the offspring of his predecessor as well. Smuts and Gubernick (1992) suggested testing three predictions to set the “mating strategy” hypothesis apart from the “genetic benefits” hypothesis: (1) the infant benefits from the care provided by the male, (2) females are able to control important benefits like mating to males, and (3) females have opportunities to compare the behavior of different males, and based on this assessment and their own choice, they benefit some males, but not others. In the following sections, we will evaluate these predictions in view of the existing evidence in primates in general, and owl monkeys in particular.

16.2.4 Proximate Perspectives of Parental Care

In this chapter we primarily discuss ultimate approaches to the question of why male care is observed at all in mammals, even when there are other complementary

Table 16.1 Overview over patterns of paternal care in different primate taxa

	Example species	Relative contribution of allo-maternal care	Type of allo-care	Allo-maternal caretakers	Support for (+) or against (-) IS, MR, GEN, and FMS hypotheses	References
Strepsirrhines ^a	Ruffed lemurs; slender loris; sifakas	Low	Grooming, playing, babysitting, allo-nursing	Related and unrelated (?) males, other females	IS: na MR: - GEN: - (weak) FMS: na	[1-6]
Tarsiers ^a	Spectral tarsiers	Low	Grooming, playing, babysitting, allo-nursing	Related (?) males, sub-adults of both sexes	IS: na MR: - GEN: + (weak) FMS: na	[7]
Colobines	Hanuman langurs	Other females: frequent; males: very rare to absent	Babysitting, carrying, huddling, allo-nursing	Females	IS: - MR: - GEN: - FMS: -	[8]
Exception	Black-and-white snub nosed monkey	Moderate	Carrying and grooming	Related and unrelated (?) males	IS: na MR: + GEN: - FMS: -	[9]
Cercopithecines	Japanese macaques; chacma baboons; savannah baboons; vervet monkeys	Low	Playing, carrying	More likely potential fathers than unrelated males	IS: + MR: + GEN: + FMS: +	[10-12]
Exception	Barbary macaque	Moderate	Carrying, babysitting	Males and females of all age-classes	IS: na MR: na GEN: - FMS: na	[13, 14]
Hominoids (exceptions)	Siamang	Moderate	Carrying	More likely potential fathers than unrelated males	IS: na MR: ++ GEN: + FMS: na	[15]

(continued)

Table 16.1 (continued)

Example species	Relative contribution of allo-maternal care	Type of allo-care	Allo-maternal caretakers	Support for (+) or against (-) IS, MR, GEN, and FMS hypotheses	References
Human	Low to very high	Carrying, provisioning, playing, babysitting, allo-nursing	Fathers, other relatives, unrelated individuals	IS: -/+ MR: + GEN: + FMS: +	[16–24]
Platyrrhines	Very high	Carrying, food sharing, grooming, playing	All group members	IS: ++ MR: ++ GEN: - FMS: -/+	[25–37]
Titi monkey	Very high	Carrying	Adult males	IS: + MR: na GEN: (prob +) FMS: na	[38, 39]
Owl monkey	Very high	Carrying	Adult males	IS: ++ MR: + GEN: (prob +) FMS: + (weak)	[40, 41, 42, this study]

Note that this is a rough overview to depict a general pattern for several groups, and that specific proximate and ultimate mechanisms might differ between species of the same taxon

IS infant survival/fitness, MR maternal relief, GEN genetic advantage to male, FMS enhanced future mating success for males (“mating strategy”), na no data available

1. Morland (1990); 2. Nekaris (2003); 3. Whitten (1987); 4. Kappeler (in press); 5. Patel (2007); 6. Bastian et al. (2007); 7. Gursky (2000); 8. Ross and MacLarnon (2000); 9. Xiang et al. (2009); 10. Itani (1959); 11. Anderson (1992); 12. Buchan et al. (2003); 13. Small (1990); 14. Paul (1999); 15. Lappan (2008); 16. Geary (2005); 17. Marlowe (2000); 18. Geary (2000); 19. Hurtado and Hill (1992); 20. Hewlett (1989); 21. Marlowe (1999); 22. Anderson et al. (1999); 23. Hewlett (2004); 24. Gettler (2010); 25. Goldizen (1987a, b); 26. Huck et al. (2004); 27. Porter and Garber (2009); 28. Savage et al. (1996); 29. Yamamoto et al. (2009); 30. Sánchez et al. (1999); 31. Achenbach and Snowdon (2002); 32. Morcillo et al. (2003); 33. Tardif (1994); 34. Fite et al. (2005); 35. Bales et al. (2001); 36. Price (1990); 37. Tardif et al. (1997); 38. Frigaszy et al. (1982); 39. Mendoza and Mason (1986); 40. Fernandez-Duque (2011a); 41. Rotundo et al. (2005); 42. Wright (1984)

^aSpecies commonly show “infant-parking”

approaches that cannot be covered in detail here. For example, the influence of hormones like prolactin, vasopressin, oxytocin, and testosterone in relation to bonding and infant care, or behavioral trade-offs between care and mate-acquisition have been extensively studied, even if still not completely understood (Bales et al. 2004; Brockmann et al. 2001; Gettler et al. 2011; Goymann et al. 2007; Gray et al. 2007; Hirschenhauser and Oliveira 2006; Huck et al. 2005; Schradin and Anzenberger 2002; Schradin et al. 2003; Trainor and Marler 2001, 2002; Wingfield et al. 1990; Ziegler 2000; Ziegler et al. 1996, 2000). Differences in hormone production, responsiveness, or ontogenetic exposure may partly explain individual differences in caretaking behavior (Birnie et al. 2011; Drea 2007; Ziegler et al. 2009). Other influential factors include the rank, age and previous experience of the caretaker, sex of the infant, group size and composition, relatedness between caretaker and infant or mother, season of conception, or predation risk (Anderson 1992; Bercovitch 2002; Hoage 1977; McGrew 1988; O'Brien and Robinson 1991; Pryce 1988). Individual differences in caretaking behavior will necessarily be the outcome of a very complex mixture of directly genetic and environmental influences that manifest themselves during ontogeny, or sometimes in a shorter time frame due to seasonal or interannual fluctuations in environmental or social factors.

16.3 The Who, How, and When of Male Care in Primates

Primates are one of the orders of mammals with the highest prevalence of male care (Ross and MacLarnon 2000; Solomon and French 1997; Whitten 1987). The intensity of male care is variable, ranging from relatively little investment like occasional short rides or play bouts, to babysitting, to intense involvement in feeding and carrying of the offspring (Fernandez-Duque et al. 2009; Nicolson 1987; Whitten 1987; Wright 1990).

16.3.1 *Strepsirrhines and Tarsiers*

In many species of strepsirrhines and tarsiers, infants are not constantly carried, but rather left behind, outside the shelter, for up to several hours while the mother is foraging. When females “park” their infants (Kappeler 1998), like in ruffed lemurs (*Varecia variegata*, Morland 1990), slender loris (*Loris lydekkerianus*, Nekaris 2003), or spectral tarsiers (*Tarsius spectrum*, Gursky 2000), they save energy compared to females in anthropoid primates, where infants are carried much more frequently. This energy-saving behavior by the mothers might render strong male involvement unnecessary. Nevertheless, male care is shown in many strepsirrhines and tarsier species, albeit at relatively lower levels (reviews in Kappeler *in press*; Patel 2007; Tecot et al. 2012; Whitten 1987). Male care usually includes grooming or playing, and occasionally carrying (Bastian and Brockman 2007; Patel 2007).

For example, in slender lorises, males visit parked infants, groom and play with them, or just stay in proximity (Nekaris 2003). Slender lorises have a multi-male, multi-female social organization, and several males may show interest in a receptive female. At times, several males might interact with a particular infant, suggesting that infants may receive care not only from biological fathers (Nekaris 2003).

The spectral tarsier from Sulawesi Island (*T. spectrum*) is of special interest in comparison to owl monkeys and titi monkeys (see below), because it shares some of the features thought to have facilitated male care in these latter genera. Tarsiers are quite small primates (ca. 100 g) that produce single infants who weigh as much as 22% of the mother's body mass at birth (Gursky 2000). Like titi and owl monkeys, tarsiers are predominantly pair-living, though not as exclusively as the former two taxa. Care behavior is occasionally shown by subadults of both sexes and adult males, but it is the subadult females that are most involved (Gursky 2000). Care takes mainly the form of grooming, playing, and staying in proximity to the infant, but only rarely of carrying it, since infants are usually parked. Unfortunately, no genetic paternity analyses are available to evaluate whether male care is restricted to probable fathers. Yet, given that most groups consist of only one adult of each sex, this is a reasonable assumption.

Thus, in strepsirrhines and tarsiers, male care, albeit not uncommon, is usually of relatively low intensity and, at least occasionally, directed at unrelated infants. Since infants are often parked, it is not likely that male care will act as "maternal relief." However, there is not enough evidence to argue for or against the hypothesis that males provide care in order to obtain better mating opportunities.

16.3.2 Catarrhines

Among colobine monkeys, mothers often allow other females to interact with infants, but direct male care is rare (Ross and MacLarnon 2000). Male black-and-white snub nosed monkeys (*Rhinopithecus bieti*), however, provide direct care in the form of carrying and grooming, albeit of moderate contribution (Xiang et al. 2009). Genetic relationships are not available, but since groups of this species can contain as many as 200 individuals, paternity certainty is likely to be low, so that care is probably not exclusively directed to genetic offspring. Thus, male care might alleviate the female's burden, that is, likely to be quite high. Snub nosed monkeys inhabit an extremely cold environment with snow cover for half of the year making resources scarce and foraging effort substantial (Xiang et al. 2009).

In various cercopithecine monkeys (e.g., Japanese macaques, *Macaca fuscata* and chacma baboons, *Papio cynocephalus ursinus*), males are quite tolerant of infants, play with and carry them occasionally (Anderson 1992; Itani 1959). Chacma baboon males carry infants significantly more when they had a higher probability of being the father (Anderson 1992). Infants that are carried more frequently have higher survival probability, and mothers of these infants have shorter inter-birth intervals (Anderson 1992). Although these findings suggests some concrete direct

benefits to infants and mothers from male care, there are other possible underlying causes, like rank or condition of the mother that cannot be ruled out. In savannah baboons (*P. cynocephalus*) males selectively supported juveniles for which they had high paternity probability (Buchan et al. 2003). In vervet monkeys (*Chlorocebus pygerythrus*, formerly *Cercopithecus aethiops*) infant care might possibly serve as a mating strategy. Male vervet monkeys appear to modify their infant care behavior depending on their “audience.” In other words, they care more for infants when the mother is present; and females, in turn, are more affiliative toward males that have previously cared for an infant (Keddy Hector et al. 1989).

Thus, among cercopithecine monkeys, there is evidence for one or several of the potential benefits of male care: baboons care predominantly for their own offspring, and females seem to benefit by shorter inter-birth intervals, and vervet males might use infant care as a mating strategy. Nevertheless, we must reiterate that in all of these taxa male care is infrequent and most of the time indirect.

There are only three species among catarrhine primates that show more significant male care: humans, siamangs (*Symphalangus syndactylus*, Lappan 2008), and Barbary macaques (*Macaca sylvana*, Small 1990). In a population of semi-free-ranging Barbary macaques, infants were held or carried by non-mothers and adult males almost a fourth of the time (Small 1990). Since females mate with multiple males during estrous, paternity is equivocal, and male care is probably directed sometimes to unrelated infants. Infant handling was, however, not random, and adult males preferentially handled infants of high ranking mothers (Paul 1999); whether infant handling also results in preferential mating with these females is not known.

Among the hylobatids, pair-living is the prevalent, though not exclusive, social structure (Fuentes 2000; Lappan 2008; Reichard and Barelli 2008). Despite this, direct male care of infants has not been reported for most gibbon species in the wild, with the notable exception being the largest species of the family, the siamang. When siamang infants are approximately one-and-a-half-year old, they are frequently transported by males, but the care patterns seem to be variable: males in monogamous groups tended to carry infants more (27%) than males in socially polyandrous groups (12%, Lappan 2008). With male helpers, female siamangs were able to reduce their own carrying effort and had shorter inter-birth intervals than when males participated less (Lappan 2008).

In most human societies, mothers are not the sole caretakers of infants, and fathers, other relatives, and even unrelated individuals may participate in infant care (Geary 2005; Hewlett 1989; Hrdy 2008; Kramer 2010; Marlowe 2000). Direct male care is facultative for our species and can range from being virtually absent to providing a substantial contribution to a child’s upbringing. The amount of care provided by men varies between individuals and peoples, and is related to, among others, the subsistence type (forager men caring most) and marriage system, with decreasing father–infant interaction with increasing degree of polygamy (Geary 2000; Hewlett 2004; Marlowe 2000). Men’s contributions, whether direct or indirect, can have a profound influence on the survival rate and physical well-being of children. In the traditional hunter-gather society of the Paraguayan Ache, mortality rates of children without father are higher compared to children with the father

present (Hurtado and Hill 1992). In industrial societies, social competitiveness of children is also positively influenced by the father's investment (Geary 2005). Additionally, male care and investment by provisioning are likely to relieve the mother's burden and may explain the comparatively short inter-birth intervals of women compared to other apes (Gettler 2010). Childcare and investment by men are often primarily directed to genetic offspring, but can be viewed at least partly also as a mating strategy, if some care is provided to stepchildren as long as the mother still lives together with the caring man (Anderson et al. 1999; Hewlett 2004; Marlowe 1999).

16.3.3 *Platyrrhines*

Within the nonhuman primates, the highest levels of male care are found in several taxa of New World monkeys, particularly in the callitrichines, titi monkeys, and owl monkeys. For example, males are the primary caregivers among socially monogamous titi monkeys (Fragaszy et al. 1982; Mendoza and Mason 1986; Welker and Schäfer-Witt 1986). When infant titi monkeys are separated from their fathers, they show a strong pituitary-adrenal stress response and vocalize intensely, whereas the response is much weaker when the mother is removed. This indicates that infants are more strongly bonded to their fathers than their mothers (Hoffman et al. 1995). Likewise, in threat situations captive cotton-top tamarin infants run to the individual that carries them the most, which is usually the father or older sibling, but never the mother (Kostan and Snowdon 2002).

In the callitrichines, infants are usually born as twins and their combined weight might be as much as 15–20% of the mother's body mass (Garber 1994; Goldizen 1990; Leutenegger 1973). All group members participate in helping, including offspring from previous litters (Goldizen 1987b; Huck et al. 2004; Porter and Garber 2009; Savage et al. 1996; Yamamoto et al. 2009). The callitrichines show a highly variable mating system, but often live in polyandrous or polygynandrous groups (Garber 1997; Goldizen et al. 1996; Goldizen 1987a; Heymann 2000; Nievergelt et al. 2000; Porter 2001). Although males are often related to each other, helpers are not always related to the infants they care for, and in mustached tamarins (*Saguinus mystax*) fathers carry infants less than any other helper (Huck et al. 2004).

Carrying infants is an energetically costly behavior. Even in captivity, cotton-top tamarin (*Saguinus oedipus*) helpers lose weight during the carrying period, while mothers, who carry less frequently, gain weight (Achenbach and Snowdon 2002; Morcillo et al. 2003; Sánchez et al. 1999). Thus, the care provided by males seems to reduce the metabolic costs of the females, and females reduce their own efforts in the presence of helpers (Fite et al. 2005; Tardif 1994). In wild golden lion tamarins (*Leontopithecus rosalia*) the number of infants born is positively correlated with the number of helpers in the previous season (Bales et al. 2001). It is therefore likely that female future reproductive success is dependent on the amount of help she receives (Price 1992b).

It is less clear whether male care could also function as a mating strategy in this taxonomic group. One study suggested that female cotton-top tamarins mount preferentially with males carrying infants (Price 1990). However, in another study female cotton-top tamarins and common marmosets (*Callithrix jacchus*) did not preferentially copulate with males that had provided more infant care (Tardif and Bales 1997).

In summary, interactions between non-mothers and infants are common among primates, not only with other females, but also with males who are often quite tolerant toward infants (Nicolson 1987; Whitten 1987). Moreover, in some primate genera the interactions take on a qualitatively different form. In the three Neotropical taxa of titi monkeys, owl monkeys, and callitrichines, as well as in the old world siamangs, and some human societies, male care is much more direct and obligatory (Fernandez-Duque et al. 2009; Geary 2005; Hewlett 1989; Marlowe 2000). Male care seems to be linked to paternity certainty in many, albeit not all species, but it is not confined to monogamous taxa. Particularly in some taxa with obligate allo-maternal care, females seem to benefit from male care through shorter inter-birth intervals or in some cases through preferential interaction with males who provide infant care.

16.4 Parental Care in Owl Monkeys

16.4.1 General Biology

The owl monkeys of the Neotropics are among the few socially monogamous² mammal species (Fernandez-Duque 2011a), and as already noted, they show intense male care (Fernandez-Duque 2011a; Rotundo et al. 2005; Wright 1984; Fig. 16.1). Owl monkeys are the only anthropoid primate with primarily nocturnal activity (Wright 1989). However, one species, the Azara's owl monkey (*Aotus azarae*) from Paraguay and northern Argentina, shows cathemeral activity, being also active during the day (Erkert and Cramer 2006; Fernandez-Duque 2003, 2011a; Fernandez-Duque et al. 2010; Wright 1989). Wild owl monkeys live in small groups, normally composed of an adult heterosexual pair, one infant, and one or two juvenile or sub-adult individuals (Fernandez-Duque 2011a). The sex ratio, both adult and operational, is apparently even, as indicated by our capturing of similar numbers of females ($N=82$) and males ($N=76$; G-test, $G=0.2$, $p=0.63$). In our study population, males and females are replaced equally often. Between 2001 and 2010, we observed 25 female and 21 male replacements in a total of 142 group years in 18 groups (Fernandez-Duque et al. 2008; Huck and Fernandez-Duque 2012). Likewise,

² We define social monogamy as a social system in which a single adult female and adult male each have only one social adult partner of the opposite sex for at least one, but usually several, breeding seasons. Such pairs will share and often defend a common home-range and may or may not develop a special pair-bond (Kappeler and van Schaik 2002; Martin et al. 2007; Wickler and Seibt 1983).

both sexes seem to have similar survival rates (survival analysis for 53 females and 52 males over 2 years of age, accounting for censored data and using a Weibull distribution, $\chi^2=0.06$, $p=0.81$).

16.4.2 *Development and Parental Care*

Our understanding of infant care and development in owl monkeys comes from both studies of captive individuals and free-ranging ones. In captivity, a few studies have examined parental behavior and infant development in different owl monkey species (Dixson and Fleming 1981; Jantschke et al. 1998; Wolovich et al. 2007, 2008; Wright 1984). Birth seasonality has been reported in wild, as well as in some captive owl monkey populations (Fernandez-Duque 2002, 2011a; Gozalo and Montoya 1990). In the Argentinean Chaco, long-term pairs of Azara's owl monkeys often have one infant every year between September and December (Fernandez-Duque 2002). Both adults groom and clean the infant frequently with the mouth in captivity (on average 0.65 bouts/h, Dixson and Fleming 1981), but grooming seems to be less frequent in the wild (Fernandez-Duque et al. unpublished data; Wright 1984). During the first month of life, infants are almost constantly carried by their parents. By the third month of life, they spend half the time off their parents, and by the fourth month they move independently more than 90% of their time (Dixson and Fleming 1981; Rotundo et al. 2005; Wright 1984, dashed line in Fig. 16.1a). The first few days after birth the infant is carried mainly by the mother, but soon afterwards, the male becomes the main caretaker (Dixson and Fleming 1981, this study, Fig. 16.1). Males carry infants much more often than females, and they also play more with them (Fernandez-Duque et al. unpublished data; Wright 1984, this study). Older siblings hardly ever participate in infant carrying, in contrast to callitrichines (e.g., Huck et al. 2004; Tardif et al. 1992). In captivity, adults actively help the infant to transfer from one parent to the other (Dixson and Fleming 1981). Many transfers are triggered by the rejection of one parent, and mothers reject more often than fathers, who rarely induce infants younger than 2 months of age to leave their back. As with so many other traits, the pattern of infant-carrying in owl monkeys resembles closely that of titi monkeys (Welker and Schäfer-Witt 1986).

In the wild, the long process of weaning starts around the end of the third month, when mothers are seen for the first time to reject infants. Nursing continues, however, at least until the fifth month, and nipple contact may be observed, albeit rarely, as late as 8 months of age (Rotundo et al. 2005). These results are similar to those reported for captive individuals; nursing frequency in captivity is very low by the 18th week of life (Dixson and Fleming 1981). Infants start to explore, manipulate, and finally consume solid food during their second month of life in both captive and wild populations. Food sharing with infants, in both captive and wild owl monkeys (Rotundo et al. 2005; Wolovich et al. 2006, 2007, 2008), is not as frequent as it is among the callitrichines (Feistner and Price 2000; Huck et al. 2004; Porter 2001; Price and Feistner 2001). It also appears to be less frequent than in wild titi monkeys (*Callicebus torquatus*), where it was observed with a frequency of 0.08 begging

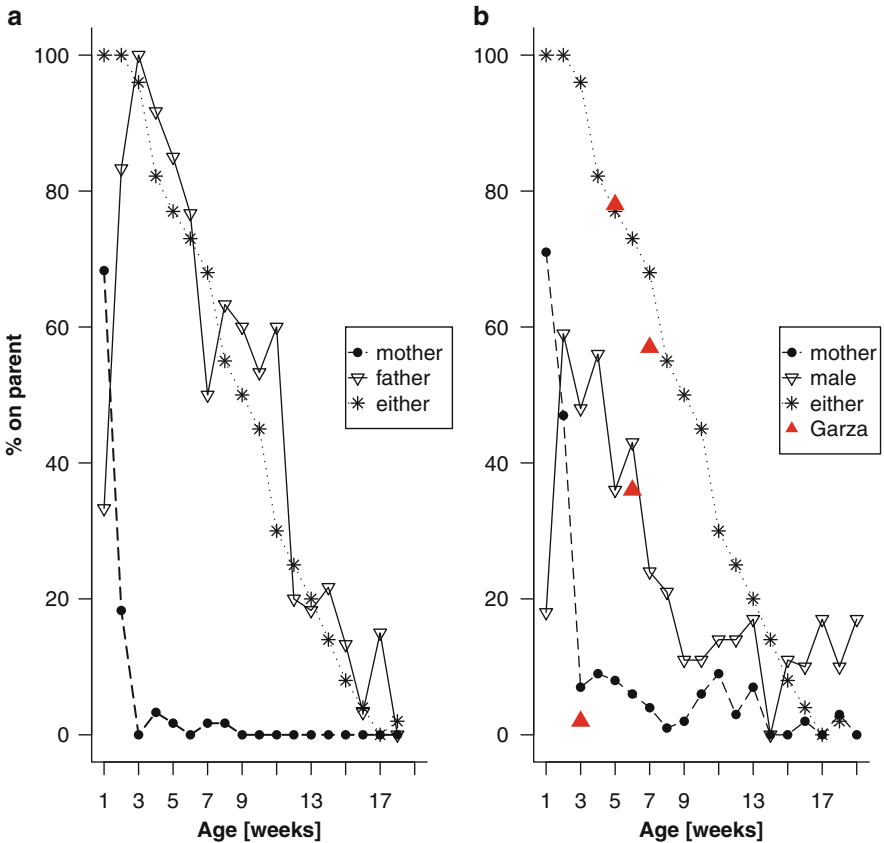


Fig. 16.1 Infant carrying. (a) Percentage of sampling points (“time”) that infants are carried by their mother or father (data from captivity after Dixson and Fleming 1981), or either parent (data from the wild after Rotundo et al. 2005). The data are in some cases interpolated. (b) Percentage of sampling points that infants are carried or nursed by their mother, the group’s adult male (this study), or either parent [after Rotundo et al. 2005, same as in (a)]. Note that the data for males and females were obtained in a slightly different manner than in Rotundo et al. (2005), where data were obtained by focal samples exclusively on infants. Here, we collected data in 20-min focal protocols on any group member, and every 4 min the carrier of the infant was noted. Since the focal animal was often not the infant, there are occasions when the carrier, if it was not the focal animal, might have been out of sight, thus resulting in lower total values for males and females. Likewise, we were occasionally not able to identify the carrier. The filled (or: upright) triangles give the weekly percentage of carrying effort by the female “Garza” before she was ousted from her group in week 4 and while she was caring for the infant on her own until the death of the infant in week 7 (see text for details). The numbers of focal samples of Garza per week were 15, 17, 16, and 2 for weeks 3, 5, 6, and 7, respectively

events/h, mainly directed toward the male and less often to an older juvenile or the mother (Starin 1978).

In the wild, the process of development differs little between the sexes (Huck et al. 2011, Fig. 16.2). Although no hormonal analyses have been conducted on any wild owl monkey population to characterize sexual maturity, based on testes size

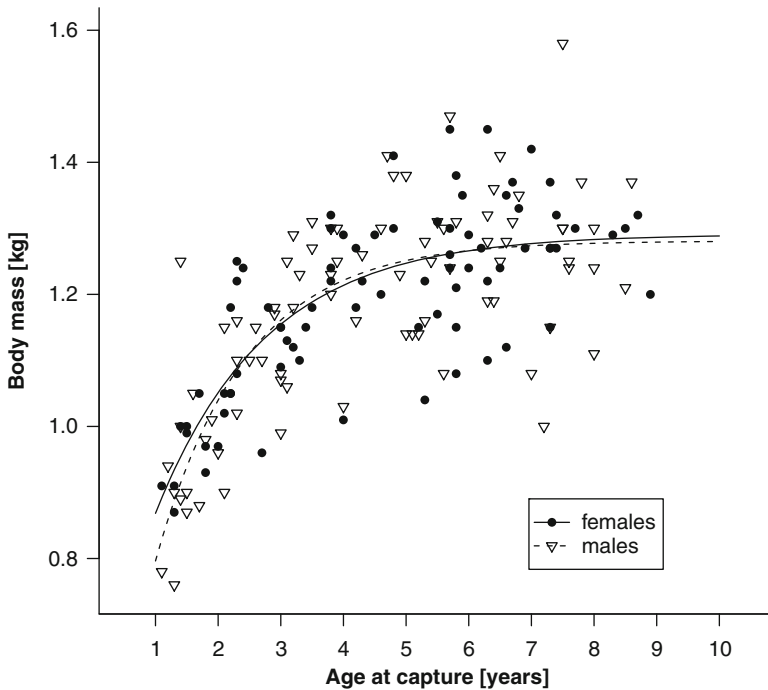


Fig. 16.2 Correlation between age and body mass in female and male owl monkeys. Von Bertalanffy curves are fitted through scatter plots (after Huck et al. 2011).

and the development of the sub-caudal gland, wild Azara's owl monkeys seem to start puberty around 2 years of age and to reach sexual maturity toward the end of their fourth year (Huck et al. 2011). A study of a smaller owl monkey species in captivity estimated an earlier onset of puberty and found that the testes reached adult size by 2 years (Dixon et al. 1980). In captivity, owl monkeys from Peru (*Aotus nancimaee*) usually had offspring when they were 3.5 years old, but sometimes when they were as young as 2 years old (Gozalo and Montoya 1990). In our population, individuals never had infants before they were 2 years old (Huck et al. 2011). Apart from the potentially younger ages at first reproduction in captivity, the postnatal development appears to be similar for different owl monkey species, both reared in captivity and in the wild.

16.4.3 Caring Dads

The described pattern of development in young owl monkeys shows that males strongly contribute to the upbringing of infants (see Fig. 16.1); but how do the males benefit from their involvement? In order to identify support for the “genetic advantage”

hypothesis, two things need to be established: the genetic relationship between the male and the infant, and a comparison of infant survival in groups with and without male caretakers. Genetic analyses suggest that the male present in the group when an infant is conceived is the genetic father of that infant (unpublished results). However, due to the replacements of adults described above, adult males may also be unrelated to infants in their group. When this happens, some evidence indicates that they still provide care in much the same way as genetic fathers (Fernandez-Duque et al. 2008). Regarding the second point, it is virtually impossible to estimate infant survival for groups without any male caretaker in the wild, because breeding vacancies that are due to the death or disappearance of one parent are usually filled up immediately by new incoming adults (Huck and Fernandez-Duque 2012).

Although the lack of groups without male care hinders an evaluation of the “maternal relief” hypothesis, there is some limited evidence to evaluate it. After the death of her mate, a captive owl monkey female had to bring up her infant with only the assistance of an older daughter (Jantschke et al. 1998). The older sibling provided substantial infant care, similar to the situation described for one wild group where the adult male died soon after the birth of the infant (Fernandez-Duque et al. 2008). In both cases, the carrying effort of the mother was essentially not higher than in groups with two adults, and in captivity the orphan infant was completely independent after 3 months, sooner than infants in groups with male caretakers (Jantschke et al. 1998, compare with Fig. 16.1). This evidence suggests that female owl monkeys may not be capable or willing to invest more in their current offspring, at least as long as adult males or older siblings are available. Siblings, however, might be not strong enough physically or too inexperienced to fully replace adult males, forcing the infant to become independent sooner. In the wild, earlier independence could lead to a higher energetic need for the infant, due to increased mobility, as well as increased predation risk. It is often in dangerous situations (e.g., an alarm call by a group member, a wide gap between tree branches) that even relatively old infants or young juveniles seek transport by the adult male (Rotundo et al. 2005). Therefore, enforced earlier independence might lower the overall fitness of young owl monkeys.

What would happen if a female had to raise an infant completely on her own? We predict that the female would increase her carrying effort, with the subsequent additional energetic cost that may result in a loss of body mass and a reduced probability of reproduction in the following year. Apparently, wild females do not lose body mass during the infant-rearing period when the male cares for the infant (Fernandez-Duque 2007, AAPA published abstract). On one occasion, a female with a dependent 1-month-old infant was replaced by a female intruder shortly after the group’s male had been replaced. During 8 months we occasionally saw the mother, ranging solitarily and in the first month with the infant, until eventually we found her radio-collar on the ground strongly suggesting she had died. Before she was ousted from the group, the mother carried the infant as infrequently as is typical for mothers (2% of time), while afterwards she carried it on average 58% of the time (Fig. 16.1b, filled (or: upright) triangles). During the first week as a “single mother” (week 5 in the life of the infant), she compensated nearly completely, and the infant was carried

as much as it would have been normally transported by the male. Yet, in the following week, the infant was carried much less than usual for that age. This natural experiment provides some data indicating that the female was not capable of completely compensating for the absence of the male's care, and the infant did not survive. Together, these two single-case observations provide some support for the "maternal relief" hypothesis, even when acknowledging that better data on energy budgets of males and females are still much needed.

As explained in the first section, we expect qualitatively different adult–infant interactions under the "genetic advantage" hypothesis than under the "mating strategy" or "maternal relief" ones. Following the replacement of the putative father by a new male, half of the immatures (0–24 months) disappeared (i.e., they probably died) before they reached 2 years of age. A similar proportion of immatures disappeared in stable groups or in groups where the mother has been replaced (Huck and Fernandez-Duque 2012). In other words, infant survival/disappearance, as a proxy for male–infant relationship, was similar in groups with the putative father and groups where the father had been replaced. Likewise, the age of natal dispersal, which can also be constructed as indicative of the relationship between young and adult male, did not differ between subadults from stable groups or those with male or female replacement (Fernandez-Duque 2009; Huck and Fernandez-Duque 2012). Finally, the spatial relationships between the infant and the adult males can also be used as a proxy for the quality of a relationship (Mitani et al. 2000; Palombit et al. 1997; Perry 1998). Intruding males are found in close proximity to the offspring of their predecessors as often as the fathers themselves before being replaced (Fig. 16.3). In conclusion, although these demographic and behavioral data provide some support for the "mating strategy" hypothesis, it is still difficult to distinguish between the hypotheses that male care relieves the female's energetic burden and that male help makes him attractive to the female.

16.5 Conclusions: Why Do Male Owl Monkeys Care to Care?

Despite some significant advances recently, we are just beginning to find answers to the question of why male owl monkeys invest so much in their offspring. Titi and owl monkeys are monogamous, but, as we have seen, not all monogamous species show extensive male care. For example, in saki monkeys (*Pithecia* spp., Norconk 2007) and gibbons with the exception of the siamang (Lappan 2008; Rafacz et al. 2012), mothers do most of the work, some occasional observations of infant carrying or babysitting notwithstanding (Schmitt et al. 2005). So it is obviously not the monogamous social system per se that makes dads help (see also Komers and Brotherton 1997; Smuts and Gubernick 1992; Whitten 1987). Rather, in several species where females mate with multiple males, males and even unrelated individuals might engage in infant care behavior, most prominently in the callictrichines (Garber 1997; Goldizen et al. 1996; Goldizen 1987a; Heymann 2000; Huck et al. 2004; Nievergelt et al. 2000; Porter 2001).

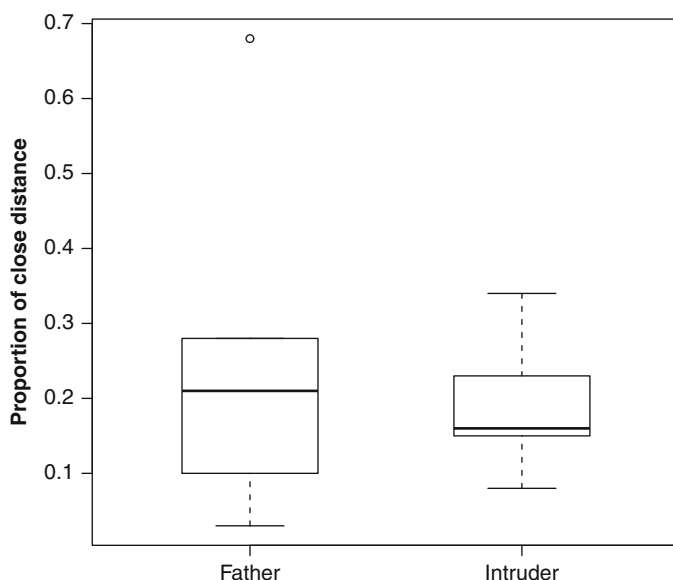


Fig. 16.3 Proportion of close distances (body contact to 1 m) between an immature and an intruding male ($N=5$ infants), or putative fathers ($N=6$). Data were collected in 20-min focal protocols, noting the distance to all other group members every 4 min. For more detailed description of the methods see Huck et al. (2011). Medians do not differ between the groups (Wilcoxon signed rank test, $W=12.5$, $p=0.71$), even if “repeated measures” for the same male are taken into account (results of mixed-effect models not presented)

We have shown that owl monkey infants rely on male care, and that the female is also likely to benefit from the male’s help (Jantschke et al. 1998, this study). Yet, rigorous analyses of energy budgets of males and females of wild owl monkeys still need to be conducted. The predictions of the “mating strategy” hypothesis are partly supported. As demonstrated above, owl monkey infants are likely to benefit by the care provided by the male. Second, given that female owl monkeys are the same size as males (Fernandez-Duque 2011b), females can probably exercise control via the offering or withholding of matings. The final prediction about the females’ ability to assess and compare males is more difficult to test in a pair-living species, because there is no day-to-day choice between several males. Studies on mate selection previous to pair formation have not been conducted, but since males care for unrelated offspring when they enter new groups (Fernandez-Duque et al. 2008), infant care as a mating strategy cannot be refuted either. Thus, from the individual male’s perspective, he might benefit in all three broad ways from providing paternal behavior.

What do our data indicate regarding the population modeling approach that considers how other individuals are behaving (Kokko and Jennions 2008)? At least two of the three conditions that are postulated to favor the traditional, female-biased, infant care pattern are not found in owl monkeys: biased sex ratio, uncertainty of

paternity, and sex differences in strength of sexual selection. In our study population, the sex ratio of captured individuals has been approximately even, and paternity certainty seems to be high. Even if future genetic studies should reveal some low levels of extra-pair paternity, there is apparently little incentive for a male to leave his mate to seek other mating partners. Finally, whereas strong sexual selection might reduce paternal behavior because it changes the operational sex ratio, it seems unlikely that sexual selection may be operating more strongly on males than on females. The species is not only monogamous, but remarkably monomorphic (Fernandez-Duque 2011a, b). This of course raises the question of why owl monkeys are monomorphic and monogamous, and leaves us with a hen-egg problem, though the evolution of monogamy before the evolution of paternal care, or even non-parental helping, seems the most likely scenario (Dunbar 1995; Goldizen 1990).

The model of Kokko and Jennions (2008) also indicates that the sex with the higher mortality rate due to caretaking behavior will be selected to provide more care due to the mortality-induced changes in the adult sex ratio. However, given the apparently even sex ratio and no significant differences in the rate of adult replacement (i.e., a possible proxy for mortality) or survival, it is unlikely that adults face different mortality rates due to either intrasexual competition or caretaking behavior. Although there might be still undetected differences in mortality, if owl monkeys have currently reached a stable equilibrium, historical differences in mortality rates might not be apparent any longer.

It is difficult to assess whether any of the sexes invests more than the other when lacking estimates of the specific energy costs of different caretaking behaviors. How many milliliters of milk equal how many minutes of carrying the infant? In mustached tamarins there seems to be a trend for an inverse relationship between the carrying effort and the amount of food shared with infants (Huck et al. 2004). Although female owl monkeys do not carry infants much, the whole energetic costs of gestation and lactation still rest with them.

A final puzzling aspect in the caretaking system of owl monkeys, like in titi monkeys, is that older siblings do not participate in the upbringing of the infants (Fernandez-Duque et al. 2009), which is in stark contrast to the callitrichines. We might speculate that it has to do with stronger intra-sexual competition in callitrichines, where dominant females often monopolize breeding positions (Löttker et al. 2004; Snowdon and Soini 1988). Additionally, it might be more disadvantageous for the smaller callitrichines to disperse at a young age and roam solitarily because of potentially higher predation pressure.

In summary, both new theoretical developments and our own data on owl monkeys suggest that when there are few differences in the strength of sexual selection between the sexes and no multiple matings, this could result in the evolution of egalitarian sex roles with regards to infant care, in a similar process as described for the evolution of equal sex ratios (Fisher 1930; Kokko and Jennions 2008). Under this light, the question might not be why monogamous and sexually monomorphic owl monkey or titi monkey males are “good dads,” but rather, why they became monogamous and sexually monomorphic. Did monogamy precede or follow from more egalitarian infant care behavior? Why do older siblings not participate in the

rearing of their brothers and sisters? And why do males in some presumably monogamous primates (like sakis and most gibbons) NOT help?

In order to answer these questions, we need comparative studies. Studies using similar methodology should be conducted on primate species living in pairs, one-male multiple-female groups, and multi-male groups. A particular focus should be on the energetics of infant care, male–infant interactions, male–female interactions, and pace of infant development. For example, analyses of C-peptide levels in captivity under varying food and activity schemes might help to determine the energetic burden of gestation, lactation, and infant carrying (e.g., Harris et al. 2010; Sherry and Ellison 2007), although this is unfortunately not feasible in the wild with such a small, arboreal species. Such studies should shed further light on the evolution of male participation in infant care, including our own species.

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Chapter 17

Ontogeny of Social Behavior in the Genus *Cebus* and the Application of an Integrative Framework for Examining Plasticity and Complexity in Evolution

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Keywords Social behavior • Development • Capuchins • Social ontogeny

17.1 Introduction

The infant primate grows up slowly in a socially complex environment. Characterized by an extended period of dependency and neuro-social development, it has an intricate web of relationships to keep track of, each with a unique history embedded in ongoing group dynamics. Information crucial to survival is often disseminated through social networks, and those networks influence how young primates experience the world. The ability to simultaneously navigate through and manipulate such a landscape results from adaptive feedback systems between the individual and the broader social environment in which it lives. How can we better contextualize the data we now have from decades of wild and captive studies, and situate such complex behavioral strategies within a modern theoretical discussion?

Developmental Systems Theory (DST) and Evolutionary Developmental Biology (evo–devo) are two frameworks that are particularly useful for examining nonlinear processes during ontogeny. They both specifically address the fact that genomes require environmental input to generate phenotypes (via regulatory pathways), which is a central theme of this volume. A primary tenet of DST is that selection acts on phenotypes, and it emphasizes the importance of developmental conditions in recreating the phenotype generation after generation (Oyama 1985, 2000; Oyama et al. 2001, and see Bateson and Gluckman 2011; Griffiths and Gray 2005). DST is really a set of theoretical perspectives that focus on neither genes nor the environment

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as the causal factors driving development, but rather views development as a complex, nonlinear emergent property of underlying genetic and environmental bases. DST focuses on the integrated system of development within an organism's lifetime, and across generations (see Gray 2001; Oyama 1985). Thus, life cycles are contingent and contextually determined, causes of development are diffuse and fluid, and ontogeny is initiated and sustained by multiple influences (Gray 2001; Griffiths and Gray 1994; Oyama 1985, 2000; Robert et al. 2001).

Evo–devo examines broader linkages between ontogeny and evolution, and had its beginnings in the field of embryology (see Thelen and Smith 1994 for review). With a historical context that likely predates Aristotle, the modern incarnation of evo–devo focuses on how development has evolved, and how developmental processes affect evolutionary change (Gould 1977; Hall 2000; Raff 2000; Robert et al. 2001; Thelen 1990; Wagner et al. 2000). A slight offshoot is Evolutionary Developmental Psychology (see Geary and Bjorklund 2000), which examines genetic and ecological mechanisms involved with social and cognitive abilities in humans, as well as the epigenetic processes that help shape those behaviors to local conditions (Geary and Bjorklund 2000; Sterner et al. 2012). Evo–devo is firmly situated in modern biology, with specific journals, monographs, and conferences devoted exclusively to such topics (see Robert et al. 2001 for brief list), yet some fields of study lag behind in their inclusion of such perspectives. While I focus on DST for the remainder of the chapter, I suggest that both DST and evo–devo should be routinely incorporated into our examinations of ontogeny in human and nonhuman primates: they provide integrated and holistic theoretical frameworks that can yield new insights into the complexity of dynamic systems.

Several key words are commonly used when discussing aspects of development. West-Eberhard (2003) and Bateson and Gluckman (2011) give excellent overviews of the history and use of this language in evolutionary biology, along with working definitions. I provide some simplified definitions here, based on their writings (see Table 17.1 for more detail). For example, ontogeny is the progression of developmental change in an organism, from conception to death; plasticity is the ability of an organism to react to an internal or external environmental input with a change in form, state, or movement of activity; and flexibility can be seen as a set of potential responses that allows an organism to adapt to heterogeneous environments (West-Eberhard 1989, 2003). I will generally use plasticity when referring to phenotypic plasticity and flexibility when referring to behavioral flexibility (see Jones 2005).

With extended life history stages for a primate of its size, capuchin monkeys (*Cebus, Sapajus*) are an excellent example of both robustness and plasticity (Table 17.1) in motor, cognitive, and social development. Their large brains, long lives, and complex behaviors characterize important facets of being a primate; such qualities provide a context for how the acquisition of species-appropriate social behaviors occurs, and allows us to examine the role that individual temperament and behavioral flexibility play in evolved patterns of sociality. The infant capuchin is shaped by variables at the individual level (e.g., genes, hormones, physiology, phenotype) at the level of the social group (e.g., mother–infant bond, peer relationships, interactions with other adults), by the local population (e.g., gene flow, transfer of socially learned traditions

Table 17.1 Glossary of terms used

Term	Definition
Ontogeny	Development of the individual from conception to death; usually refers to the processes by which an individual acquires its characteristics, generating the phenotype. Ontogeny is sometimes contrasted with experience, which might reflect behavioral change as a result of accommodating the vagaries of a specific environment
Development	All phenotypic change during the lifetime of the individual organism. Development encompasses ontogenetic change in all aspects of organismal structure other than genetic; this can include morphological, physiological, or behavioral elements (see Waddington 1942, 1953, 1957 for discussion of the epigenetic landscape, which he first described as connecting development with genetics and evolution)
Plasticity	The ability of an organism to react to an internal or external environmental input with a change in form, state, rate, or movement of activity. Such reactions can be adaptive or not, reversible or not, active and passive, and continuously and discontinuously variable. During development, individuals with the same genotype may respond to their environments in qualitatively distinct ways
Flexibility	Behavioral responses that allow an organism to adapt to heterogeneous environments. Flexibility can be used interchangeably with plasticity in some cases
Robustness	Generally defined as the consistency of the phenotype despite environmental or genetic perturbation

Sources: Bateson and Gluckman (2011), Jones (2005), MacKinnon (2002), West-Eberhard (2003), Wright et al. (2010), and Waddington (1942, 1953, 1957)

among groups, effects of food seasonality, disease and predation), as well as across the species (e.g., phylogenetic constraints, stabilizing selection). Development is embedded in these integrated systems and is subject to the interplay among them; with such a prolonged period of dependency and social development, young capuchins serve as good models for examining which aspects of ontogeny are subject to fixed metabolic and developmental constraints, and which are more malleable and susceptible to ongoing influences. For example, the in utero environment influences the developing brain and physiology (Stern et al. 2012; Rutherford 2012), and temperament differences affect circulating hormone levels, and vice versa (Kinnally 2012; Smith et al. 2012, and see Sapolsky and Share 2004 and Sapolsky 2005); these foundations impact an individual's relationships with its mother and others in the group and these patterns of interactions will help determine its position in the social hierarchy later on, or perhaps how/when it leaves the natal group. All of this has a cumulative effect on an animal's relationships and reproductive history.

Ultimately, at a population level, these interwoven layers influence the success of a given species. We see a cascading and revolving series of connected events—but not one that is strictly linear. Development unfolds as a sequence—an interwoven set of stages—beginning in the in utero environment and continuing on throughout the lifetime. Most of these statements can be applied broadly to other social mammals, and contextualizing primates (including humans) within such a group can yield a rich comparative evolutionary story.

In this chapter I review patterns of social ontogeny in the genus *Cebus* and point to examples where DST offers a useful explanatory framework. I include examples from my own field studies on wild *Cebus capucinus*. There is an intriguing range of variation across capuchin species in life history stages such as age at first conception and birth, and time spent as a dependent infant. This phenotypic plasticity among closely related taxa can inform our understanding of how life history chapters are adaptive. Moreover, data from wild-living primates are crucial when examining the breadth of evolved strategies, and I argue that using integrated theoretical frameworks such as DST can help better contextualize phenotypic plasticity, behavioral flexibility, and the resulting individual variation in ontogeny.

17.2 The Genus *Cebus*: Brief Background

Capuchin monkeys in the genus *Cebus* (see Lynch Alfaro et al. 2012 for recent taxonomic changes) are found throughout Central and South America, and these monkeys can be classified generally as arboreal, diurnal, and medium-sized primates with prehensile tails (and see Bezanson and Morbeck 2012). They are moderately sexually dimorphic and live in multi-male, multi-female social groups of 4–40 individuals (Fedigan and Jack 2001; Freese and Oppenheimer 1981; Jack 2011). All species display dominance hierarchies, with an alpha male and alpha female; however, it is often difficult to determine specific individual rankings lower than beta in wild groups (Crofoot et al. 2011; Perry 1996, 1997, 1998; Tiddi et al. 2011, and see Jack 2011 for review).

Capuchins are highly adaptable and are found in a wide array of habitats such as lowland tropical rain forest, cloud forest, tropical dry forest with marked seasonality, and mosaic agricultural/forested areas with much anthropogenic disturbance. They can exploit food resources that are hard to obtain and/or process including larvae from embedded substrates, hard-shelled fruits and nuts, and fast-moving vertebrate prey such as squirrels, tree rats, birds, bats, and lizards (Fedigan 1990; Gunst et al. 2010; MacKinnon 2006; O'Malley and Fedigan 2005; Panger et al. 2002; Rose 1997). Along with some documented studies of tool/object use (Boinski 1988; Visalberghi et al. 2007; 2008, however see Garber and Brown 2004; Garber et al. 2012, and see Humle and Frigaszy 2011; Panger 2007 for review) the combination of manipulative skills and an opportunistic feeding strategy allow capuchin species to exploit food sources that other sympatric primates cannot.

Certain stages of development occur rather late when compared to similar-sized primates (Fragaszy 1990a, b; Fragaszy and Bard 1997; Robinson and Janson 1987). For example, an adult female *C. capucinus* in the wild first gives birth around age 7 (Fedigan and Rose 1995, personal observation); males at age 7–10 years are still considered subadult but are on the threshold of adult status and engage in sexual mountings with adult females (see Table 17.2 for *C. capucinus* age/sex class definitions). *C. capucinus* tend to have a longer inter-birth interval, and a longer period of time before they reach sexual maturity than the other capuchin species

Table 17.2 Developmental stages of *Cebus capucinus*

Age/sex class	Characteristics
Dependent infant	Birth to 6 months: dependent infants are the smallest members in the social group. For the first 2 months of life the infant's coat color is dark, without the sharp contrast of dark and light fur that characterizes this species. During this period, the infant is carried by its mother and is dependent on her for food, social contact, and travel. The infant may crawl off of her, explore its surroundings, and interact with other group members. Other individuals in the social group carry infants for short periods of time from as early as 3 months. Infants will return to their mothers to be carried during times of rapid group movement
Independent infant	6–12 months: independent infants are larger than dependent infants but smaller than small juveniles. They are no longer dependent on their mothers for food and travel, although they often return to nurse. They are carried by others in the group, including adult females, juveniles, and occasionally adult males. During this stage, individuals actively explore their surrounding physical and social environments. Their faces are usually light in color and free of marks, scars, and discolorations. At the end of this stage, weaning begins
Small juvenile	1–3 years: small juveniles are larger than independent infants, but smaller than large juveniles. They are extremely active and curious and are able to obtain all of their nutritional requirements from the surrounding habitat. Although weaned, they may still go back to their mothers for comfort and occasional suckling (if allowed). Like independent infants, small juveniles usually lack the distinguishing facial marks that are commonly seen in older individuals (i.e., scars and discoloration). This stage is marked by a lot of play behavior, usually in the form of “wrestle play” in peer groups
Large juvenile	3–5 years: large juveniles are larger than small juveniles yet lack the robust body morphology of fully mature adults. Their limbs often appear disproportionately long and gangly. Play is still common, but more “chase play” occurs among peers. The first clear evidence of sex differences appears during this stage, with males spending more time on their own and females spending more time grooming others
Adult female	5–6 years on: adult females are larger than large juveniles, but smaller than adult males. Some adult females are immediately obvious because of strong mother–infant interactions (e.g., carrying or nursing an infant). Fully mature females often have noticeable hairs on their “brows,” and older females have pronounced “bushy brows.” Distinguishing facial characteristics are also apparent. All adult females show great interest in infants, and typically have their first infant around the age of 7 years
Subadult males	7–10 years: subadult males are larger than large juvenile males, yet not as robust in form as adult males. Their faces are lighter in color, and they usually lack distinctive scars or marks. They still appear somewhat gangly and their behavior is often juvenile-like. They play with the small and large juveniles, but show increasing signs of sex play. They occasionally mate with adult females, but have not yet reached full adult male status in the group
Adult males	10 years on: adult males are the largest individuals in the social group, with a robust body morphology. They are “filled out” and more muscular than subadult males. Distinguishing facial characteristics such as scars or discolorations are usually apparent. Adult males are the most vigilant members of the group, and are groomed often by adult females and juveniles

Table 17.3 Life history stages across the genus *Cebus*

	<i>C. albifrons</i>	<i>C. apella</i>	<i>C. capucinus</i>	<i>C. olivaceus</i>
Weaning age	9 months	12 months	12 months	24 months
Infant age	Birth to ?	Birth to 6 months	Birth to 12 months	Birth to 24 months
Juvenile age	?	6–24 months	12–60 months	24–72 months
Subadult age	?	2–4 years	Females 5–6 years Males 7–10 years (?)	6–12 years
Sexual maturity	3.6 years	Females 7 years Males 4.6 years	Females 6–7 years Males 7–10 years	?
Gestation	162 days	149–158 days	157–167 days	?
Age at first birth	4 years	3.5 years	7 years	6 years
Inter-birth interval	18 months	22 months	26 months	12–24 months
Life span (max. in captivity)	44 years	54+ years	46.9 years	?

Sources:

C. albifrons: Harvey et al. (1987) and Ross (1991)

C. apella: Byrne and Suomi (1995), Freese and Oppenheimer (1981), Harvey et al. (1987), Robinson and Janson (1987), Hakeem et al. (1996), and Fragaszy et al. (2004)

C. capucinus: Freese and Oppenheimer (1981), Robinson and Janson (1987), Ross (1991), Fedigan and Rose (1995), and Jack 2011

C. olivaceus: O'Brien and Robinson (1987) and DiBitetti and Janson (2000)

(Table 17.3). As with most primates, age at first birth, inter-birth interval, and time to sexual maturity may be affected by ecological factors in wild living groups (e.g., resource abundance and distribution) (Di Bitetti and Janson 2000). However, while some developmental markers are prolonged, others are reached more quickly such as certain aspects of adult-like locomotor and foraging skills (Bezanson 2006, 2009; Bezanson and Morbeck 2012; MacKinnon 2006). One estimate of average lifespan for captive capuchins is 41 years, with a record of 54 years (Hakeem et al. 1996). However, lifespan in wild-living capuchins is often considerably shorter, perhaps by at least half when considering predation, disease, injury, and infections from fight wounds (Fedigan 2003). Even so, with an estimated average lifespan in the wild of 20+ years, capuchins are longer-lived compared to other smaller-bodied New World monkeys [e.g., 15 years for *Saimiri* and *Aotus* (Fernandez-Duque 2011; Jack 2011; Stone 2006)], and their longer lifespans align more closely with the larger heavier-bodied Atelids who are up to four times their size [wild lifespan of 30+ years for muriquis (Strier and Mendes 2012)], and 20–25 years for mantled howlers and spider monkeys (Fiore et al. 2011; Glander 2006). In some taxa there appears to be at least a correlation between having a larger brain and living a longer life: in a recent comparison of brain sizes and other aspects of ontogeny in 28 wild-living primate species, Barrickman et al. (2008) found that primate species with larger brains take more time to reach sexual maturity, and also live longer (and see Kaplan et al. 2000, 2003; Walker et al. 2006). Thus, these species seem to balance the metabolic costs of growing big brains with the presumed benefits of reaching an older age (and see Isler and van Schaik 2009). I discuss aspects of large brain size in the developing capuchin below.

17.3 Brain Growth in the Young Capuchin

Every species has phenotypic and behavioral characteristics that mature relatively early in development and others that mature relatively late. As several authors have discussed in detail, classifying species as having either a slow or fast life history trajectory obscures the disassociations that are present among individual traits, such as the timing and duration of growth seen in tissues that are metabolically expensive (Blomquist et al. 2009; Leigh 2004; Leigh and Blomquist 2011). For example, capuchins have a relatively small brain size at birth at 29–34 g, or about 50% of the adult brain weight (Elias 1977; Hartwig 1996; Martin 1983; Vinicius 2005, and see Phillips and Sherwood 2008), but the largest neonatal brain size relative to maternal weight of all primates (Harvey and Clutton-Brock 1985). Adult capuchins have an unusually large brain for their body size and have well-developed cerebellum and neocortex areas (Bauchot 1982; Passingham 1973; Rilling and Insel 1999). The cerebellum is involved with processing cognitive information as well as coordinating motor actions (Diamond 2000; Phillips and Hopkins 2007; Ramnani 2006); the neocortex receives input from the senses (vision, hearing) is involved in motor control, and also includes association areas related to higher cognitive processes and memory (Passingham 1973; Reader and Laland 2002; Rilling and Insel 1999). The sensory and motor cortices that are involved with vision and movement of the hand are particularly enlarged in capuchins compared to other New World monkeys (Clark 1960). Overall, among mammals primates show a disproportionate increase in the size of association areas (compared to the sensory and motor areas), suggesting the primate brain is capable of more plasticity in cognitive functioning (Reader and Laland 2002; and see Gibson 1990).

Throughout the first few years of life capuchin brain development is characterized by fast growth in total brain size, mainly due to the increase of white matter volume (white matter is involved in coordinating communication between different regions of the brain, while gray matter is associated more with cognitive processing). Phillips and Hopkins (2007) suggest that in species with relatively immature brains at birth (e.g., humans and capuchins) “experience-dependent plasticity” during infancy could provide expanded opportunities for learning to affect neural pathways. They also note that the rapid increase of (frontal lobe) white matter in the early years of capuchin brain growth correlates with skill acquisition via social and foraging contexts (Phillips and Hopkins 2007). The manipulative and extractive foraging behaviors of capuchins require complex sets of coordinated skills produced in part by maturing areas of the brain (Gibson 1986). By the time capuchins are off of their mothers and foraging independently around 6 months of age, they are able to perform many aspects of the adult foraging repertoire. These behaviors continue to be refined in the months to come (Adams-Curtis and Fragaszy 1994; Fragaszy 1990a; Fragaszy and Adams-Curtis 1997; Fragaszy and Bard 1997; MacKinnon 2006).

While foraging and locomotor skills approximate an adult-like level of proficiency earlier on than expected (Bezanson 2006; Bezanson and Morbeck 2012; MacKinnon 2006, but see Gunst et al. 2010), postnatal brain growth and development continues over a longer period of time than in any of the other New World monkey species

(Hartwig 1996). Thus, learning in a social context and the feedback effects on cognitive structure—particularly in the neocortex—occurs over many years in the developing capuchin. An extensive period of brain development results in individual differences that lead to variable social relationships that can then shape young lives in myriad ways. Also, the unique local social context into which every animal is born can also affect social experiences: an infant of a low-ranking peripheralized female may have fewer opportunities to observe and learn a wide array of behavioral strategies compared to an infant born to a high-ranking female who is centralized in the group's social core. However given a long period of development, the alliances and relationships the infant capuchin will eventually form on its own will likely modify the effects of such earlier social restrictions.

17.4 Development in Infant *C. capucinus*: Overall Trends and Individual Differences

When reviewing the literature on capuchin ontogeny, one sees a heavy bias towards one species in particular (*Cebus apella*, now *Sapajus apella*, see Lynch-Alfaro et al. 2012), with most data coming from captive studies (e.g., Dindo et al. 2009; Fragaszy 1990a, b; Fragaszy et al. 1990, 1991, 2004; Phillips and Sherwood 2008). While some generalizations can certainly be made (e.g., robust characteristics), there is much variation across the genera, species, and among individuals.

The following sections give an overview of dependent and independent infant stages for wild *C. capucinus*. I also use examples from three specific infants (MA, RO, and SI) observed during the first year of life (see Fig. 17.1 for general behavioral time budgets across different months of life for these individuals).

17.4.1 Dependent Infant: Birth to 6 Months

In *C. capucinus* “dependent infant” is typically defined as birth to 6 months of age (see Table 17.2, Fragaszy et al. 2004; MacKinnon 2002, 2006, but see Bezanson 2006 for alternative categories, Fig. 17.2). On the first day of life infants have several erupted deciduous teeth (Fragaszy et al. 2004, personal observation on a retrieved 2-day-old dead infant) and their eyes are open. Despite being altricial at birth, some infants can be surprisingly mobile from day 1, crawling around on the mother's ventrum, back, and neck in between nursing and resting bouts.

By 1–2 months of age infant capuchins crawl off of their mothers for up to 5 min. There is some variation: for wild *C. capucinus* Mitchell (1989) recorded the first time off mother at 10–11 weeks, while I observed this at 4 weeks (Table 17.4). In captive *C. apella*, crawling off of the mother has been observed at 9 weeks (Fragaszy 1990a; Fragaszy et al. 2004). By the 3rd month, infants start to make longer forays off their

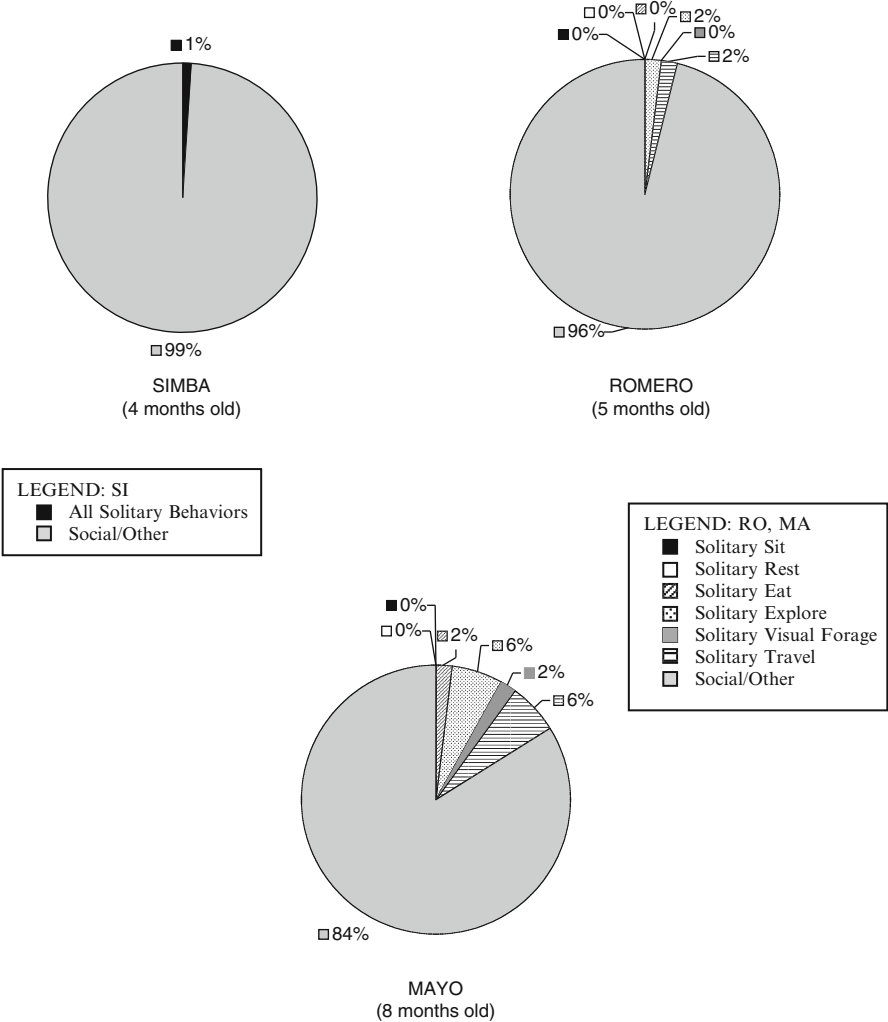


Fig. 17.1 Social versus solitary behavioral time budgets for infant *Cebus capucinus*. Source: MacKinnon (2002)

mothers, travel greater distances from her, and crawl onto and are carried by other individuals in the social group. Generally, the first 3 months of capuchin life are marked by a period of locomotor dependency, followed by several months of independent locomotion while still nursing (Escobar-Páramo 1989; Fragaszy 1990a, b; Fragaszy et al. 2004; MacKinnon 2002; Mitchell 1989). Infants up to a year old may still be carried by various individuals during periods of rapid group movement, especially if a potential predator has been spotted or the group is otherwise nervous and traveling quickly in the canopy. By comparison, squirrel monkey infants are first off of their mothers at 3 weeks of age (Rosenblum 1968; Stone 2006, 2007), and in some Old World monkeys (e.g., langurs, Barbary macaques) infant transfer by adults



Fig. 17.2 *Cebus capucinus*: dependent infant with its mother (photo by Matthew A. Wyczalkowski)

Table 17.4 Age at first appearance of behaviors for wild infant *Cebus capucinus*

Behavior	Age
Crawl around on mother	1st day of life
Crawl off mother, but in proximity to her	4th week
Crawl off mother, but not in proximity to her	7th week
Crawls onto male	5th week
Crawls onto other female	5th week
Carried by other than mother	7th week
Independent locomotion, not in proximity to another individual	11th week
Social play	11th week
Solid food	9th week (caterpillars) 16th week (fruit)
Weaning	~12 months

Source: MacKinnon (2002)

occurs during the first day of life (Dolhinow and Murphy 1982; Small 1990). Even in Old World monkey species where infant transfer is not common (e.g., baboons and some macaque species), infants first venture off their mothers as early as 2 weeks (Altmann 1980; Nash 1978; Rasmussen 1979). Thus, capuchins are not as precocious as other primates in motor development. There is much variation, which may be explained by differences between captive and wild studies, variation in local

ecological conditions across field sites as well as in captivity, differences in behavioral categories used by researchers, and a high degree of variability among the individual animals themselves.

For at least the first 6 months of life, an infant capuchin is the object of great interest and attention. The earliest social interactions, apart from those with its mother, are with individuals the mother associates with. All group members approach, stare at, sniff, touch, and genital-inspect the infant, but certain individuals are allowed longer (and closer) contact, depending on their relationship with the infant's mother; there is much variation between social groups and among individuals. Juveniles seem especially attracted to new infants and approach often, spending much time in proximity or contact. I have often observed juveniles touching and sniffing newborn infants; some are even allowed to chew on the still-attached umbilical cord while the mother rests.

Once an infant is continually crawling off of its mother around 8–10 weeks of age, its social world expands and is marked by an increasingly complex set of social interactions. It can decide whom to approach, and when to leave, in addition to being the recipient of invitations for play and other affiliative contacts. The mother's preferred affiliative partners are those with whom an infant first interacts. For example, MA's mother, KL, interacted most with DB (alpha male), and early on MA watched, crawled on, vocalized to, and was carried by him. In fact, during the first 2 months, MA had very few interactions with the other adult males. In contrast, RO's mother, BQ, interacted often with both DB and SI (beta male). RO, more than MA, interacted with both these males across a wide range of behaviors; BQ's affiliation with SI appears to have influenced RO's initial attraction to him. For example, BQ and RO often rested in contact or proximity with SI, and thus RO had a greater opportunity to interact with him in a relaxed, comfortable context.

Mothering styles, the number of infants she has had, her dominance rank, and the infant's own temperament (e.g., shy/cautious, bold/curious) help shape early social experiences, and these experiences in turn help to shape the pathway of infant social development. Thus, because of proactive associations with certain group members, infants play a crucial role in their own development (also see Fairbanks and Hinde 2012).

Infant capuchins have extremely low rates of receiving agonistic behaviors from all group members, especially adult males; they are the subjects of much attention and are treated with tolerance. When infants are dependent they nurse frequently and so are in contact with their mothers and other adult females throughout the day. Individuals in the group are gentle in their behaviors towards and with infants, and early interactions are often mediated and controlled by their mothers.

17.4.2 Independent Infant: 6–12 Months

During the developmental stage of independent infant (Table 17.2, Fig. 17.3), *C. capucinus* show a marked increase in solitary locomotion, travelling on their own for longer periods of time. They might still be carried during rapid group movement,

Fig. 17.3 *Cebus capucinus*: independent infant exploring its environment (photo by Matthew A. Wyczalkowski)



or across substantial gaps between trees and in areas that are difficult to traverse; in addition to mothers, non-mother adult females and older juveniles also contribute to the carrying of independent infants (MacKinnon 2002). Infants are both the receivers of “ride invite” behaviors from others (e.g., an individual approaches the infant, leans down and over to the infant, the infant climbs on) as well as the instigators of getting their own transportation assistance (e.g., the infant approaches an individual and climbs on if allowed). Along with greater independence comes an increase in exploring the natural environment. This often involves learning how to maneuver through complex substrates, coming into contact with potential predators, and learning first-hand what to eat and what to avoid.

Once an infant is off of its mother and foraging more on its own, its social world changes. It can decide whom to approach and when to leave, in addition to being the recipient (without the influence of a mother in close proximity or contact) of invitations for play and other affiliative interactions (e.g., grooming, huddling, resting in contact). During this stage infant capuchins seek out adult males. In most primate species adult males are a source of great interest to the younger animals. Infants intensely watch adult males, and also follow and play on or near them. Overall, youngsters are highly aware of where the males are and what they are doing. In addition to protection, infants may gain experience with social situations they might not otherwise have access to, such as intergroup encounters and male–male social interactions.

Towards the end of the first year of life, infants still nurse and so are often near their mothers and other adult females during the day. As noted earlier, group members are gentle with and tolerant of infants, and any interactions while the infant is nursing are moderated by the mother. Weaning (defined here as the cessation of nutritional dependence on the mother, Altmann 1980) in wild *C. capucinus* usually occurs around 12–14 months. By 3–4 months, infants are beginning to ingest their first solid foods (MacKinnon 2002, Table 17.4), but they rely on milk as a nutritional component in their diets across the first year of life.

When an infant is independent, it is able to try out some of the behaviors first observed while on its mother (Dindo et al. 2009; Perry 2011). In addition to such observational learning, an individual might also employ a trial-and-error strategy when exploring its natural environment (Mitra et al. 1994; Visalberghi and Frigaszy 1995). While it may seem intuitive that adult primates would exhibit more complex behaviors, there is evidence that in some species younger animals have repertoires similar to the adult pattern when searching and manipulating substrates for food (Bezanson 2006; MacKinnon 2006; Schmitt 2010; Stone 2006). This suggests that a wide range of behaviors is present early on, which then become refined and improved as the individual gets older: adults may use fewer but highly efficient foraging techniques (and have higher rates of successful food intake), whereas younger animals may use a wider range of foraging techniques yet have lower rates of successfully ingesting food.

17.4.3 *Learning What to Eat*

There seems to be a marked behavioral shift around months 3–4 when infants start experimenting more with potential food items. Rates of “solitary eat” increase as dependent infants mature and are off of their mothers; young capuchins eat a wider variety of foods when they are foraging on their own, and not in contact or proximity with their mothers or others in the group. This sets the stage for what will become the normal (i.e., robust) pattern of foraging behavior, where adults spend up to 70% of their foraging time not in close proximity to others in the group (MacKinnon 2002, 2006; Panger et al. 2002).

Seasonal differences are important to consider when looking at the ontogeny of foraging behaviors in wild capuchins, and dietary flexibility is key to a young omnivorous primate learning about potential food items. Food choice is also dependent on local habitat characteristics (e.g., if a particular fruit species is ripe when an infant first starts to sample solid food), as well as socially learned and mediated traditions (Perry et al. 2003a, b). As noted by Parker and Gibson (1977), complex object manipulation would be expected in a habitat with highly seasonal food sources. Byrne and Suomi (1995) reported that detailed manipulation of food and objects in *C. apella* begins at 3–4 months and increases to stable levels in the second half of the first year. Even if infants are not directly taught to eat certain foods,

social context/facilitation and visual cues have been found to play a role in the acceptance of novel foods in capuchins (Visalberghi and Addessi 2001).

17.5 Discussion

Dependent *C. capucinus* infants spend almost all of their time engaged in some form of social contact. At approximately 3–4 months of age, there is a shift away from the mother as the primary social partner and towards others in the group. Juveniles, in particular, become influential components of infants' social worlds. As infants develop, the amount of time spent in solitary behaviors increases. There is evidence supporting a complex interaction of factors contributing to the formation of social relationships in capuchins, notably dominance patterns and temperament characteristics, kinship, and affiliative histories of nonrelated individuals (Jack and Fedigan 2004a, b, 2009; Perry 1996, 1997, 1998, 2011). Thus, individual variability and group composition are important factors to consider when examining infant social dynamics.

Why mature slowly? Capuchins may need a longer period of development for brain growth and cognitive functioning associated not only with their specific array of manipulative foraging skills, but also with their social behavior repertoires. Increasing data sets support the hypothesis that a long period of maturation in primates who live in large, complex social environments is linked to the time needed to gain sufficient social competency to be successful adults (Janson and Boinski 1992; Janson and van Schaik 1993; Joffe 1997; Stone 2007). Complex behavioral repertoires and slower rates of early development have been documented in several New World monkey species (Harvey and Clutton-Brock 1985; Harvey et al. 1987), and Schmitt (2010) found social behavior, rather than ecological constraints, to be more directly correlated with differences in life history patterns in wild spider monkeys (*Ateles*) and woolly monkeys (*Lagothrix*).

Hypotheses for the acquisition of both foraging and social skills need not be mutually exclusive. A DST framework focuses on the integrated system of developmental facets across an individual's lifetime, as well as across generations (Gray 2001; Oyama 1985), and in this way, impacts on development are seen as dynamic and interrelated, with ontogeny initiated and sustained by multiple influences. The central theme of extended inheritance in DST illustrates how epigenetic and social aspects of the developmental milieu (not just genes) are also transferred between generations (Griffiths and Gray 2005; Robert et al. 2001). Influence on development is thus shared by multiple factors that act together to construct a new individual with both robust and plastic traits. A compelling example of this scenario is provided by the strong physiological and emotional bonds between a primate mother and her offspring for a significant portion of their respective lives: each brings to the relationship a set of inherited traits for the other, providing epigenetic factors that are as consistent as genes, and just as important for influencing ontogeny. Weaver and de Waal (2002) found that an infant capuchin's relationship with its mother is related

to and predictive of temperament differences when the individual is older. This illustrates a DST feedback system among aspects of the social context (patterns of behavioral interactions, or the relationship quality between individuals) and the individual's temperament formation which will then go on to influence its own social interactions as an adult. Behavioral flexibility allows the young primate to maximize its opportunities for learning in a social context by affording it the ability to choose from a multitude of optional pathways (Reader and MacDonald 2003; see MacKinnon 2011). For example, in times of stress an independent infant might return to its mother or seek out an older juvenile or another adult in the group. Each of these scenarios can work to strengthen the particular interindividual bond; this can in turn feed back into and reinforce social roles in a future context. The youngster might receive support from an adult male s/he spent previous time with and with whom a familiar history has been established.

Related to this behavioral flexibility on a broad scale, capuchins have also demonstrated a rich array of learned traditions convergent with those described in some macaque and chimpanzee societies (e.g., Boesch 1996; McGrew et al. 2001; Nakamura 2002; Nakamura et al. 2000; Tanaka 1995; Whiten et al. 1999; and see Caldwell and Whiten 2011). For example, Perry and colleagues have documented a remarkable range of variable social conventions across several *C. capucinus* sites in Costa Rica (Perry et al. 2003a, b). In an examination of a 19,000-h combined data set collected on 13 social groups at four study sites over a 13-year period, five behavior patterns qualified as social traditions according to the study's criteria. These included strange idiosyncratic behaviors such as the sucking of body parts and hand-sniffing in social contexts, as well as three types of "games." Some conventions were virtually identical at multiple sites and appear to have been independently invented and then passed on; the documented behaviors rarely lasted longer than 10 years. Perry et al. (2003a, b) hypothesize that capuchins use these group-specific social conventions to test the quality of social relationships. These phenomena are especially important in an evolutionary context, as new behaviors and traditions can shift the social (and sometimes physical) conditions in which animals live and differentially reproduce, thus affecting patterns seen in subsequent generations (see Jablonka and Lamb 2005; Odling-Smee et al. 2003).

Finally, framing development as operating along a linear pathway results in reductionist explanations for what is in reality a dynamic, complex system (e.g., Wallen 1996). For example, the accumulation of age-specific social skills in young primates has traditionally been portrayed as a direct outcome of the steady acquisition of sequential skill sets. However, development is now better understood as an emergent property of feedback interplays among various physiological and social influences throughout the life course, often with periods of stasis and/or regression as crucial components (Heimann 2003; MacKinnon and Fuentes 2012; Sadurní and Rostan 2003; van de Rijt-Plooij and Plooij 1992). With the documented variation across genera, species, and individuals, capuchins provide us many insights into this system; DST is a particularly useful set of explanations for how phenomena such as plasticity and flexibility evolve and are maintained in a species.

17.6 Conclusion

Data from capuchins are useful when examining social ontogeny due to their extended life history stages for such a small-bodied primate. Similar to humans, capuchins undergo rapid brain growth in the first few years of life. These large brains coupled with delayed maturation, complex foraging traditions, and elaborate social behavior repertoires (including learned conventions and traditions) provide fascinating clues to the evolution of sociality as well as illustrating the phenotypic plasticity and behavioral variability characteristic of a long-lived primate. A key component of such a dynamic nonlinear system is that the sources of the developmental continuum cannot be reduced into the separate and distinct categories of “gene” and “environment”—rather it is the interplay among such factors that produces ontogeny. The process of development becomes the central focus.

The contributions of DST for contextualizing development do not fall along the lines of generating specific hypotheses to test. Rather, viewed as more of an umbrella structure over a collection of central tenets, DST forces us to fundamentally re-frame our questions and view ontogeny as the result of complex interplays among various components across a temporal landscape, resulting in multi-leveled developmental systems.

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Part VI
Transitions to Juvenility
and Reproductive Maturity

Chapter 18

Identifying Proximate and Ultimate Causation in the Development of Primate Sex-Typed Social Behavior

Stephanie L. Meredith

Keywords Development • Sex differences • Socialization • *Lemur catta*
• Comparative method

18.1 Introduction

Much like adult body size dimorphism (Leigh 1992; Leigh and Terranova 1998; O'Mara et al. 2012), the diversity of sex differences in social behavior that characterize adult primates must develop during the postnatal period because primate infants are only subtly sexually differentiated in behavior at birth (e.g., *Chlorocebus aethiops*, Lee 1984; *Papio anubis*, Bentley-Condit 2003; *Papio cynocephalus*, Nguyen et al. 2010, 2012). To the extent that adult sex-typed social behaviors are an important element of adult behavioral competence and to the extent that adult behavioral competence translates into reproductive success, the proximate mechanisms underlying the development of sex-typed social behaviors will be targets of selection. Understanding how those proximate mechanisms function to produce sex-typed adult social behaviors will clarify the adaptive nature of adult sex roles by yielding insight into the factors that influence and/or constrain their development (Beaupre et al. 1998; Duvall and Beaupre 1998).

We know from experimental research that social, ecological, and endocrinological experience (and their interactions) may all be important for the development of sex-typed social behavior, but we don't know which of those elements *actually* shapes sex-typed behavioral development in naturally occurring populations and in

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what ways. Compared to our understanding of primate development in captivity, little is known about the developmental processes that drive sex-typed behavioral development in the wild. This chapter explores the available evidence for social, physiological, and ecological drivers of the development of sex-typed social behavior in wild-living primates and highlights areas in need of increased research, emphasizing the strengths of the comparative method in maximizing the incisiveness of individual studies. Throughout, an infant is defined as an unweaned individual; a juvenile is a prepubescent, weaned individual; an adolescent is a peripubescent or postpubescent individual who has not achieved full adult size or first reproduction; and an adult is a sexually mature individual (Altmann and Pereira 1985). The term subadult refers collectively to infants, juveniles, and adolescents.

18.2 Adult Sex Differences in Wild Primates

Numerous and varied sex differences have been documented in wild adult primates in social behavior, resource use, and endocrine profiles. Socially, adults of some species exhibit sex differences in aggressive behavior (*Cercopithecus mitis*, Cords et al. 2010), dominance, overt sociability (*Alouatta palliata*, Clarke 1990; *Brachyteles arachnoides*, Strier 2002; *C. mitis stuhlmanni*, Cords et al. 2010), social network diversity (*A. palliata*; Clarke 1990), and three-dimensional spacing (*Cebus olivaceus*, Robinson 1981; *C. mitis stuhlmanni*, Ekernas and Cords 2007). Ecologically, adults exhibit sex differences in reliance on certain shared food sources (*Cebus capucinus*, Rose 1994; *Cebus nigrinus*, Agostini and Visalberghi 2005; *Cercocebus atys*, McGraw et al. 2010; *C. aethiops*, Harrison 1983; *C. aethiops* and *Erythrocebus patas*, Nakagawa 2000; *Lemur catta*, O'Mara 2012; *Macaca fascicularis*, van Noordwijk et al. 1993), daily and/or annual time budgeting of foraging (*C. aethiops*, Baldellou and Adan 1997; Harrison 1983; Nakagawa 2000), three-dimensional spacing specifically during foraging, (*C. nigrinus*, Agostini and Visalberghi 2005; *C. olivaceus*, Robinson 1981; *L. catta*, O'Mara 2012), reliance on particular types of foraging behaviors (*C. capucinus*, O'Malley and Fedigan 2005; *Cebus libidinosus*, de A. Moura and Lee 2010; *L. catta*, O'Mara 2012; *Pan troglodytes*, McGrew 1979), and foraging efficiency (*P. troglodytes*; Boesch and Boesch 1981). Hormonally, adults are characterized by sexually differentiated patterns of circulating androgens and estrogens (*C. aethiops*, Whitten and Turner 2009; *Pan paniscus*, Dittami et al. 2008).

Sexually differentiated resource use and endocrine profiles both will influence social behavior. While sex-differential dietary activities may not represent sex-typed social behavior per se, some elements of sexually differentiated ecology (such as sex-segregated spacing during foraging) may induce or constrain the nature of sexually differentiated social behavior. Circulating testosterone has been linked to aggressive behavior involved in male mate guarding and territorial defense in some (*L. catta*, Gould and Ziegler 2007; *P. troglodytes*, Muller and Wrangham 2004) but not all primate species (*Eulemur fulvus rufus*, Ostner et al. 2008). In females of

some species, circulating levels of testosterone are correlated with individual rates of aggressive behavior and dominance rank (*P. anubis* × *hamadryas*; Beehner et al. 2005). And adult female circulating levels of estradiol and progesterone are reliably associated with behavioral estrus and gestational state (*E. fulvus rufus*, Ostner and Heistermann 2003; *P. cynocephalus*, Beehner et al. 2006; Stavisky et al. 1995; *Propithecus verreauxi*, Brockman and Whitten 1996).

By adolescence, some behavioral sex differences are most likely motivated and maintained by the activational effects of gonadal hormones (reviewed in Wallen 2005) and, in sexually dimorphic species, by sexually differentiated energetic costs (*C. capucinus*, Rose 1994), predation risk (*C. capucinus*, Rose 1994), substrate use (*C. capucinus*, Rose 1994; *C. nigritus*, Agostini and Visalberghi 2005), and food resource accessibility (*C. capucinus*; O'Malley and Fedigan 2005; Rose 1994) that result from sex differences in body size. Preadolescent behavioral sex differences, though, are not likely explained either by the activational actions of pubertal hormones or by sexually dimorphic nutritional demands resulting from body size dimorphism. Available data suggests that gonadal hormones are not in production until puberty (reviewed in Wallen 2005), and substantial sex differences in body size do not emerge until the beginning of the pubertal growth spurt (*P. cynocephalus*, Altmann and Alberts 1987; *Papio ursinus*, Johnson 2003; *P. troglodytes*, Pusey 1990). A number of sex differences in primate juvenile social behavior and feeding ecology do emerge prior to sex differences in body size and hormonal maturation, implicating proximate drivers other than body size dimorphism and gonadal hormone surges in the development of those behaviors.

Due to the interactions of social behavior, ecology, and individual endocrinology, any consideration of sex-typed social development must also consider sex-typed ecological and hormonal development. Fortunately, this endeavor is synergistic, as the mechanisms underlying development in other domains may also apply directly to social development. For example, infant primates must eventually acquire adult diets at some point in their behavioral development (Lonsdorf 2012; Mackinnon 2012), and the mechanisms by which they do so may lend clues as to how the development of social behavior is accomplished.

18.3 Evidence for Proximate Causes of Sex-Typed Development from Captivity

Studies of captive primates demonstrate that sexually differentiated behavioral trajectories emerge from and are maintained by complex, interactive systems of extrinsic and intrinsic proximate factors. Research in this area has mainly targeted the outcomes of manipulating specific elements of social and hormonal experience and has clinched the importance of each in shaping primate developmental trajectories (e.g., Bentley-Condit 2003; Brown and Dixson 1999; Capitanio 1984; Chamove et al. 1967; Champoux et al. 1989; Deputte and Goy 1991; Eisler et al. 1993; Goldfoot 1977; Goy and Phoenix 1971; Harlow 1962; Herman et al. 2003;

Mondragón-Ceballos et al. 2010; Pasterski et al. 2005; Pomerantz et al. 1986; Thornton et al. 2009; Tomaszycski et al. 2001; Wallen and Hassett 2009).

In addition to demonstrating the importance of the rearing environment in shaping developmental outcomes in general (*Macaca mulatta*, Capitanio 1984; Champoux et al. 1991; Harlow 1965; Maestripieri 2005; Mason 1978; McCormack et al. 2006; *Macaca radiata*, Andrews and Rosenblum 1991; Rosenblum and Paullly 1984; *P. troglodytes*, Bard and Gardner 1996), captive work has shown that socially complex and/or less stressful environments result in more competent sexual behavior (*M. mulatta*, Capitanio 1984; Champoux et al. 1991; Goldfoot 1977; Goy and Wallen 1979; Mason 1978; Wallen 1996; Wallen et al. 1977, 1981) and more sex-typical play (*M. mulatta*; Wallen 1996, 2005). Some of these early environmental perturbations have been outside the range of variation that primates in wild-living populations are likely to experience (Schino et al. 2001). But even variation in social experience during captive rearing that mirrors variation expected or observed in the wild has short-term effects on important developmental behaviors related to environmental exploration (*M. mulatta*; Sackett 1972) and maintenance of mother–infant contact (*M. mulatta*; Suomi 1987), as well as long-term effects on fitness-related behaviors such as infant care (*M. mulatta*; Maestripieri 2005) and social dominance (*M. radiata*; Andrews and Rosenblum 1991). In sum, the early social environment plays an important role in structuring individuals' behavioral repertoires, and these effects can be lifelong (*P. troglodytes*; Bard and Gardner 1996; Meredith and Fritz 2005).

Endocrinological experience is a key driver of sex differentiation in social behavior through its organizational and activational effects (Becker 2009; Phoenix et al. 1959; Schulz et al. 2009). In primates, prenatal and neonatal androgenic hormones influence the development of sex-typed play behavior and sexual behavior in both males and females (Smith et al. 2012, *M. mulatta*; Thornton and Goy 1986; Wallen 1996, 2001; Wallen et al. 1991). Pubertal and postpubertal androgens and estrogens activate and shape the expression of sex-typed aggression, sexual behavior, and infant interest (*Callithrix jacchus*, Dixson 1993; *L. catta*, Cavigelli and Pereira 2000; *P. troglodytes*, Anestis 2006; *M. mulatta*, Dixson and Nevison 1997; Maestripieri and Zehr 1998; Wallen 2001).

Social and hormonal factors also interact to shape sex-typed behavioral outcomes (reviewed in Wallen 2005). Even behaviors that are largely organized and activated by hormones depend on the social environment to facilitate their expression by providing appropriate behavioral experience. For example, appropriate sex-typed mating behavior does not develop in physiologically normal individuals unless they are reared in a social environment that is appropriate for expressing and shaping it. Rhesus macaques (*M. mulatta*) gonadectomized at birth will develop sex-typed mounting behavior if raised in a social environment, whereas intact rhesus monkeys raised without access to peers will not (Goy and Wallen 1979; Harlow 1965; Wallen 1996, 2005; Wallen et al. 1981).

Although it is well established that social and physiological experience and their interactions shape the development of later sex-typed social behavior, it is still uncertain which particular elements of early social experience underlie the

development of specific adult sex-typed behaviors in natural developmental conditions. Additionally, it is unknown how the ecological developmental domain influences the social and hormonal, and vice versa.

18.4 Importance of Research on Proximate Causation on Wild-Living Primates

The captive experimental approach to disentangling primate developmental complexity has made great strides in elucidating the primate developmental system, but comparative study of development in wild populations has a substantial and largely untapped potential to yield insight into the processes that drive sex-typed development. The study of wild populations examines behavioral sex differentiation under conditions of species and sex-typical ecology and can consider its importance directly (Altmann and Alberts 1987). This advantage cannot be overstated—captive research has confirmed that ecological stress can affect the social milieu in ways that affect infants' attachment to their mothers (*M. radiata*; Andrews and Rosenblum 1991) and, later, their stress hormone profiles (*M. radiata*; Rosenblum et al. 1994), social competence, and dominance (*M. radiata*; Andrews and Rosenblum 1994). Intraspecific comparisons of males and females from natural populations produce results that are relevant to understanding developmental processes as they play out in complex socioecological environments that, hopefully, resemble the environments of selection that produced and/or maintain those developmental processes. Interspecific comparisons of male and female development in the wild and intraspecific comparisons of male and female development across captive and wild settings can leverage the knowledge gained by individual studies in the wild to further elucidate general patterns of proximate causation in primate sex-typed development. Additionally, interspecific comparative approaches are uniquely suited to revealing the evolutionary history of primate sex-typed behavioral development (Nunn 2011) and, therefore, to producing data relevant to evaluating hypotheses about the adaptive nature of particular processes and outcomes of sexual differentiation.

18.4.1 Social Behavior

Only a few infant sex differences in social behavior have been reported, despite having been at least a partial focus of a number of studies in the wild (Barthold et al. 2009; Cords et al. 2010; Förster and Cords 2002; Gould 1990; Meredith 2012; Nash 1978; O'Mara 2012). Both blue monkey (*C. mitis stuhlmanni*) and olive baboon (*P. anubis*) male infants play longer and rougher than their female peers (Förster and Cords 2005; Owens 1975). Female vervet monkey (*C. aethiops*) infants tend to

exhibit more independence from their mothers at earlier ages (Lee 1984). Female mantled howling monkey (*A. palliata*) infants react more positively to social interactions initiated by non-maternal group members than male infants do (Clarke 1990). And newborn male yellow baboon (*P. cynocephalus*) infants initiate more changes in contact with their mothers than female infants (Nguyen et al. 2012). However, sex differences have not been found in the social behavior of infant red-fronted brown lemurs (*E. fulvus rufus*; Barthold et al. 2009), ring-tailed lemurs (*L. catta*; Gould 1990; Meredith 2012), or young blue monkey infants under the age of 6 months (Förster and Cords 2005).

Like the pattern of sex differences in social behavior exhibited by infants, sex-differential treatment of infants by others is also subtle in wild populations. Among common marmosets (*C. jacchus*), female twin pairs are carried more by fathers than male or mixed-sex twin pairs (Yamamoto et al. 2008). Mantled howling monkey infant females are engaged in social interactions with more group members than are male infants (Clarke 1990). High-ranking vervet monkey mothers tend to reject their infant daughters more often than their infant sons (Lee 1984). And in yellow baboons, mothers with more experience seem to promote their sons' independence more strongly than their daughters' via reduced infant carrying (Samuels and Altmann 1992), and infant sons are buffered from the effects of maternal rank on suckling time that female infants experience (Nguyen et al. 2012).

Mothers (and sometimes fathers) may tailor the amount and nature of their investment to foster the sexually differentiated social and somatic developmental trajectories that will increase the likelihood of their offsprings' eventual reproductive success. Decreased rates of infant carrying and more changes in infant contact are thought to promote infant independence (Schino et al. 2001), which may in turn promote the earlier acquisition of social and ecological competence. This is an important potential impact—at least in female yellow baboons, foraging efficacy as a yearling (with respect to protein and energy intake) has been shown to reliably predict the probability of surviving to adulthood, fertility, and reproductive lifespan (Altmann 1991). The apparent maternal bias toward encouraging the independence of sons more than daughters in this species and the apparent maintenance of suckling rates for sons (despite mechanisms that reduce them in daughters when mothers are high ranking) could reflect the much greater potential impact that increased caloric intake has on subadult male growth rates and maturational schedules as compared to those of subadult females (Altmann and Alberts 2005). Alternatively, some of these sex-differential interactions could be initiated by the infants themselves—for example, other group members may find female howling monkey infants more attractive because they react more positively to social interactions initiated by others than do male infants (Clarke 1990).

In contrast to the early infant period, sex differences in social behavior during juvenility are fairly common and robust in the wild. Juvenile females show more interest in infants than their male peers in many species (*A. palliata*, Clarke et al. 1998; *Alouatta seniculus*, Crockett and Pope 2002; *C. mitis stuhlmanni*, Cords et al. 2010; Förster and Cords 2005; *L. catta*, Meredith 2012; *P. ursinus*, Cheney 1978). As with infants, when sex differences in play are found, males play more frequently and

more intensely than females (*C. mitis stuhlmanni*, Förster and Cords 2005; *P. anubis*, Nash 1978; Owens 1975). Juveniles of many species preferentially associate and interact with same-sex partners (*A. seniculus*, Crockett and Pope 2002; *Ateles geoffroyi*, Milton 2002; *L. catta*, Meredith 2012; *M. fascicularis*, Van Noordwijk et al. 1993; *P. cynocephalus*, Pereira 1988; *P. ursinus*, Cheney 1978), although the intensity of those social associations varies by species and the pattern is not ubiquitous. Muriqui (*B. arachnoides*) juveniles associate preferentially with opposite-sex individuals up until older juvenile males shift their association preferences toward adult males (Strier 2002), and blue monkey (*C. mitis stuhlmanni*) and Hanuman langur (*Semnopithecus entellus*) juveniles of both sexes prefer female grooming partners over males (Cords 2000; Nikolei and Borries 1997). Several species also exhibit sex differences in the diversity of their social partners that are adultlike in nature. For example, juvenile female blue monkeys and Hanuman langurs are more sociable than their male counterparts in a number of measures of sociality (Cords et al. 2010; Ekernas and Cords 2007; Nikolei and Borries 1997). Similarly, male juvenile chimpanzees (*P. troglodytes*) direct their grooming attention toward all age-sex classes, while juvenile females restrict their grooming attention to their mothers and siblings (Pusey 1983). In some species, though, juvenile sex differences remain subtle, as in mantled howling monkeys, which exhibit no detectable sex differences in social time budgets or proximity to other age/sex classes except that juvenile males spend more time in proximity to adult males than juvenile females do (Clarke et al. 2007).

Subadults (who have the most to gain from their successful development) are expected to be active participants in shaping their own developmental trajectories, and their choices of social partners are expected to maximize current and/or future benefit (Cords et al. 2010; Pereira 1988). For male yellow baboons, coalitionary support from other males is important for the acquisition and maintenance of male dominance and/or access to females (van Schaik et al. 2004), which is, in turn, closely tied to male reproductive success (Schülke et al. 2010). As might be expected, juvenile male yellow baboons put more effort into maintaining proximity to adult males than do juvenile females. For females, which are philopatric, resident females will be lifelong social partners, while males will come and go. Accordingly, juvenile females put more effort into maintaining proximity to unrelated adult females than do juvenile males. Among unrelated adult females, juvenile females prefer lactating females as social partners. Lactating individuals provide the possibility of interacting with their infants. Infants are attractive to females of most species probably because female primates have long been under selection to respond to infants because doing so makes them better mothers (Silk 1999). Additionally, for females, relationships with higher-ranking females are likely to be of more current and future benefit than relationships with lower-ranking ones; as expected, among unrelated females, juvenile females prefer adult females from high-ranking matrilineal lines as social partners. Males, though, rise above all females in dominance rank when they surpass females in physical size (Pereira 1995), so the rank of their female social partners is likely to be much less important than the reproductive status of those partners; juvenile males thus prefer cycling females and are indifferent to female rank.

Regardless of the motivation underlying juvenile sex differentiation in social space, when it occurs, it will almost certainly drive sex differentiation in other social behaviors. Preferential social association with same-sex behavioral role models will facilitate social learning of other sex-typed behaviors through mechanisms such as imitation or goal emulation (Hoppitt and Laland 2008; Lonsdorf 2005) and may also constrain the expression of particular behaviors in sex-typed ways.

18.4.2 *Foraging Behavior and Diet*

Studies focusing on the development of sex-typed foraging behavior in the wild are few, but they illustrate that some sex-typed foraging behaviors probably depend on social learning for their development, while others rely on some other proximate cause. Juvenile wedge-capped capuchins (*C. olivaceus*) (Robinson 1981) and long-tailed macaques (*M. fascicularis*) (Van Noordwijk et al. 1993) exhibit some elements of adult, sex-typed foraging behaviors, and they also associate preferentially with same-sex individuals. While particular types of social learning in these species have yet to be identified, social learning of any type (Lonsdorf 2005, 2012) would be facilitated by sex-segregated spacing during foraging. A number of sex differences in the foraging behavior of juvenile male tufted capuchins (*Cebus apella*) are correlated with social measures in ways that are consistent with their acquisition via social learning (Agostini and Visalberghi 2005). Juvenile males preferentially associate with and direct their attention toward the feeding of same-sex adults, and the amount of time juvenile males spend in association with adult males is positively correlated with their targeting of animal prey. The authors suggest that especially complex sex-typed foraging behaviors, such as the extractive foraging habits characteristic of male capuchins, may require some type of social learning and that the acquisition of complex sex-typed foraging behaviors may be facilitated by preferential association with and attention to same-sex adults. In the same vein, Lonsdorf (2012) demonstrated that juvenile female chimpanzees spend more time than males watching their mothers termite fish (Lonsdorf 2004) and ultimately imitate their mothers' termite fishing techniques, while juvenile males do not and ultimately become less proficient termite fishers than females (Lonsdorf 2005).

While some primate sex-typed foraging behaviors depend on social input for their development, not all do. The amount of time juvenile tufted capuchin males spend in association with adult males is not correlated with male-typical foraging characteristics other than their targeting of animal prey, such as microhabitat foraging preference. And juvenile females neither preferentially associate with nor direct attention toward the feeding of same-sex adults (Agostini and Visalberghi 2005). Agostini and Visalberghi (2005) suggest that simple foraging behaviors arise independently and do not rely on any kind of social learning for their development. As with sex-typed social behavior, Milton (2002) reports that black-handed spider monkeys (*A. Geoffroyi*) who survived initial release onto Barro Colorado Island as

subadults went on to develop species-typical diets without adult role models. And in some species, such as vervet monkeys, the sex differences in adult diet and foraging schedules are not found in juveniles at all (Harrison 1983), suggesting that they are related to the constraints of adult activities, nutritional requirements, or social relationships and do not rely on learning for their development.

As this field of study progresses, intraspecific observational comparisons will continue to reveal the specific processes that canalize particular types of foraging behavior, generating clues about how sex differences in other domains might be motivated. Where different elements of foraging behavior are driven by different developmental mechanisms, they may have evolved in response to distinct selection pressures and are likely to have had different evolutionary histories. Data from wild primate populations are best suited to further elucidating these issues.

18.4.3 *Hormones*

Data on hormonal development in wild primates are still rare but are increasingly becoming a focus of investigation (Beehner et al. 2009; Gesquiere et al. 2005; Seraphin et al. 2008; Whitten and Turner 2009). In yellow baboons, late gestational maternal fecal estrogen and testosterone concentrations are significantly higher when carrying male fetuses than female fetuses (Altmann et al. 2004). Neonatal males and females are characterized by high and rapidly declining levels of fecal testosterone and estrogen, respectively, which remain low through juvenility and increase again during the months just before testicular enlargement and menarche (Gesquiere et al. 2005). As expected based on captive research on endocrinological development, testosterone levels increase as individuals approach sexual maturity in male chimpanzees (Seraphin et al. 2008), vervet monkeys (Whitten and Turner 2009), yellow baboons, chacma baboons (*P. ursinus*), and geladas (*Theropithecus gelada*) (Beehner et al. 2009).

Despite the relative rarity of information on hormonal development in wild primates, some studies have been able to draw inferences about social factors that may shape sexually differentiated hormonal development. Maternal dominance rank during pregnancy and shortly after birth may influence the development of offspring endocrine profiles in yellow baboons. Maternal rank at the time of a male's conception accounted for 42% of variance in adolescent male fecal glucocorticoid concentrations in the 20 months prior to their natal dispersal, when sons of high-ranking mothers had lower fecal glucocorticoid levels than sons of low-ranking mothers (Onyango et al. 2008). Onyango et al. (2008) suggest that this could be selectively important because chronically elevated levels of glucocorticoids are associated with stress-related disease pathology. However, maternal rank at conception was not associated with sons' fecal glucocorticoid concentrations during other times in the subadult period (Gesquiere et al. 2005). Perhaps maternal effects on sons' stress physiologies are only detectable during the developmental stage when sons are

gearing up for natal dispersal—which will likely be their most costly life history event (Alberts and Altmann 1995)—and, over the subadult period in general, underlying maternal effects on sons' stress physiology are attenuated by other factors.

If, among other social factors, mother–infant interactions are somehow involved in shaping the development of offspring endocrine profiles, maternal physiology may be involved in modulating those mother–infant interactions. Late gestational fecal glucocorticoids in yellow baboons are positively correlated with maternal responsiveness to infants (Nguyen et al. 2008), and prenatal fecal estrogen concentrations and maternal rank are negatively correlated with suckling time in infant daughters (Nguyen et al. 2010, 2012), suggesting that hormonal modulation of some characteristics of the mother–infant relationship does occur. Late gestational fecal estrogen and testosterone concentrations in multiparous females are significantly higher when the fetus is male versus when the fetus is female (Altmann et al. 2004), suggesting that fetal sex may shape maternal hormone profiles in different ways, which may in turn influence maternal behavior toward infants in ways that vary according to infant sex. In other words, sexually differentiated mother–infant interactions begin before birth and may be initiated by the fetus (Nguyen et al. 2010). In contrast to the patterns seen with daughters, suckling time for sons is not influenced by prenatal estrogen concentrations (Nguyen et al. 2010, 2012), indicating that the relationships among fetal sex, maternal gestational physiology, and maternal–infant interaction are not straightforward, much like the hormonal influences on the development of sexual behavior that have been studied in captivity.

18.4.4 Systematic Integration Is Needed

Intraspecific comparative work has documented in wild primate populations all of the factors we expect to shape sex-typed development—sex-typed treatment of subadults by others, sex-typed three-dimensional spacing during feeding and otherwise, sexually differentiated subadult diets, and sexually differentiated prenatal, neonatal, and pubertal hormone profiles. Due to the sample size constraints inherent in studies of subadults, large-scale, holistic attempts to pin down how these myriad factors actually function to shape the development of adult sex-typed behaviors within species are still largely absent. There is limited, but clear, evidence that the development of some sex-typed foraging behaviors depends on social modeling of adults by juveniles. Research on sexually differentiated development in yellow baboons at Amboseli has made impressive strides toward illuminating the workings of the complex and interactive system of social, ecological, and endocrinological factors that together underpin life histories and social development (at least in this species). Work from this site clearly illustrates the promise of naturalistic observational research that seeks to understand linkages between maternal physiology, offspring physiology, ecology, and behavior in naturally living primates.

The most thorough studies of sexually differentiated development beg a number of interesting questions about causation of the developmental patterns they document.

Some aspect of maternal rank ultimately shapes at least some aspects of offspring endocrine response in baboons, but are sons of high-ranking mothers less stressed because they enjoyed more social support or more access to resources? Or did sons simply inherit their reactivity to major stressors from their mothers? Or did mothers' stress levels during gestation shape their sons' eventual stress reactivity profiles, as occurs in snowshoe hares conceived in high- and low-predation environments (Sheriff et al. 2010)? Naturally occurring variation in the prenatal hormone environment may influence postnatal mother–infant interactions (Nguyen et al. 2010), but is variation in suckling time controlled by infants or mothers or both? Do juvenile female blue monkeys groom more partners (Cords et al. 2010) because they are more often in proximity to more individuals, or are they more often found in proximity to others because they are actively seeking out more grooming partners? And, do these patterns actually depend on social input to shape their development, or are they somehow “preprogrammed” to arise, *de novo*, as suites of correlated sex-typed behaviors in every generation? Milton (2002) reports that black-handed spider monkeys who survived initial release onto Barro Colorado Island as subadults went on to develop species-typical sex-typed behavior and association patterns in the absence of adult role models, suggesting that adult sex-typed social behavior does not rely on behavioral models or social interactions with adults for its development in this species. Fortunately, these studies are ongoing and are constantly making gains in their abilities to infer causation.

A few areas of research still await attention in the wild. The effects of neonatal and early postnatal hormones on later behavior have not yet been investigated. This is probably due to the challenges of collecting biological samples from infants, but gains in this area should help clarify the relationships among maternal and offspring physiology and behavior. Additionally, the effects of ecological variation on hormonal development have not yet been addressed. In general, hormonal development in the wild seems to correspond well with patterns seen in captive primates (*M. mulatta*, Brown and Dixon 1999; *P. cynocephalus*, Castracane et al. 1986; Muehlenbein et al. 2001; *Saguinus oedipus oedipus*, Ginther et al. 2002), but there are still important reasons why these data are needed from wild populations. In many species, adult steroid hormone concentrations of both sexes vary according to ecological and/or social conditions (*E. fulvus rufus*, Ostner et al. 2002, 2008; *L. catta*, Gould and Ziegler 2007; *P. anubis*, Sapolsky 1985, 1986, 1991; *P. anubis* × *hamadryas*, Beehner et al. 2005; *P. cynocephalus*, Gesquiere et al. 2005, 2008, 2010, 2011; *P. verreauxi*, Brockman et al. 2009; *Saguinus mystax*, Huck et al. 2005), and there is substantial and selectively important intra- and interpopulation endocrine variation (*C. aethiops*, Whitten and Turner 2009; *L. catta*, Gould and Ziegler 2007; *P. cynocephalus*, Altmann et al. 2004). It stands to reason that infant and juvenile hormone profiles are also subject to such influences. If so, appropriate interpretation of subadult hormonal development and its behavioral effects requires knowledge of adult and subadult endocrinological variation in the study population.

Although sex differences in infant behavior and treatment by others have rarely been found in wild populations and are not marked when present, their potential

impact on the developmental trajectories of infants should not be underestimated, and they merit continued attention. In captivity, even subtle differences in the social milieu can impact infant development in selectively important ways (*M. radiata*, Andrews and Rosenblum 1994), such that eventual adult behavioral sex differentiation may be rooted in these types of very early sex differences in interactions with mother and others (Nguyen et al. 2012). If subtle differences in social interactions at early ages are important in shaping the development of later sex-typed behavior, early infancy deserves continued research attention even in taxa for which no sex differences have been found (*E. fulvus rufus*, Barthold et al. 2009; *L. catta*, Gould 1990; Meredith 2012). As infant samples are often characterized by small sizes and high dropout due to infant mortality (e.g., Meredith 2012), single studies often lack the statistical power to detect the small effect sizes expected in infants.

18.5 Interspecific Comparison in the Wild

Interspecific developmental comparisons—either in closely related species with divergent adult sex-typed behavior or in distantly related species with striking social similarities—can strengthen the inferential power of single-species investigations. Pereira's (1995) comparison of the development of sex-typed dominance patterns in yellow baboons and ring-tailed lemurs exemplifies this type of analysis. Although it was not limited to wild populations, his detailed comparison of ring-tailed lemur dominance acquisition to that in cercopithecine monkeys raises the question of why ring-tailed lemurs do not intervene in agonistic interventions on behalf of their matrilineal relatives as cercopithecine monkeys reliably do. There is no obvious reason why ring-tailed lemurs would not benefit from “top-down” agonistic intervention” (Pereira 1995); yet, the lack of matrilineal agonistic intervention in lemurs does not seem enigmatic until lemur behavior is compared to the cercopithecine species with which it shares so many other features of social organization and behavior (multi-male, multi-female social structure, promiscuous mating, stable dominance relationships, and matrilocality) (Pereira 1993).

Examining the intraspecific comparative studies in social and foraging behavior outlined above with an eye toward interspecific comparison lends support to some of the conclusions already drawn from intraspecific comparisons. Sex-segregated social association among juvenile primates is a fairly robust interspecific pattern among wild primates. The acquisition of sex-typed behaviors may be facilitated by sex-differential spatial patterning of juveniles (Agostini and Visalberghi 2005; Pereira 1988), which seems to bear similarities to adult spatial patterning in many species. In cases where juveniles choose sex-typed social association patterns, whether sex-typed social behaviors are acquired by social learning or not can be determined by detailed studies such as those by Lonsdorf (2005) and Agostini and Visalberghi (2005).

The interspecific variation in the developmental schedules of sexually differentiated foraging behavior—for example, that it develops before puberty in tufted capuchins (Agostini and Visalberghi 2005) but not in vervets (Harrison 1983)—supports the

conclusion that not all foraging behaviors are canalized by the same proximate mechanisms and that the same foraging behaviors may not be canalized by the same mechanisms in all primate species. The similarities in the types of foraging behaviors that seem to rely on imitation or emulation for their development in both chimpanzees and tufted capuchins—complex, extractive foraging behaviors—support Agostini and Visalberghi's (2005) position that simple foraging behaviors are learned independently and that only complex foraging skills require social input for their acquisition.

There are few datasets yet available to make incisive interspecific comparisons of sex-differential social behavior in the wild. Given the relative completeness of the baboon work already, species that would make good comparative taxa for baboons are efficient research targets. For example, ring-tailed lemurs are a useful comparator for investigating the importance of social and hormonal mechanisms of behavioral development given their important similarities to (enumerated above) and differences from (body size monomorphism, female dominance, and phylogenetic distance) baboons. Furthermore, the Lemur Biology Project at Beza Mahafaly Special Reserve and its associates have been amassing a large dataset on ring-tailed lemur ecology (O'Mara 2012; Sauther et al. 1999), health (Sauther et al. 2002), life history (Gould et al. 2003), social behavior (Gould 1997), and endocrinology (Gould and Ziegler 2007; O'Mara 2008), which is well suited to comprehensive comparisons with the baboon work. An impressive collection of data on the social development of blue monkeys, which have more relaxed dominance hierarchies than baboons (Cords 2000; Cords et al. 2010; Ekernas and Cords 2007; Förster and Cords 2002, 2005), is also promising. Once a sufficient number of taxa are well represented in the literature, interspecific comparative analyses can reveal important correlations among aspects of sex-typed development, phylogeny, and ecology, as well as explicitly test evolutionary hypotheses about primate sex-typed development.

With regard to better understanding the learning mechanisms underlying the acquisition of sex-differential foraging behavior, more focused studies in the vein of Lonsdorf (2005) and Agostini and Visalberghi (2005) should be pursued in both chimpanzees and capuchins, at minimum, which have been shown to possess sex differences in their reliance on complex foraging behaviors. This area of research has promise for understanding the development of sexually differentiated behavior in general because mechanisms for the acquisition of complex foraging behavior may also apply to the acquisition of behavior in the social domain.

18.6 Intraspecific Comparisons Between Wild and Captive Settings

In cases where results from captivity do not accurately characterize wild populations, those differences themselves are another useful comparative dataset that can help to tease apart the proximate drivers of particular elements of behavioral development. For example, scent-marking is a sexually differentiated behavior in adult ring-tailed lemurs. Both sexes scent-mark substrates with secretions from their anogenital glands (Scordato and Drea 2007). But only males typically have

keratinous antebrachial spurs and brachial and antebrachial scent glands (Sauther and Cuzzo 2008), which they use to gouge and deposit brachial and antebrachial secretions onto small tree trunks and branches (Jolly 1966; Scordato and Drea 2007). The developmental timing of these behaviors has been documented in captivity by Palagi et al. (2002) and Pereira (1995, 2002) and in the wild by Meredith (2012) and O'Mara (unpublished data). As in other species (colobines and macaques, Borries et al. 2011; *P. cynocephalus*, Altmann and Alberts 1987; Altmann and Altmann 1981), growth and sexual maturation in ring-tailed lemurs are greatly accelerated in captivity compared to the wild. At the Duke Lemur Center, ring-tailed lemurs are sexually mature by around 18 months of age, and it is common for females to have their first offspring at the age of two (Pereira 1995). At Beza Mahafaly Special Reserve, Madagascar, sexual maturation appears to occur around 26–28 months of age (as assessed by behavioral markers in both sexes and the onset of testicular enlargement in males; Meredith, unpublished data; O'Mara, unpublished data; Pereira 1995), and females have their first offspring at the age of three, at the earliest (Gould et al. 2003).

The developmental trajectories of scent-marking behaviors in captive and wild ring-tailed lemurs are quite different (Fig. 18.1). In wild infants, there is first a period between 3.5 and 6 months of age in which male infants tail play, wrist mark (Gould 1990; Meredith 2012), and even brachial mark at low frequencies (Meredith 2012). Then, all three behaviors disappear from the behavioral repertoire and do not appear again until the age of 13 months, at which point they persist (Meredith 2012). In captive infants, the timing of wrist and brachial marking has not been reported. Tail play appears at 6 months of age and is observed every month thereafter (Palagi et al. 2002). Wrist marking and brachial marking appear at 13 months and continue thereafter (Palagi et al. 2002), coincident with the reappearance of those behaviors in the wild. Anogenital marking appears in both sexes at 16 months in captivity, coincident with sexual maturation (Palagi et al. 2002; Pereira 2002), but not in the wild until 26–28 months (Meredith 2012; O'Mara, unpublished data; Pereira 1995).

If the development of all scent-marking behaviors were driven by the same proximate factor, then they should all vary in the same way between the captive and wild settings—they should either all be accelerated or all be delayed. The observed pattern of variation suggests a more complex story. The fact that the timing of juvenile wrist and brachial marking is invariant across settings, despite drastically different ecological constraints and maturational schedules, suggests that they are not shaped by postnatal environmental cues. Perhaps instead, the juvenile onset of antebrachial and brachial marking is determined by individual prenatal and neonatal hormone physiology, as seems to be the case with the development of male-typical urinary behavior in domestic dogs (Ranson and Beach 1985). In contrast, the fact that the timing of the appearance of anogenital marking, which is coincident with gonadal maturation in captivity, is substantially delayed in the wild suggests that anogenital marking is directly caused by sexual maturation, as has been previously suggested (Pereira 1995, 2002). The early appearance and subsequent disappearance of the

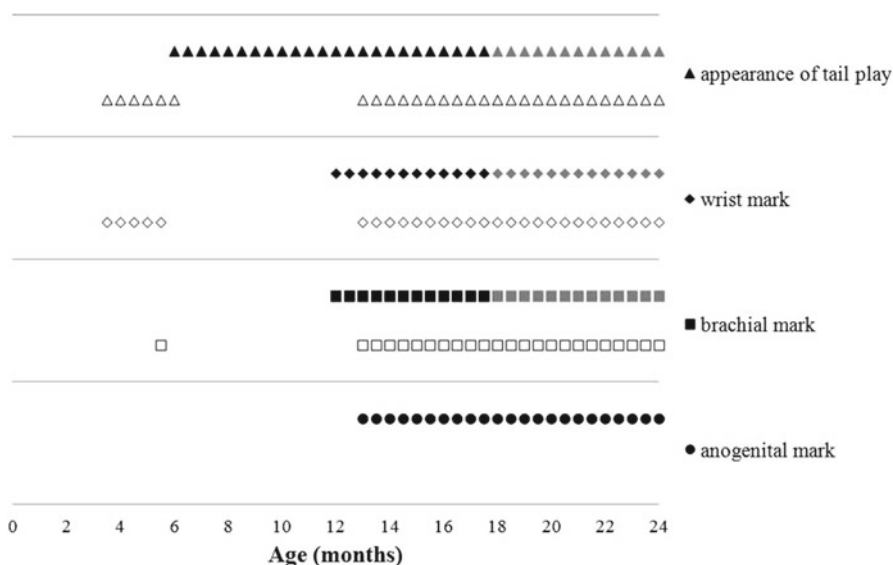


Fig. 18.1 Developmental timing of scent-marking behaviors in captivity (*solid symbols*) and in the wild (*open symbols*). Tail play, wrist mark, and brachial mark data are from Palagi et al. (2002), which observed individuals only through the age of 18 months. As these behaviors are unlikely to have ceased between the ages of 18 and 24 months in captivity, they are presented here in *gray*

suite of brachial and antebrachial marking and tail play in the wild is enigmatic. Perhaps the appearance of these behaviors in infants is socially mediated; if so, it should be correlated with increased rates of marking by adult males or with proximity of infant males to adult males. The initial disappearance of tail play occurs just after the transition from infancy to juvenility (Sauther et al. 1999). Perhaps the disappearance of tail play from the behavioral repertoire of infants is due to a decrease in all types of play due to ecological stress due to the seasonal decline in food availability during this time of the year (Sauther et al. 1999); if so, it should be correlated with increased levels of glucocorticoids in males of that age, decreased rates of play behavior, and/or actual changes in food availability. These hypotheses require additional data for testing and are variably appropriate for further testing in experimental and naturalistic settings, but one thing is clear—the development of anogenital marking is yoked to the pace of somatic growth, while the development of the other elements of scent-marking behavior is not.

The behavioral and well-known somatic developmental variation between wild and captive settings helps to tease apart, exclude, and generate reasonable testable hypotheses about the proximate factors that underlie the development of particular elements of scent-marking behavior in a way that an exclusive focus on either one or the other would not. Future research can easily incorporate more of this approach, which would extend the inferential reach of observational studies in the wild.

18.7 Conclusion

Sex-typed social and ecological behavior is not acquired as a single behavioral suite; instead, individual sex-typed behaviors depend on different causal factors for their development, suggesting that they may have resulted from different selective pressures. Studies of wild primates have identified several key causal relationships: social and ecological factors that shape individual hormonal profiles; social factors that drive ecological sex differentiation; and social, ecological, and hormonal factors that may drive sexual differentiation in social behavior. These studies also reveal that the relationships among social, ecological, and hormonal developmental factors vary across primate species. This complexity presents substantial challenges to research, but confirms the importance of studying these phenomena in natural populations, because substantial alteration of any system component will affect the relationships among all others in unknown ways, and no other method can definitively capture developmental processes as they occur in complex, evolutionarily relevant socioecological environments.

There are still large and important gaps in the dataset on wild primate development that need to be filled before we are positioned to understand the proximate and ultimate causes of primate sex-typed development from a holistic standpoint. We are just beginning to unravel the complex developmental processes that tie an individual primate's gestation, infancy, and juvenility to its adult behavioral outcomes and to discover how male and female subadults make choices that help them maximize the benefits and minimize the challenges of their circumstances. Once these processes are understood across a range of primate species, interspecific comparisons can be used to infer the polarity of primate sex-typed behavioral characters and of the proximate mechanisms that drive them, as well as to pinpoint processes and outcomes of sexual differentiation that are likely to represent adaptations to particular environmental and/or social circumstances.

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Chapter 19

Future Adults or Old Children? Integrating Life History Frameworks for Understanding Primate Positional Patterns

Michelle Bezanson and Mary Ellen Morbeck

Keywords Positional behavior • Ontogeny • Life history • Posture • Locomotion

19.1 Introduction

Positional behavior is a measurable and observable link between the functional morphology/physiology and behavior of an animal in its environment. Locomotion, posture, and the morphology that allows movement abilities and expressed behaviors throughout the life stages interact with every aspect of an individual primate's life and are important life history characteristics. Locomotion and posture in adults relate to survival and maintenance, thus allowing for reproduction, whereas in infants and juveniles, positional behavior is essential to survival and *growth* to reproductive maturity. The timing of life stages and biobehavioral strategies for survival and reproduction in different species are the products of natural selection. A life history perspective integrates knowledge of evolutionary processes with understanding the multifaceted roles of positional behavior in primates.

Traditionally, primates are characterized by longer gestations, larger neonates, slower growth, lower reproductive rates, later maturation, and longer lives relative to other orders of mammals. However, within primates, there is much variation in the timing/onset of particular life history features (e.g., brain growth, molar eruption, age at first reproduction) (Leigh and Blomquist 2011), and these life history factors potentially impact locomotor patterns in infant, juvenile, and adult primates

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in myriad ways (Morbeck et al. 1979, 1997; Zihlman 1992). Studies of positional behavior in sympatric species have shown that among species, body mass, limb proportions, and other anatomical features (e.g., a prehensile tail) can influence positional patterns in a variety of ways (e.g., Fleagle and Mittermeier 1980; Gebo and Chapman 1995; Bergeson 1996; McGraw 1998a, b; Youlatos 1999). Recently, there is increased focus on how growth and development potentially influence positional patterns within species (Doran 1992, 1997; Fontaine 1994; Wells and Turnquist 2001; Workman and Covert 2005; Wright 2005; Bezanson 2006, 2009; Lawler 2006; Wolf et al. 2011).

How does life history influence locomotion and posture in young primates? And, how can locomotion and posture influence life history? Recent studies stress the importance of theoretical frameworks that integrate ideas about modularity and ecology in evaluations of life history variation. Incorporation of this perspective in conjunction with an increasing database on life history features in free-ranging non-human primates is beginning to provide a better understanding of the interaction of behavioral features (e.g., foraging, positional behavior, social behavior), biological features (e.g., growth, nutrition, physiology), and environmental features (e.g., substrate selection, resource availability, seasonality) in influencing life history variation in individuals, groups, and higher-level organizational categories. The fact that some juvenile primates are similar to their adult counterparts in foraging strategy and positional repertoire, whereas others are not, provides an exciting avenue for explorations of variation in primate life history.

In this chapter, we discuss positional behavior of infants and juveniles using a life history framework. We begin by defining positional behavior and providing a brief background on life history theory. We then review how a life history framework can be used in studies on primate positional behavior and present information from field research on young primates. We focus on variation that characterizes positional development, the contexts with which positional data are interpreted, and conclude with a discussion on the exciting potential for future research in this area.

19.2 Positional Behavior: Integrating Morphology, Behavior, and the Environment

Positional behavior as an interface between morphology and the environment allows interpretation of how selection has operated to influence movement capabilities and expressed behavior. Positional behavior as defined by Prost (1965) is posture and locomotion. Locomotion is "...the displacement of the center of gravity..." while posture is described as an alternative to locomotion, where the body mass remains stationary (Prost 1965: 1200). Implicit in examinations of primate positional behavior are evolutionary and anthropological frameworks. Two fundamental questions underlie field studies of positional behavior. First, are primate positional behaviors and the morphology that underlies positional patterns adaptive? Second, if positional

behavior is adaptive, what possible features of the environment exert influences? The importance of integrative views has been recognized since the first quantitative studies of primate positional behavior (Ripley 1967, 1979; Richard 1970; Rose 1974, 1979; Morbeck 1974, 1977, 1979; Fleagle 1976, 1978; Mendel 1976; Fleagle and Mittermeier 1980, and reviewed in Dagosto and Gebo 1998; Garber 2011).

The study of positional behavior is necessarily integrative as locomotion and posture require interaction with the environment. Bock and von Wahlert (1965) provided a detailed framework for understanding relationships among form/function, biological role, selection, and adaptation. These authors argued for consideration of the form–function complex or a phenotypic analysis of features (i.e., traits, characters) combined with environmental features to understand adaptation from the perspective of the individual. The primary goal of this framework is to understand biological role—or how a given form–function complex is used during ontogeny and adulthood within an environment. While clearer understanding of form–function relationships, biological roles, and positional adaptations in primate positional behavior is a worthwhile goal, we often move between very detailed considerations of anatomical features to describe broad behaviors (e.g., arboreal quadruped) or more fine-grained descriptions of positional behavior to describe broad anatomical features (e.g., mobile shoulder joint) as researching both behavior in the field and anatomical features in the lab is beyond the confines of a discipline, that is, undergoing increased specialization (but see Rawlins 1982; Turnquist and Wells 1994; Wells and Turnquist 2001; Wright 2005; Wunderlich et al. 2011).

Biomechanical analyses in lab settings (e.g., Shapiro and Raichlen 2005; Sockol et al. 2007; Wallace and Demes 2008; Young 2009; Hanna and Schmitt 2011) shed light on the kinematic basis of the behaviors we observe in living primates and therefore the interpretation of fossil primates. In turn, most positional behavior studies integrate a form–function approach as positional modes are defined to reflect the kinematic basis of a given behavior (Hunt et al. 1996; Dagosto and Gebo 1998; Garber 2011). Application of lab biomechanical techniques in field settings is revealing more precise ways that substrate influences postural and locomotor modes (e.g., quadrupedal gait selection) and is allowing more precise comparisons among different age classes, different individuals, and in varying environmental contexts (resource differences, habitat structure, and predator avoidance) (Blanchard and Crompton 2011; Schmitt 2011; Shapiro et al. 2011; Stevens et al. 2011; Wunderlich et al. 2011; Youlatos and Gasc 2011). Thus far, data on ontogenetic patterns of gait have revealed that age-based differences are observed in some species (vervets: Hurov 1982, baboons: Shapiro and Raichlen 2005, 2006, and macaques: Hildebrand 1967; Nakano 1996; Dunbar and Badam 1998). However, the direct influences of relative body size, forelimb use (e.g., manipulation and tool use), prehensile feet, and the arboreal substrate (support diameter, support flexibility, and support predictability) on gait remain unknown (e.g., Vilensky and Larson 1989; Shapiro and Raichlen 2005, 2006; Stevens 2007; Lemelin and Cartmill 2010; Shapiro and Young 2010).

19.2.1 *The Importance of Substrate*

The arboreal or terrestrial substrate mediates movement, foraging strategy, and way of life. The study of positional behavior integrates data on substrate and habitat utilization in order to identify the ecological context of postural and locomotor adaptations (Mendel 1976; Morbeck 1977; Garber 1984). Essential to this context is the importance of understanding how primates negotiate an arboreal environment. The suite of unique primate traits that link to arboreal movement capabilities is fundamental to understanding the evolution of positional adaptations. Negotiating mass distribution in the most terminal portions of the tree during feeding and travel between trees requires critical movement decisions and agility (Prost and Sussman 1969; Grand 1978, 1984). In this regard, smaller and younger primates may encounter larger gaps, use smaller branches, and differ in regard to center of gravity and limb dimensions (Grand 1981; Fleagle 1978; Cartmill 1985; Jungers 1985; Hurov 1991; Cant 1992; Dunbar and Badam 1998). For example, the center of gravity may be more forward (toward the forelimbs) than adults, and this may influence stability (Grand 1984). Larger and older primates may bridge more, climb more, and leap less (Fleagle and Mittermeier 1980; Cartmill 1985) than their smaller counterparts.

19.2.2 *Does Size Matter?*

Several researchers have tested the effects of relative body size on positional behavior and support use in sympatric primate communities (Dagosto 1994; Gebo and Chapman 1995; McGraw 1998a, b; Youlatos 1999; Garber 2011) with varying results. One important question to consider in body size predictions is what it means to be a small (or younger) or a large (or older) primate. Although it is easy to understand how a primate of 0.1 kg may differ in positional strategy than a primate of 9 kg, researchers often are not explicit in the meaning of large or small, and they are often used as relative terms. In addition, the effects of energetics, diet, and strategies for predator avoidance rarely are discussed in this context. Results from studies on sympatric species show that among species, body size alone does not serve as a straightforward predictor of positional strategy (reviewed in Garber 2011) and that the relationships among forest structure, resource use, limb proportions, and distribution of mass in body segments should be examined using a more integrative approach to understand more precise details of the behavior/environment/morphology interface (Gomberg et al. 1979). Gebo and Chapman (1995) examined five sympatric species in Kibale National Park, Uganda. The heaviest species, the western red colobus [*Piliocolobus* (publ. *Colobus*) *badius*, 8.2 kg], was observed to climb during 37% and leap during 16% of feeding locomotor modes. The smallest species observed was the red-tailed monkey (*Cercopithecus ascanius*, 3.0–4.1 kg), and leaping (11%) and climbing (50%) did not follow body size predictions expected for a smaller-bodied species. McGraw's (1998a, b) study of

seven sympatric species at Tai National Park in West Africa revealed similar results. The king colobus (*Colobus polykomos*, 8.3 kg) was observed to leap 14.5% and climb 14.3% of all observations, while Campbell's guenon (*Cercopithecus cambelli*, 2.7 kg) was observed to leap 5.2% and climb 14.5% of all observations. Similarly, the smaller-bodied lesser spot-nosed guenon (*Cercopithecus petaurista*, 2.9 kg) was observed to leap 10.1% and climb 18.8% of all observations, while the larger-bodied western red colobus (8.2 kg) was observed to leap 17.8% and climb 17% of all observations. These results indicate that some sympatric primates do show patterns that fit previously presented body size hypotheses, while others deviate from predictions based on body mass alone. In addition, intraspecific variation (e.g., western red colobus) is important. Currently, it appears that these differences may be related to diet, seasonal availability of resources, or foraging patterns rather than differences in forest structure (Dagosto 1995; Gebo and Chapman 1995; Bergeson 1996; Garber 2011).

19.3 Life History Theory and Positional Behavior

Life history theory (as viewed in this chapter) emphasizes a whole animal, whole life perspective to understand how the life cycle and attributes of that life cycle evolve in concert (Leigh and Morbeck et al. 1979; Altmann 1980; Zihlman 1992; Morbeck 1997; Morbeck et al. 1997; Fedigan 1997; Altmann 1998; Leigh and Blomquist 2011; and Sherrow and MacKinnon 2011). Activities that *promote* survival and reproduction—for example, positional behaviors, diet, and social behavior, are essential to our understanding of life history evolution. A holistic life history framework helps to better understand “what it means” to be an infant, juvenile, and adult in terms of movement capabilities and expressed positional behaviors to understand variation between and within species (Table 19.1). Furthermore, it is becoming increasingly clear that intraspecific variation in life history timing can relate to individual experience, resource availability, and the nature of social relationships (Shea 1990; Morbeck et al. 1997; Altmann 1998; Pereira and Leigh 2003).

A few key studies have emphasized the role of ecological factors such as unpredictable habitats and arboreal lifestyles and how they may influence life history variation (Williams 1966; Austad and Fischer 1992; Janson and van Schaik 1993). Janson and van Schaik (1993) provided an explanation for late maturation age (i.e., long juvenile periods) in primates that focuses on juvenile risks. They suggest that a long juvenile period allows primates to reduce risks of starvation imposed by high rates of intragroup feeding competition. Therefore, juveniles face especially high risks of predation related to small size, low rates of vigilance, and lack of experience in recognizing predators. Juveniles minimize predation risk by foraging in the center of the group, where surrounding group members provide protection. This protection comes at the cost of increased feeding competition, and high levels of feeding competition are especially risky for juveniles because they are less

Table 19.1 Life history traits incorporating ontogenetic features of positional behavior where information is available

Species	Average adult female body mass (kg)	Adult female cranial capacity (cm ³)	Gestation (days)	Independent locomotion/travel (weeks)	Age at weaning (days)/postcanine permanent dentition present at weaning*	Age at first reproduction (AFR) (years)	Age when no significant differences in frequencies of common positional behaviors between juveniles and adults are observed (months)
<i>Lemur catta</i>	2.2	23.4	135	3–4	105–179 M1	2.01–2.63	12
<i>Propithecus verreauxi</i>	2.95	29.7	140	8	180–183 P4 (erupting) M1 M2	3.5	<12
<i>Cebus apella</i>	2.2	63.1	154	5–10	261 M1 (erupting)	5.5	>72
<i>Cebus capucinus</i>	2.54	79.2	157–167	8–10	510–517 n/a	7	6
<i>Cebus olivaceus</i>	2.5	n/a	n/a	n/a	730 n/a	6	<6
<i>Saimiri oerstedii</i>	0.68	23.2	n/a	4	365–456 n/a	2.5	<6
<i>Alouatta caraya</i>	4.3–4.8	47.9	187	7	325 M1 (erupting)	3.71	n/a

<i>Alouatta palliata</i>	5.35	55.4	186	8	325–630 M1	3.99	>24
<i>Macaca mulatta</i>	5.3–8.8	81.3	165	<8	192 None	3–4.5	18
<i>Papio cynocephalus</i>	9.7–13.6	145.5	173	4	365–456 None	5.5	n/a
<i>Gorilla gorilla</i>	71.5	455.6	260	30	1,004 None	10	72
<i>Pan troglodytes</i>	40.3	380	n/a	60	1,702 None	13	60
<i>Pan paniscus</i>	33.2	n/a	240	n/a	1,080	n/a	24

Diet and social behavior also relate to the development of positional behavior. Data in table are from sources listed below and are combined information from captive and free-ranging populations
n/a not available

Information from Altmann (1980), Baldwin and Baldwin (1978), Rawlins (1982), Boinski (1989), Ross (1991), Valenzuela (1992), Doran (1992, 1997), Godfrey et al. (2001), Wells and Turnquist (2001), Kappeler and Pereira (2003), Fragaszy et al. (2004), Wright (2005), Lawler (2006), Bezanson (2009), and Wolf (2011)

*Lacking sub/super script = both upper and lower

efficient foragers. Accordingly, a long juvenile period may allow juveniles to minimize ecological risks and increase chances of surviving to reproductive maturity (Janson and van Schaik 1993).

The risk aversion model is based on a framework that juveniles are less efficient foragers than adults. Several researchers have tested ecological risk aversion, and it appears that some primates fit the predictions while others do not. Research on (*Saimiri sciureus*) indicates that infants were as successful in capturing insects as their adult counterparts by 6 months of age (Stone 2006). Wild young squirrel monkeys exhibited predator-sensitive foraging when compared to adults, but they did not appear to have differential access to food patches or exhibit intraspecific competition for resources (Stone 2006, 2007a, b). Wild wedge-capped capuchin (*Cebus olivaceus*) exhibited a pattern of adultlike manipulative efficiency early during the juvenile period (Fragaszy and Boinski 1995; Wright 2005). Once past infancy, juveniles were as efficient as adults in the amount of fruit and insects ingested and in the way they foraged for insects and fruits (manipulative activities). Additionally, research on captive groups of captive tufted capuchins (*Cebus apella*) showed that long before the weaning process is complete, infants exhibited adultlike dexterous manipulative abilities (Fragaszy and Adams Curtis 1997) but differed from adults in locomotor behaviors while foraging (Wright 2005). White-faced capuchins (*Cebus capucinus*) showed a similar pattern to wedge-capped capuchins (MacKinnon 2006; Bezanson 2009). Young juveniles acquired an adultlike foraging repertoire (with further refinement during ontogeny) early even though they have a relatively prolonged juvenile period. Foraging efficiency, manipulative capabilities, and their development link directly with positional behavior. Young white-faced capuchins and mantled howlers (*Alouatta palliata*) exhibit adultlike feeding success (effort vs intake) at the same developmental stage that they match adults in positional frequency (capuchins = 6 months, howlers ≥ 24 months) (Bezanson 2009). Variation in the genus *Cebus* may be the result of different foraging strategies (wedge-capped capuchins process physically demanding foods), smaller group sizes, smaller ranges, or differences in growth and development (Jungers and Fleagle 1980; Wright 2005; Young et al. 2010; Russo and Young 2011). These results from different primate species suggest that habitat features exert different pressures on growing individuals and that some species may face higher metabolic risks when compared to adults while others do not.

Most data on life history timing in primates are from captive studies as records of free-ranging primate lifeways are too cumbersome for single researchers and relatively short-term field sites (Kappeler and Pereira 2003). However, the database is increasing with data from several longer-term study sites (e.g., Goodall 1986; Altmann 1998; Gould et al. 2003; Cords and Chowdhury 2010; Strier et al. 2010), and shorter-term field studies are providing more precise information on the interactions among life history, foraging, social behavior, and positional behavior in young primates (e.g., Boinski 1989; MacKinnon 2002, 2006, 2012; Jack and Fedigan 2004; Stone 2006; Workman and Covert 2005; Wright 2005; Lawler 2006; Bezanson 2009; Wolf 2011). A life history perspective is necessary to address particular components of primate lifeways as it allows elucidation of the influence

of body size on locomotion; behavioral, morphological, and environmental aspects of infancy, juvenescence, and adulthood; and social, cognitive, and manipulative development.

19.4 Learn to Move... Move to Learn

In most mammals, infancy—the time between birth and weaning—is characterized by dependence on a parent. This period of dependence applies directly to locomotion. In most primates, this dependence is focused solely on the mother. From birth, the infant grips and rides on its mother (dorsal or ventral) as she eats, sleeps, learns, travels, and engages in social interactions with other members of the group. Infants acquire and use energy primarily for growth and development as they move from reliance on mother's milk to chewing solid foods (Milligan 2012; Hinde 2012). At the same time, they shift from having no or few teeth to a functional set of primary dentition with corresponding growth of the mandible and associated muscles of the face and cranium that provide attachment areas for muscles. Similarly, the shift from reliance on clinging to a mother by gripping with hands and feet to independent locomotion is accompanied by allometric growth of the trunk and proximal limb segments. This involves increased size and load bearing as the skeleton becomes more developed. Morphologically, from the perspective of body mass and distribution of body mass in limb segments, primate infants are characterized as having well-developed hands and feet when compared to other mammals (Grand 1977, 1981; Jungers and Fleagle 1980; Turnquist and Wells 1994; Raichlen 2005; Young 2005). During growth, the trunk and other limb muscles increase in mass as forearm and hand muscles decrease in proportion to the total body mass. Greater limb development or adjustment for relatively underdeveloped extensor muscles may confer a locomotor advantage during certain behaviors early in primate (and mammalian) ontogeny in that it allows greater acceleration away from predators (Carrier 1983, 1996; Raichlen 2005; Young 2005). In addition, some primate infants (e.g., capuchins) are reported to have relatively strong bones when compared to older individuals, allowing complex positional behaviors with less chance of injury (Ruff 2003; Young et al. 2010).

Early movement by the infant takes place immediately on the mother and involves moving toward suckling or short excursions on or near the mother. While dependency on the mother for nutrition, protection, and comfort characterizes infancy, locomotor independence occurs relatively early given the length of the juvenile period in primates (e.g., Altmann 1980; Turnquist and Wells 1994; Raichlen 2005; Young 2005; Bezanson 2009). In yellow baboons (*Papio cynocephalus*), infants locomote independently on the ground at 1 month, locomote in trees by the third and fourth month, and by 6 months, move independently in all behavioral contexts (Altmann 1980). Young howlers (*A. palliata*) locomote independently at 5 weeks, and by 11 weeks, 34.4% of all locomotor activities were independent of the mother (Lyall 1996). The infancy life stage is characterized by interrelated life threatening

risks, including falling, predation, low nutrition, low immunity (higher rates of infection), and aggression from other group members (e.g., Altmann 1980, 1998; Goodall 1986). The ability to move quickly and respond via locomotion to risky situations means survival to the next life stage.

Behaviorally, infancy can be considered a period of learning via exploration, play, and observation of a mother's environment. All of these features are mediated by locomotion and posture. Young infants move away from their mother during rest and foraging to touch, taste, and explore their physical and social environment. Play with nonmothers becomes more common over time (6 months in baboons; 3–5 months in chimpanzees) (Altmann 1980; Goodall 1986). As the infant matures, it begins to forage and feed and depend less on its mother for sustenance via milk (Milligan 2012; Hinde 2012). Locomotor modes become more refined and complex, and this can be a time of conflict as the mother prepares her infant for independence by not allowing it to suckle or depend on her for transportation (Altmann 1980, 1998). Nutrition is important because survival is influenced by foraging success associated with locomotor independence during the beginning of the weaning process (Janson and van Schaik 1993; Altmann 1998). Social status may be changing, and as the infant spends increasing proportions of time away from its mother, it loses direct protection from predators and conspecifics.

The juvenile period, or the time between weaning and sexual maturity, is considered to be a stage of phenotypic limbo; individuals are too old to receive complete and direct care from their mother while too young to reproduce (Pagel and Harvey 1993). Juvenile periods are characterized by larger body size, substantial play behavior, continued association with the mother during social behavior, increased locomotor independence, and continued social learning. In some primates, juveniles may continue brief bouts of travel either on the mother or near the mother (e.g., howlers: Bezanson 2006, 2009). Juveniles increase in body mass and locomotor, postural, and manipulative coordination to acquire and expend energy as independent foragers. Secondary incisors and canines and, later, permanent molars emerge with ongoing growth and maturation of the jaws, face, and cranium. Body proportions and skeletal mechanical advantages of joints and body segments generally are more similar to those of adults. Positional and manipulative abilities become more refined as juveniles develop and practice movements and travel longer distances. Bones lengthen and become stronger internally both in terms of cross-sectional dimensions (i.e., geometric properties) and mineralization (i.e., material properties) (Carrier 1983; Currey 2002; Ruff 2003). Size, shapes, and orientation of joints and distances between them allow species-typical movement abilities and expressed behaviors (Morbeck et al. 1997).

Juvenescence is not easy. Observers often view juveniles as imperfect adults, as these young group members move, forage, and compete with conspecifics in a physical and social environment where they seem unaware of adult rules (Fagen 1993; Janson and van Schaik 1993; Joffe 1997). In this regard, juveniles are considered subadults, preadults, miniadults, or individuals who are just not quite there yet. Using this perspective, young primate movement has been considered within a framework of “what it takes to be an adult.” Yet, infants and juveniles are not small

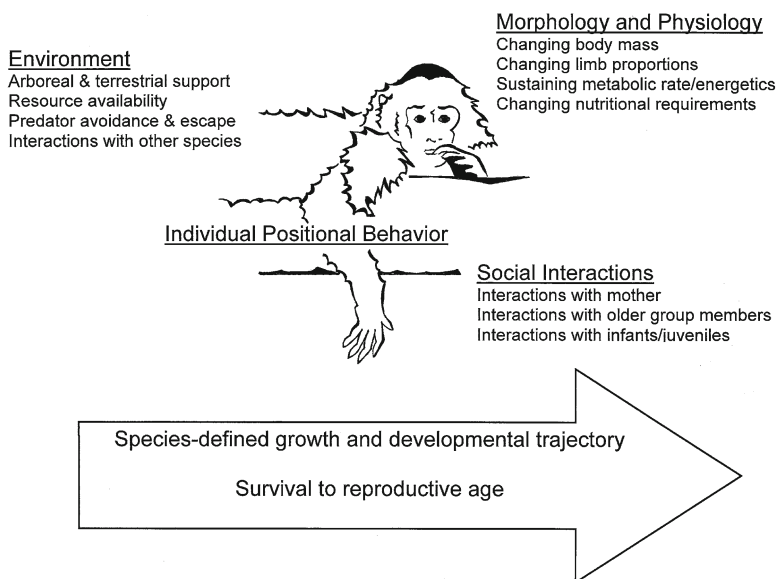


Fig. 19.1 The interaction of morphology/physiology, environment, and behavior in influencing the ontogeny positional behavior in primates

adults. Each set of movement capabilities and expressed behaviors for infants and juveniles reflects species-defined patterns of growth and development that lead to reproductive maturity in the adult life stage (Fig. 19.1).

19.5 What Do We Know About Positional Behavior of the Youngest Individuals?

While attempting to understand adult primate positional behavior has enjoyed a long history (Dagosto and Gebo 1998; Garber 2011), attempting to understand ontogenetic patterns of positional behavior and its biological foundations is a much-needed and relatively recent phenomenon. Field studies of ontogenetic effects on primate positional behavior are rare and have largely focused on older juveniles (Table 19.2) (Doran 1992, 1997; Fontaine 1994; Wells and Turnquist 2001; Workman and Covert 2005; Wright 2005; Bezanson 2006, 2009; Lawler 2006). As of publication, emphasis on infant movement has been presented for few primate species (Crompton 1983; Boinski 1989; Escobar Páramo 1989; Doran 1992, 1997; Lyall 1996; Wells and Turnquist 2001; Wolf et al. 2011). For example, Doran (1997) reports that mountain gorillas (*Gorilla gorilla*) were characterized by developmental shifts from infancy to adulthood that differed in the frequency of quadrupedalism, climbing, and suspensory behaviors. The pattern of positional behavior among younger and older individuals was very similar, while frequencies exhibited marked

Table 19.2 Examinations of ontogenetic patterns on positional behavior

Species	Age comparisons recorded in study	Age when juvenile positional behavior matches adults in frequency of major positional modes	Theoretical framework
<i>Propithecus verreauxi</i> (Lawler 2006; Wolf et al. 2011)	Yearling vs adult 0–2 years	Infancy	Form/function, life history
<i>Lemur catta</i> (Wolf et al. 2011; Wolf 2011)	0–2 years	1 year	Form/function
<i>Cebus apella</i> (Wright 2005)	Juvenile (6 months to 6 years) vs adult	>6 years	Form/function, environment, behavior, morphology
<i>Cebus capucinus</i> (Bezanson 2009)	Infant I (birth to 2 months), infant II (2–6 months), juvenile I (6–12 months), juvenile II (12–36 months) vs adult	<6 months	Life history
<i>Cebus olivaceus</i> (Wright 2005)	Juvenile (6 months to 6 years) vs adult	~6 months	Form/function, environment, behavior, morphology
<i>Saimiri oerstedii</i> (Boinski 1989)	Immature (infants to 1 year) vs mature (1 year to adult)	<6 months	Body mass
<i>Alouatta caraya</i> (Prates and Bicca Marques 2008)	Infant (<1 year), juvenile (F1–3, M1–4), subadult (F3–4/5, M4–5), adult (4/5 years and older)	3–5 years	Body mass

<i>Alouatta palliata</i> (Bezanson 2009)	Infant I (birth to 3 months), infant II (3–6 months), juvenile I (6–12 months), juvenile II (12–24 months) vs adult	>24 months	Life history
<i>Pygathrix nemaeus</i> (Workman and Covert 2005)	Juvenile (8–18 months) vs adult	Not reported	Play, body mass
<i>Trachypithecus delacouri</i> (Workman and Covert 2005)	Juvenile (8–18 months) vs adult	Not reported	Play, body mass
<i>Trachypithecus hatinhensis</i> (Workman and Covert 2005)	Juvenile (8–18 months) vs adult	Not reported	Play, body mass
<i>Macaca mulatta</i> (Wells and Turnquist 2001)	Infant I (birth to 3 months), infant II (3–10 months), juvenile (10–18 months), and adult (> 18 months—includes preadults)	18 months	Form/function
<i>Gorilla gorilla</i> (Doran 1997)	14 categories—exact ages through year 8 and adult males and females	6 years	Body mass
<i>Pan troglodytes</i> (Doran 1992, 1997)	Six categories: three infant categories, juvenile, adolescent, and adult	~5 years	Form/function, body mass
<i>Pan paniscus</i> (Doran 1992)	Four categories: infant, juvenile, adolescent, and adult	~2 years	Form/function

differences when considered within all behavioral contexts. Younger individuals (age 0–23 months) engaged in locomotor modes such as climbing and suspension more frequently than adults, and juveniles closely matched the adult repertoire by 4 years of age. Crompton (1983) examined infant locomotion in the southern lesser galago [*Galago moholi* (publ. *senegalensis*)] and the thick-tailed greater galago [*Otolemur* (publ. *Galago*) *crassicaudatus*]. Smaller-bodied infant (age 45 days) southern lesser galagos exhibited greater differences when compared to adults in the frequency of positional modes and substrate use than did thick-tailed greater galagos. Crompton (1983) reports that these differences likely reflect differential use of the environment and diet rather than differences in body mass.

Primates vary greatly with regard to acquisition of what are considered adultlike behaviors, and in some cases, juveniles appear to exhibit a greater number of positional modes than their adult counterparts. Rhesus macaque (*Macaca mulatta*) juveniles on Cayo Santiago (10–18 months) exhibited more arboreal positional modes (adults: 35% and juveniles: 49.5%) and less quadrupedal walking (adults: 70.85% and juveniles: 31.54%) than adults (Wells and Turnquist 2001). In addition, Dunbar and Badam (1998:543) describe the juvenile period as “the golden age of posture and locomotion” of rhesus macaques, bonnet macaques (*Macaca radiata*), and Hanuman langurs [*Semnopithecus* (publ. *Presbytis*) *entellus*], where adult behaviors represented a subset of the juvenile positional repertoire. These results were argued to reflect risk-sensitive behavior and predator avoidance. Workman and Covert (2005) describe similar results in langurs. Red-shanked douc langur (*Pygathrix nemaeus*) juveniles exhibited 19 suspensory modes while adults exhibited only seven suspensory modes. Chimpanzees (*Pan troglodytes*) showed delayed competence when compared to gorillas, matching adults in most locomotor modes at 6 years of age. Ontogenetic effects on locomotor behavior in juveniles have been described for a number of primate species [Verreaux’s sifaka (*Propithecus verreauxi*: Lawler 2006; Wunderlich et al. 2011; Wolf et al. 2011), ring-tailed lemurs (*Lemur catta*: Wolf et al. 2011) tufted capuchins (*Cebus apella*: Wright 2005), white-faced capuchins (*C. capucinus*: Bezanson 2009), wedge-capped capuchins (*Cebus olivaceus*: Wright 2005), Central American squirrel monkeys (*Saimiri oerstedii*: Boinski 1989), black and gold howlers (*Alouatta caraya*: Prates and Bicca Marques 2008), mantled howlers (*Alouatta palliata*: Bezanson 2009), Red-shanked douc langurs (*P. nemaeus*: Workman and Covert 2005) Delacour’s langur (*Trachypithecus delacouri*: Workman and Covert 2005), Hatinh langurs (*Trachypithecus hatinhensis*: Workman and Covert 2005) rhesus macaques (*M. mulatta*: Rawlins 1982; Wells and Turnquist 2001), Bornean orangutans (*Pongo pygmaeus*: Thorpe and Crompton 2005), lowland gorillas (*G. gorilla*: Doran 1997), common chimpanzees (*P. troglodytes*: Doran 1992, 1997), and bonobos (*Pan paniscus*: Doran 1992)].

Researchers of positional behavior tend to focus on behaviors during feeding/foraging and travel because these activities are considered to have bigger influences on adaptation as they are a more straightforward link to survival and reproduction. Integrative studies also should address locomotion and posture during social behavior, especially during ontogeny. To our knowledge, positional behavior during social

behavior has only been presented in three studies (Fontaine 1994; Workman and Covert 2005; Bezanson 2006). Behaviors such as playing and exploring are where young infants and juveniles begin using the positional behaviors that promote survival and reproduction. While play as an aspect of social behavior is perceived to be a critical time of practice of motor control and cognitive development in mammals (Beckoff and Byers 1998; Graham and Burghardt 2010), studies rarely emphasize locomotion and posture during play even though this activity can be associated with disparities in relative amounts of postural and locomotor modes (Grand 1981; Hurov 1991; Dunbar and Badam 1998). Fontaine compared play and nonplay positional behaviors in five species of New World primates: mantled howling monkeys, black-handed spider monkeys (*Ateles geoffroyi*), uakaris (*Cacajao calvus*), white-faced capuchins, and South American squirrel monkeys. In all five species, he found increased use of complex suspensory behaviors (e.g., upside down quadrupedalism and arm swinging) and faster locomotor modes (e.g., quadrupedal bounding and galloping) in juveniles during play (Table 19.3).

Workman and Covert (2005) discuss the possible importance of positional practice during play in captive red-shanked douc, Delacour's, and Hatinh langurs. The young langur positional repertoire differences emphasized suspensory, swinging, and leaping categories during play. These authors caution that juvenile behaviors may be more "clumsy" than adult behaviors but that diversity and frequency of complex behaviors during play were remarkable. Bezanson's field observations of play in white-faced capuchins (Table 19.3) show large differences in suspensory (32.7%) and nonsuspensory (67.3%) postures by infants and even greater variation in juveniles (nonsuspensory: 7.7% and suspensory: 92.3%). Mantled howler infants and juveniles showed a different pattern. Percentages of suspensory and nonsuspensory behaviors vary only slightly. These results not only illustrate the importance of play and locomotor development but also suggest that studies of ontogenetic patterns of positional behavior consider differences among more precise behavioral contexts. If play behavior represents a time of great positional diversity, then these behaviors might best mirror the types of quick responses and complex behaviors necessary when encountering predators or other risky situations.

19.6 Life History and Locomotion: Where Do We Go from Here?

Field studies of the ontogeny of positional behavior and how it links growth and development focus on individuals. Biological and behavioral features of individuals together are considered in terms of local populations, species, and higher-order levels of organization. Recent discussions of variation in features and form–function relationships within and among species enrich our understanding of biological roles and selection of positional behaviors. Pereira and Leigh (2003), Leigh (2004), Leigh and Blomquist (2011), for example, have examined the mosaic nature of morphological development during ontogeny and the importance it may play in primate life

Table 19.3 Use rates of suspensory (susp) vs nonsuspensory (non) postures observed during play and other behavioral contexts in infants, juveniles, and adults

Species/study	Play				Nonplay behaviors (e.g., feeding, foraging, travel, rest)							
	Infant		Juvenile		Infant		Juvenile		Adult		Susp	Non
	Susp	Non	Susp	Non	Susp	Non	Susp	Non	Susp	Non		
<i>Cebus capucinus</i> La Suerte (Bezanson 2006)	32.7	67.3	7.7	92.3	2.2	97.8	9.1	90.9	3.2	96.8		
<i>Alouatta palliata</i> La Suerte (Bezanson 2006)	52.9	47.1	58.6	41.4	8.7	91.3	10.5	89.5	4.2	95.8		
<i>Alouatta palliata</i> (Fontaine 1995)			86.8	13.2			12.3	87.7	4.8	95.2		
<i>Ateles geoffroyi</i> (Fontaine 1995)			80.7	19.3			29.0	71.0	16.7	83.3		
<i>Cacajao calvus</i> (Fontaine 1995)			35.3	64.7			2.2	97.8	0.4	99.6		
<i>Cebus capucinus</i> (Fontaine 1995)			34.4	65.6			4.4	95.6	1.2	98.8		
<i>Saimiri boliviensis</i> (Fontaine 1995)			22.2	77.8			1.5	98.5	0.4	99.6		

history evolution. Building on an evolutionary framework of “modularity” (e.g., Needham 1933; Gould 1977; Raff 1996; Wagner 1996), development involves “dissociability among functionally integrated character complexes and their recombination to express alternative modes” (Pereira and Leigh 2003: 152). Specifically, varying rates of growth of morphological features may be the result of natural selection targeting phenotypic plasticity and the mitigation of metabolic risks during the juvenile period. Although modularity has been long appreciated in examinations of phenotypic plasticity in the developmental biology literature (reviewed in West-Eberhard 2003), studies of primate life history just recently incorporated this perspective (Pereira and Leigh 2003; Leigh 2004; Leigh and Blomquist 2011). Neurological development required for efficient foraging and locomotor capabilities can be dissociated from physical development (i.e., somatic growth). For example, some small-bodied primates with relatively long juvenile periods (e.g., capuchins) exhibit early positional competence and associated foraging behaviors when compared to some larger-bodied primates that exhibit shorter juvenile periods and complex positional behaviors relatively later (Doran 1992, 1997; Wright 2005; Bezanson 2006, 2009). Larger-bodied hamadryas baboons travel independently at 6 months of age even though it is less costly energetically for an infant to continue riding than the combined cost of independent travel for both mother and infant (Steudel 2000).

When examining infant and juvenile positional behavior, it may be more fruitful to follow a framework that addresses the specific ways that primates solve problems in the environment. Cant and Temerin (1984) and Cant (1992) provided a problem-oriented theoretical framework to address how positional behavior as a foraging and feeding adaptation solves problems in an arboreal canopy with specific regard to body mass. This comprehensive framework defined the constraints that a primate faces in day-to-day foraging from a biological, behavioral, and individual basis. Primates devise complex solutions for resource acquisition with extensive behavioral plasticity. Foraging ultimately influences life history and population features and should be examined in terms of feedback relations through ecological and evolutionary time (Cant and Temerin 1984; Cant 1992). Using this framework will allow clearer understanding of how smaller and younger primates distribute mass above and below branches and increase their feeding sphere and the following related questions (Grand 1972, 1977, 1978): How do movement capabilities or different limb lengths, proportions, and center of gravity influence expressed behavior between larger (older) or smaller (younger) individuals of the same species? How does variation in stamina, agility, and energetic costs influence positional behaviors of younger and older individuals?

The ontogeny of positional behavior and how it relates to growth and other life history features is characterized by great variation within primates. Understanding this diversity requires additional research at several levels including social behaviors, body mass, growth, physiology, anatomy, skeletal kinematics, and loading conditions. Primate positional behavior and its ontogeny provide examples of the lifeways that can be interpreted from a holistic life history framework. Locomotor, postural, and manipulative biological abilities and expressed behaviors interact with

all aspects of an individual's survival activities throughout the life stages. These include feeding, social interactions, and avoiding predators. Carrier (1983, 1996) suggests that in some vertebrates, juveniles exhibit greater jumping or sprinting abilities (response to locomote away from predators) while exhibiting less agility and stamina. Additionally, research on Verreaux's sifaka (Lawler 2006) squirrel monkeys (Boinski 1989; Stone 2006), wedge-capped capuchins (Wright 2005), and white-faced capuchins (MacKinnon 2006, 2012; Bezanson 2006, 2009) indicates that foraging efficiency and/or locomotor competence appears early in some primates and not in others. Application of a holistic life history framework will shed light on why variation exists from the perspective of what it means to be a locomoting infant, juvenile, and adult. While primates are characterized by species-defined trajectories of growth and development, the degree to which positional behavior varies within species and during varying contexts is unknown. We are still in the early stages of understanding the complexities of potential interactions of individual positional behaviors in biological, social, and physical environments. However, data collected thus far indicate that positional development offers the potential for exciting research on individual, intraspecific, and interspecific differences exhibited in primates.

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Chapter 20

Quantitative Genetic Perspectives on Female Macaque Life Histories

Heritability, Plasticity, and Trade-Offs

Gregory E. Blomquist

20.1 Introduction

All life histories are a complex of trade-offs that depend on individual conditions—including size, age, and sex—and adaptively mold suites of traits through the biased intergenerational transmission of successful physiological strategies. I explore intrapopulation variation in how female rhesus macaques on Cayo Santiago have negotiated a central life history trade-off: when to start reproducing. I emphasize how evolutionary quantitative genetic models require explicit links between hypothesized or measured patterns of selection and the genetic substrates that influence phenotypes and change intergenerationally. Perhaps counterintuitively, I also show how genetic models offer valuable insights on how environments, including those provided by mothers and other kin, affect offspring development and later female life histories. The emerging picture of female macaque maturation is one of the great flexibility and environmental responsiveness coupled with an important genetic component that is significantly entangled with later life history events.

Studies of mothers and infants have been central to understanding primate life histories. Investigators from a diverse set of disciplines and theoretical backgrounds have used a variety of approaches and scales of analysis to explore the behavioral and physiological details of this intense relationship, its life-long and intergenerational consequences, and ultimately how such patterns could be honed into adaptations by selection on genetic variation. Historically, the field has been dominated by laboratory-based experimental approaches, interspecific comparative analysis, and ethological studies in the wild (Altmann 1980; Hrdy 1999).

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In this chapter, I try to make the case for quantitative genetics, which is an underutilized method for studying primate mothers and infants. Quantitative genetics is a set of statistical techniques (described briefly below), but it is also a body of theory that links very directly with rich evolutionary population genetic models that incorporate and formally arrange information on variation in interesting maternal or infant traits and their fitness consequences (Arnold 1994; Lande 1982). Laboratory and wild studies of mothers and infants provide information on the styles of interactions, their social and ecological correlates, and sometimes how this variation translates into predictable fitness differences that result in selection in action. Interspecific comparative studies suggest adaptive patterns that may have resulted from many generations of past selection. However, none of these techniques provide the requisite information for a realistic evolutionary model about genetic variation or covariation in traits (Cheverud and Moore 1994). Quantitative genetic methods are thus complementary to the other more common approaches for studying the ecology and evolution of mother–infant interactions. In what follows, I provide a brief introduction to quantitative genetics tailored to thinking about primate life histories and then offer a handful of examples from research on female rhesus macaques (*Macaca mulatta*).

20.2 Quantitative Genetics

The core tenet of quantitative genetics is that kin should resemble one another phenotypically because they have copies of the same alleles. These alleles in common are said to be identical by descent because the copies are made by DNA replication during gamete production and transmitted across generations in fertilization. The number of genes involved and where they are located in the genome are usually unknown, although if molecular data are available they can be used to map genes that affect a given phenotype (Visscher et al. 2008). Instead, the standard assumption is that the trait is polygenic—there is a very large number of genes whose summed action results in a continuous distribution of genotypes (Fig. 20.1). The statistical match between phenotypic resemblance and predictions from rules of Mendelian inheritance (e.g., mother and infant have 1/2 of their alleles identical by descent, half siblings on average have 1/4 of their alleles identical by descent) is then used to partition phenotypic variance into genetic and nongenetic sources.

Quantitative genetics is intimately tied into the origin of statistics in the late nineteenth and early twentieth centuries (Roff 1997; Kevles 1985; Provine 1971). Galton, Pearson, and Fisher invented regression, correlation, and analysis of variance in part to measure resemblance among kin and perform this partitioning of variance. A hypothetical example of this process is shown in Fig. 20.2 where birth weights of daughters are regressed on maternal birth weights and total phenotypic variance (V_P) is broken down into additive genetic (V_A) and residual variance (V_R). The sum of the genetic and residual components is the phenotypic variance ($V_P = V_A + V_R$).

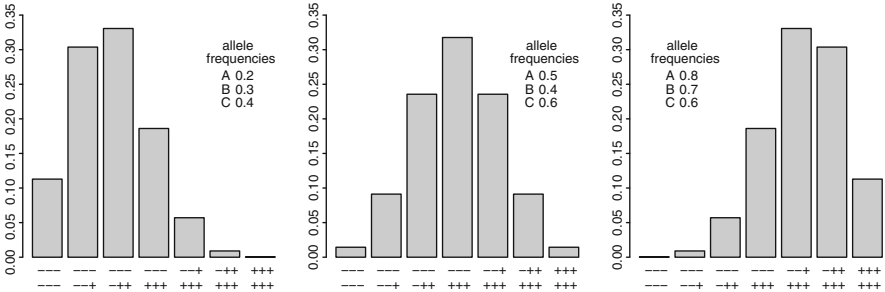


Fig. 20.1 Frequency distributions of genotypes for a polygenic trait, such as birth weight, with two additively acting alleles at each of three loci (A, B, and C). Alleles are indicated by a + (representing A, B, or C alleles) that causes slight increase in birth weight, and an alternative - (representing a, b, or c alleles) that causes reduction in birth weight. Larger infants are to the *right* in each panel. Changes in the frequencies of the alleles shift the average birth weight in the population

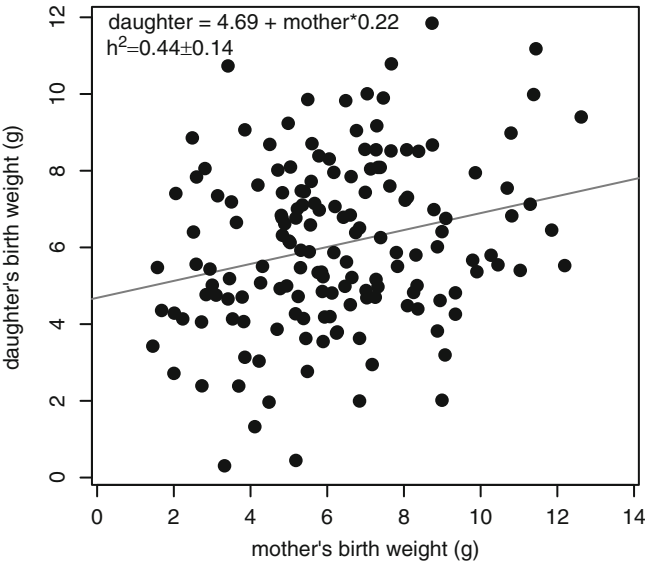


Fig. 20.2 Mother–daughter regression to estimate the heritability of gryphon birth weight in the simulated data of Wilson et al. (2010)

The key part of the regression equation in Fig. 20.2 is the slope, which by definition is the ratio of the covariance between mother and daughter phenotypes to the variance in the maternal phenotype, or $\text{Cov}(\text{mother}, \text{daughter}) / \text{Var}(\text{mothers})$. Because mothers and offspring only have 1/2 of their alleles identical by descent, $\text{Cov}(\text{mother}, \text{daughter})$ is 1/2 of the additive genetic variance. This allows the slope to be rewritten in terms of variance components as $V_A / 2V_P$. To make communication easier, variance components are scaled to sum to one by dividing each component

by the phenotypic variance. Multiplying the slope from the regression by two brings the additive genetic variance onto this scale and yields a familiar term in quantitative genetics—the narrow-sense heritability $h^2 = V_A / V_P$. In Fig. 20.2 the heritability is 0.44 ± 0.14 which means that 44% of the variation in birth weight in the population is due to additive gene action, which is significantly greater than zero ($t = 0.44 / 0.14 = 3.2$, $P < 0.01$).

Heritability is an important concept in quantitative genetics, but it is crucial to recognize that its meaning is circumscribed by the statistical and biological models used in its estimation (Kruuk et al. 2008; Kruuk and Hadfield 2007; Templeton 2006; Vitzthum 2003). From the description above, it may be apparent that heritability does not identify some phenotypes as “genetic” and others as environmental. Instead, it is a within population partitioning of *variation* that depends on the allele frequencies of the population and the environments population members encounter. If either of these change (allele frequencies or environmental circumstances), so will the heritability. The importance of variation to heritability cannot be overstated. Many traits that certainly have large networks of interacting genes that make them possible, such as rhesus macaque mothers producing a hemochorial placenta during gestation, do not vary within macaque populations and thus have undefined heritabilities because their phenotypic variance is zero. Moreover, heritability estimates say little to nothing about between-group differences.

For traits that do vary, the quality of the variance components or resulting heritability estimates is very much dependent on how well the statistical model reflects the factors that could cause population members to resemble each other. In Fig. 20.2, a very simple model is used in which a phenotype is the sum of additive genetic and residual effects. Residual effects or residual variance refers to any variation that cannot be ascribed to additive effects or any other modeled factor (e.g., dominance, environmental factors, maternal environment). More elaborate models will be discussed below, but in this simple case the only reason for mothers and daughters to resemble one another in the population is the additive effect of alleles they have in common. Additivity means that alleles do not interact with one another at a locus (dominance) or across loci (epistasis). This is a simplistic view of the genetics of most quantitative phenotypes but it may be defensible in many situations. For example, dominance cannot affect this mother–daughter similarity because only a single allele per locus is transmitted between generations meaning that mothers and daughters cannot share a pair of alleles at a locus (i.e., a genotype) that are both identical by descent.

More importantly, for the heritability estimate to be strictly valid, we must assume that relatives do not experience environments that might cause them to resemble one another. There are two ways to ensure that heritability estimates or variance components are not affected by this problem of shared environment. In a controlled breeding setting offspring can be randomized across environments, including cross-fostering which is the transferring of infants or even embryos between mothers (Maestripietri 2003). For unmanaged populations, this is rarely possible and the only recourse is to attempt to measure as much as possible about

the environments individual's experience and account for them in more elaborate statistical models that reflect this biological complexity.

In recent decades, the quantitative genetic techniques used by many animal breeders, ecologists, and medical geneticists have expanded to accommodate this complex reality. Animal breeders and ecologists call the most common of these approaches the “animal model” (Kruuk 2004). The techniques offer two main advantages for the problem of shared environments just described. First, they leverage all of the genealogical information in a given pedigree rather than picking a single type of relationship like parent–offspring pairs for regression or sets of siblings or cousins for analysis of variance. This increases statistical power and helps reduce the problem of relatives sharing environments because pedigrees can span large numbers of individuals and there are more likely to be some kin living in different environments. Second, an individual's phenotype is modeled in a more flexible manner as the sum of fixed and random effects allowing for a much more complex partitioning of phenotypic variance. The importance of the animal model can be understood by revisiting the genetics of birth weight. The simplest animal model for birth weight is:

$$\text{Birth weight} = \bar{x} + \text{Genotype} + \text{Residual},$$

where $\bar{x}$ is the population mean. The model can be augmented to account for known environmental differences among individuals. An important kind of shared environment for mammalian offspring is that provided by mothers (Cheverud and Wolf 2009; Cheverud and Moore 1994). Several different kinds of “maternal effects” have been studied by primatologists that differ from the way they are typically conceptualized in quantitative genetics (Wolf and Wade 2009; Räsänen and Kruuk 2007). For quantitative geneticists, maternal effects are additional causes for resemblance among kin, particularly the offspring of the same mother. This can be modeled as another random effect in the animal model for maternal identity, which will have a variance component estimated (V_M), which is the maternal effect $m = V_M / V_P$ when scaled by the phenotypic variance. The characteristics of mothers that cause differences among their offspring are not identified by this approach, but it has the benefit of providing a general index of maternal performance.

$$\text{Birth weight} = \bar{x} + \text{Genotype} + \text{Maternal identity} + \text{Residual}.$$

In contrast, primatologists have typically studied maternal effects by measuring maternal characteristics and looking for statistical associations in populations with offspring phenotypes (e.g. dominance rank, birth order, maternal age Altmann and Alberts 2005; Maestripieri 2009). Depending on how permanent maternal characters are, these could either cause offspring of the same mother to resemble each other or be causes for dissimilarity. For example, if dominance rank is stable through adulthood, it should be a source of similarity among offspring of the same mother. On the other hand, primate mothers typically only give birth at a given age once, and being born to the same mother when she is in her prime is likely better for offspring

than when she is very young or very old. These sorts of maternal characters can be entered into the linear model as fixed effects. Additional factors unrelated to maternal effects can also be used such as neonate sex and population density.

$$\begin{aligned} \text{Birth weight} = & \bar{x} + \text{Sex} + \text{Density} + \text{Maternal rank} + \text{Maternal age} \\ & + \text{Maternal age}^2 + \text{Genotype} + \text{Maternal identity} + \text{Residual}. \end{aligned}$$

The importance of fixed effects is assessed through their regression coefficients. One would expect a negative slope for density (smaller infants due to increased feeding competition or elevated psychosocial stress under crowded conditions). Maternal age has linear and quadratic terms which would be expected to have positive and negative coefficients, respectively (older mothers have larger infants, but the effect attenuates as mothers age).

Fixed effects are generally those that are included because they have some clear influence on the phenotype that needs to be estimated, and the categories of the fixed effect are all present in the current data. Sex is a good example, having only two categories that would always be present for any comparison to be made. Random effects are different because the categories are typically only a sampling of a larger population of categories that are the focus of analysis. The additive genotype or maternal identity effects are both good examples. There is either one or just a few records in the dataset for each category and were we to repeat the analysis at a later time there would be more individuals to include (Wilson et al. 2010). Generally, regression coefficients are the result of interest for fixed effects while variance components are for random effects.

In contrast to the pattern in Fig. 20.2, most studies of birth weight in humans and livestock identify small heritabilities and relatively large maternal effects (Robson 1978; Wilson and Réale 2006). Shared uterine environment rather than sharing alleles identical by descent drives much of the similarity among a mother's offspring. Because the uterine environment provided by mothers can be influenced by her own genotype, this environment she provides has a partly genetic basis and evolves in response to selection on her or her offspring (Cheverud and Moore 1994; Wolf et al. 1998).

Ultimately, the meaning of heritability or other variance component estimates like maternal effects is limited by our knowledge of the biology of the organisms we study. The variance components identify statistical patterns that can be explained by more detailed analysis of proximate mechanisms including anatomy, energetics, endocrinology, and socioecology of primate reproductive biology and life histories. Rather than a static description of genetic variation, heritability can be viewed as the dynamic outcome of interactions within individuals, between individuals, and between the organisms and their environments over the course of their lifetimes. Continuing with the example of birth weight, this phenotypic outcome plays out as a negotiation of physiological mechanisms manipulated partly by fetal genes and partly by mothers. The theater of their effects is the molecular cross talk between mother and uterine resident situated within the larger socioecological context of the mother. Heritabilities and other quantitative genetic statistics are simply summary measurements of these complex biological processes.

20.2.1 Linking Up with Life History Evolution

These summary measurements are very useful in modeling the evolution of quantitative traits such as those that make up primate life histories. As in any model, simplifications are required. However, knowing there is a large or small amount of polygenic variation for traits in a population for selection to work on is better than knowing nothing at all about their genetics.

Much of life history theory has focused on the evolution of traits that impact components of the Euler–Lotka equation (Roff 2002), one form of which is given in Eq. (20.1). This equation relates the probability of a newborn surviving to age x (l_x) as well as the number of like-sexed offspring produced by an adult at age x (m_x) to fitness (λ). The summation covers only reproductive ages from first reproduction, α , to final reproduction, ω . Although the equation was developed by demographers to describe population growth (the λ term) it can also be interpreted as the rate of increase of a genotype specifying a particular life history pattern within a population (Stearns 1992; Charlesworth 1994).

$$1 = \sum_{x=\alpha}^{\omega} \lambda^{-x} l_x m_x. \quad (20.1)$$

Selection acts to increase the average value of λ in a population (Fisher 1930; Caswell 2001; Charlesworth 1994). Increases in λ can be achieved by earlier reproduction (smaller α), lengthening the reproductive lifespan (larger ω), and increases in the age-specific survival and fertility rates (larger l_x and m_x). Whether any of these changes to the life history can actually happen depends on the heritability of the individual life history traits and whether they are affected by phenotypic and genetic correlations with each other.

In the simplest (and least accurate) model, a single trait evolves in response to direct selection upon it. For example, initial fertility (m_α) is predicted to evolve as

$$\Delta \bar{m}_\alpha = \frac{1}{\lambda} V_A \frac{\partial \bar{\lambda}}{\partial \bar{m}_\alpha}, \quad (20.2)$$

where $\Delta \bar{m}_\alpha$ is the change in the mean between generations, V_A is its additive genetic variance, and $\frac{\partial \bar{\lambda}}{\partial \bar{m}_\alpha}$ measures the strength and direction of selection, or how λ responds

to a minute increase in initial fertility. Because variances are never less than zero, initial fertility will respond in the same direction it is selected (i.e., $\frac{\partial \bar{\lambda}}{\partial \bar{m}_\alpha}$ and $\Delta \bar{m}_\alpha$

have the same mathematical sign). Thinking about Eq. (20.1) indicates that m_α will always be selected for larger values. Taking the same univariate approach to each life history trait will lead us to expect an ideal life history of an animal born reproductively mature ($\alpha \approx 0$), which produces large numbers of healthy offspring at every age (all $m_x \gg 0$ and $\omega \approx \infty$) and lives forever (all $l_x \approx 1$). That this life history is so unfamiliar says there is something very wrong with this simplistic model (Law 1979).

Thinking about real life histories highlights the underlying problem—traits cannot change without affecting one another through their phenotypic and genetic correlations. Finite resources limit the ability of organisms to maintain or grow their own bodies while attempting to reproduce at the same time (Stearns 1989). Putting more energy into current reproduction often curtails future reproductive opportunities. In other words, the simple univariate model ignores *trade-offs*. The physiological decisions about the allocation of finite resources likely reflect evolved strategies for coping with the trade-offs faced by a given organism (Ricklefs and Wikelski 2002; Stearns and Magwene 2003). The familiar female primate way is slow growth and late maturation, with few offspring produced over a long reproductive career (Harvey et al. 1987).

Phenotypic and genetic correlations among traits, which allow for important trade-offs, do appear in multivariate extensions of Eq. (20.2) (Lande 1982; Lande and Arnold 1983; Caswell 2001). A two-trait example of this is given in Eq. (20.3) where the simultaneous evolution of survival from the beginning of reproduction to 1 year later ($p_\alpha = l_{\alpha+1}/l_\alpha$) and initial fertility is modeled. Like the simpler equation for a single trait, Eq. (20.3) can be read as “response = genetics $\times$ selection.”

$$\begin{bmatrix} \Delta \bar{m}_\alpha \\ \Delta \bar{p}_\alpha \end{bmatrix} = \frac{1}{\bar{\lambda}} \begin{bmatrix} V_A(m_\alpha) & \text{Cov}_A(m_\alpha, p_\alpha) \\ \text{Cov}_A(m_\alpha, p_\alpha) & V_A(p_\alpha) \end{bmatrix} \begin{bmatrix} \frac{\partial \bar{\lambda}}{\partial \bar{m}_\alpha} \\ \frac{\partial \bar{\lambda}}{\partial \bar{p}_\alpha} \end{bmatrix}. \quad (20.3)$$

$\Delta \bar{m}_\alpha$ and $\Delta \bar{p}_\alpha$ are evolutionary response or changes in the mean between generations. The V_A s are the respective additive genetic variances, while $\text{Cov}_A(m_\alpha, p_\alpha)$ is the additive genetic covariance between the two life history traits. They summarize the influence of genetics on both traits and are often the results of pleiotropy—alleles for a single locus affecting multiple phenotypes. They are measured by the same techniques as heritabilities and all the same caveats discussed above still apply. Selection on the life history traits is described by $\frac{\partial \bar{\lambda}}{\partial \bar{m}_\alpha}$ and $\frac{\partial \bar{\lambda}}{\partial \bar{p}_\alpha}$, which indicate how λ would respond to a minute increase in m_α or p_α while the rest of the life history is held constant.

In Eq. (20.3), response in each life history trait is the result of direct selection on it and indirect selection on the other trait. For example, the response in initial fertility is $\Delta \bar{m}_\alpha = \frac{1}{\bar{\lambda}} V_A(m_\alpha) \frac{\partial \bar{\lambda}}{\partial \bar{m}_\alpha} + \frac{1}{\bar{\lambda}} \text{Cov}_A(m_\alpha, p_\alpha) \frac{\partial \bar{\lambda}}{\partial \bar{p}_\alpha}$. Although selection on both traits is positive, response is likely to be ≈ 0 because of strong *negative* genetic covariance which reflects the trade-off between the traits. Any alleles in populations that increase both traits are likely to be rapidly fixed; those with opposite effects are likely to be quickly purged. Remaining variation is that which allows for roughly equivalent levels of fitness along an allocation continuum between the two traits (Fig. 20.3). While this two-trait approach is simplistic, it is a useful heuristic for

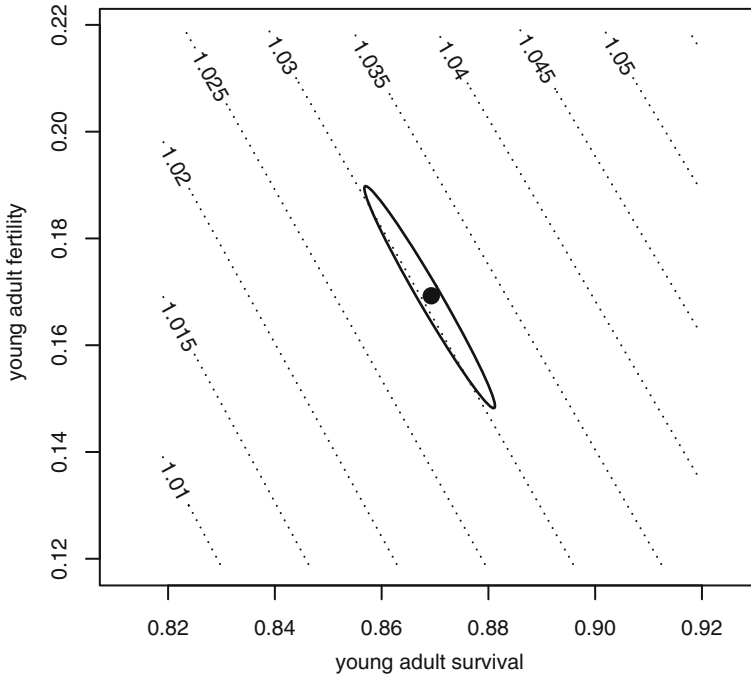


Fig. 20.3 Hypothetical negative genetic covariance between two life history traits on a landscape of fitness (λ) values using a life history model for female macaques described in Blomquist et al. (2011). The negative genetic covariance places most genetic variation along a fitness isocline at $\lambda \approx 1.03$. Selection is for increased survival and fertility (movement to the *upper right* of the figure) but the lack of genetic variation in this direction will limit response

thinking about trade-offs in life history evolution and why they ought to be reflected in genetic correlations (cf. Houle 1991; de Jong and van Noordwijk 1992; Roff 1997). Building on Eq. (20.3), more traits can be modeled but visualizing and describing the multi-way trade-offs among them becomes much more difficult.

20.3 Three Vignettes on Macaque Mothers and Infants

The remainder of this chapter demonstrates applications of these ideas to understanding the life histories of female macaques using long-term demographic data from Cayo Santiago. I will omit many of the details provided in original publications and focus on the important results and implications.

Cayo Santiago is a small island (15.2 ha) located just off the coast of Puerto Rico. Rhesus macaques have lived there since 1938, when about 400 individuals were released on the island after a long ship voyage from India (Rawlins and Kessler 1986b; Sade et al. 1985). Continuous demographic records have been kept by

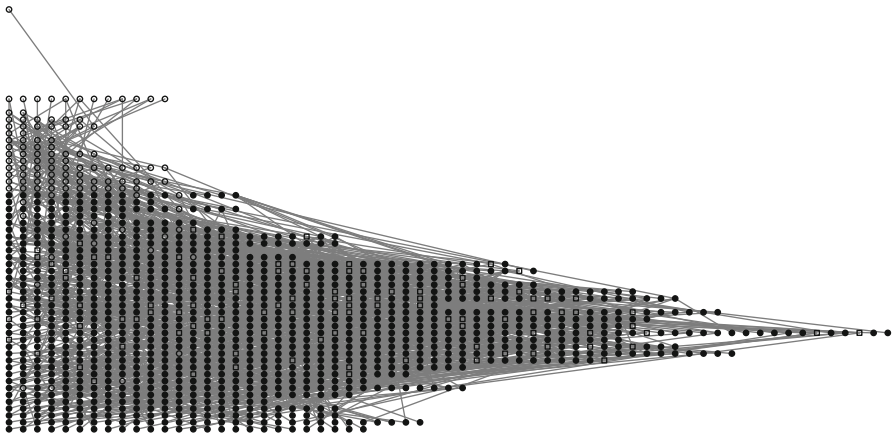


Fig. 20.4 Example pedigree for Cayo Santiago females. *Filled symbols* indicate females with reliably known age of first reproduction ($N=975$). *Open symbols* are unphenotyped individuals that provide additional pedigree links. Each row is a single birth cohort with the oldest at the *top*

diligent observation since the mid-1950s. Monkeys are fed commercial monkey chow and provided water *ad libitum* but forage on natural vegetation and live in naturally formed social groups (Rawlins and Kessler 1986a). At the time this research began in 2005, there were nearly 8,000 known individuals who had lived on the island. The population has been managed through the removal of social groups and a random cull of juveniles such that only 34% of the individuals who had exited the population did so because of death with the other 66% taken to other facilities or sacrificed. The population was inoculated against tetanus in the mid-1980s (Kessler et al. 2006), and some animals had medical experiments conducted on them prior to the early 1970s (Sade et al. 1985). Otherwise, there has been a veterinary policy of nonintervention. Extensive maternal genealogies spanning up to nine generations in some cases are (Fig. 20.4) linked by paternities known from microsatellite markers in recent decades (Nurnberg et al. 1998). Rhesus macaques are seasonal breeders which arranges the population into well-defined birth cohorts (Rawlins and Kessler 1985). Clearly then, Cayo Santiago is not a natural/wild population, but the rich demographic and pedigree information make it a valuable group for exploring primate life history evolution.

20.3.1 Female Age of First Reproduction Is Weakly Heritable

The timing of female sexual maturation or age of first reproduction (AFR) (α in Eq. (20.1)) is one of the life history traits most frequently studied by primatologists (Kappeler and Pereira 2003; Charnov and Berrigan 1993). Within population variation in AFR has been a particular focus of research on the fitness benefits and costs

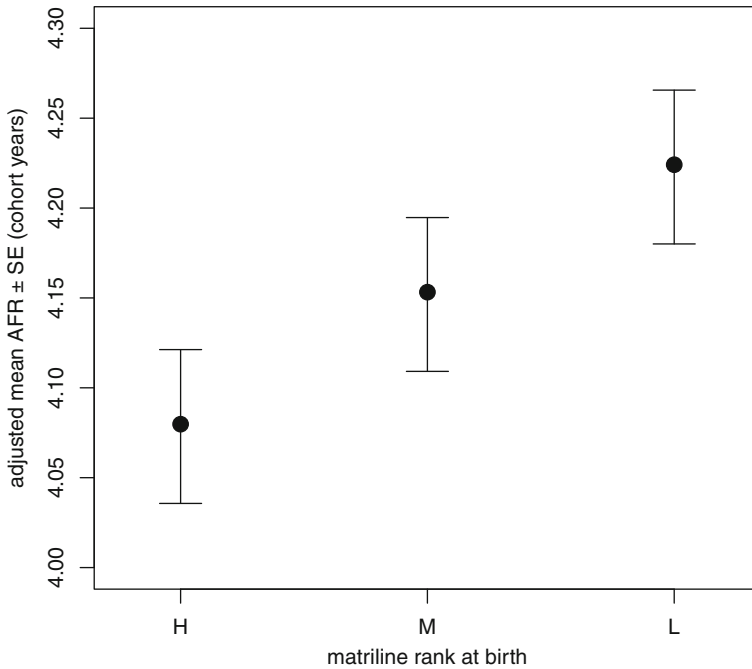


Fig. 20.5 Relationship between matriline dominance rank and female age of first reproduction (AFR). On average, high (H) ranking females mature at earlier ages than middle (M) or low (L) ranking females. Data are from the 975 individuals illustrated in Fig. 20.4

of social status in cercopithecine primates like macaques that have strong, stable dominance hierarchies and female philopatry (reviewed in Ellis 1995). Female philopatry is important because the formation of cooperative coalitions within matriline (sets of females descended from a single founding female ancestor) is instrumental in maintaining and acquiring rank (Chapais 2004). Rank affects health by providing priority of access to limited resources (Koenig 2002) and shelter from stress induced by aggressive interactions (Sapolsky 2005). Females of higher rank tend to mature earlier which, as discussed above, yields higher fitness if no other aspects of the life history are affected by this physiological decision.

Rank-related trends in AFR are well-established among females at Cayo Santiago (Fig. 20.5, cf. Bercovitch and Berard 1993; Stucki et al. 1991). Additional environmental factors also have effects, such as being born later or earlier in a birth cohort and birth cohort membership, which is a proxy for population density and temporal changes in management or local climate. Together, these account for a little over 20% of the variance in female AFR (Table 20.1).

Using the “animal model” described above, it is also possible to estimate variance components and the heritability of female AFR with this dataset (Blomquist 2009b,a). There is very little comparative primate data to gauge our expectations for

Table 20.1 Linear model analysis of variance table predicting female age of first at Cayo Santiago ($R^2=0.242$)

	SS	df	F	P
Age in cohort	9.56	1	35.32	<0.001
Mother’s age at birth	0.41	1	1.52	0.218
Matriline rank at birth	3.09	2	5.71	0.003
Birth cohort	69.24	34	7.52	<0.001
Residuals	253.35	936		

These are the fixed effects for the “animal model.” Data are from the 975 individuals illustrated in Fig. 20.4

Table 20.2 Variance components and ratios for female AFR at Cayo Santiago

Variance	Component±SE	Ratio±SE
V_A	0.040±0.018	$h^2_{anim} = 0.149 \pm 0.065$
V_M	0.000±0.010	$m = 0.000 \pm 0.036$
V_R	0.230±0.019	$r = 0.851 \pm 0.065$
$V_{P_{anim}}^a$	0.270±0.013	
$V_{P_{total}}^b$	0.343	$h^2_{total} = 0.117$
		Fixed effects = 0.211

^aPhenotypic variance after fixed effects are removed

^bTotal phenotypic variance including fixed effects

the results. The only primate taxa with maturation heritability estimates are captive baboons and humans (Towne et al. 2005; Williams-Blangero and Blangero 1995). For both species the heritability is usually moderate to high ($h^2>0.5$). This is somewhat unexpected given theoretical expectations that traits under strong selection should have little additive genetic variance, and low heritabilities, because selection quickly fixes or purges new mutations affecting the trait (Merilä and Sheldon 1999; Price and Schluter 1991; Blomquist 2009c). The heritability for female AFR at Cayo Santiago is more in line with theoretical expectations—12% of total phenotypic variance is due to additive genetic variation in the population, about half of what is attributable to fixed effects such as rank or birth cohort. The remaining two-third of the phenotypic variance is unexplained residual (Table 20.2). The heritability of AFR is small but significantly greater than zero, which suggests exploring genetic relationships between other life history traits searching for trade-offs is statistically justified (see below).

The main point of this vignette is to show that an interesting primate life history trait can be analyzed from extensive demographic data that provide both phenotypes and pedigrees. The quantitative genetic approach requires thinking clearly about environmental effects but it goes beyond this to provide variance components that appear in the equations for modeling the trait’s evolution. Even from this univariate

perspective we would expect female AFR to evolve very slowly in macaques because of its low heritability. Furthermore, this low value itself may reflect a history of intense past selection because selection is expected to erode additive genetic variance by fixing beneficial and purging deleterious alleles (Roff 1997).

20.3.2 Environments Provided by Mothers Affect Infant Survival

In the previous vignette, maternal effects were not responsible for any variation in female AFR. This may be because the pedigree and data set do not allow separating maternal from additive genetic variance (Wilson et al. 2010), or because AFR is late enough in offspring life that the environment provided by mothers has been diluted by other factors.

However, the environment provided by mothers should surely have an effect on the mortality of infants in the first month of life. Infant mortality has been examined in many primates in either wild or captive settings. Most studies have focused on the social and other ecological factors affecting infant death rates, with a handful of genetic studies on inbreeding-related mortality risk (Cheney et al. 2006; Schino and Troisi 2005; Silk et al. 2003; van Schaik and Janson 2000; Takahata et al. 1998; Smith 1986; Busse 1982; Ralls and Ballou 1982; Wilson et al. 1978; Altmann et al. 1977; Hird et al. 1975). Two trends in infant mortality have already been described in good detail at Cayo Santiago. Hoffman et al. (2010) showed that infant death rates increased with maternal age, and this increase was more dramatic in their late teens and twenties. It is also known that tetanus inoculation in the early 1980s reduced death rates (Kessler et al. 2006). Infant death is a binary phenotype (1 = death, 0 = survival) which requires some additional statistical machinations. These are readily handled in generalized linear mixed models (GLMM) that allow variance component estimation for non-normally distributed phenotypes (Bolker et al. 2009; Gilmour et al. 2009).

Analysis of death in the first month of life at Cayo Santiago identifies strong maternal effects of both kinds discussed above, and consistent with previous studies of Cayo Santiago mortality. For the primatologist, older mothers are less likely to lose infants (negative linear coefficient), but very old mothers have higher infant death rates (positive quadratic coefficient, Table 20.3). From the animal breeder's view, there is a large variance component for infant death associated with maternal identity. Adjusting for the maternal age and time period (Table 20.3), about 12% of the variance in first month mortality can be attributed to maternal identity. The heritability of infant death is essentially zero (Table 20.4).

Not surprisingly, it is the aspects of the environment provided by mothers rather than infant genes that explain variation in infant death rates. The different views of maternal effects are complementary here. The variance components identify average differences among mothers in the risk of death for their infants, while the fixed effect regression coefficients measure an age-related pattern of risk common to the population. At the population level, Hoffman et al. (2010) note that older mothers

Table 20.3 Fixed effect GLMM coefficients for infant death in the first month of life at Cayo Santiago from 1960 to 2003

	Coefficient	SE	Wald <i>P</i>
(Intercept)	−0.924	0.127	
1975–1984 cohorts	0.004	0.072	<0.001 ^a
1985–2003 cohorts	−0.254	0.064	
Maternal age	−0.132	0.026	<0.001
Maternal age ²	0.007	0.001	<0.001

^aTest for significance of all levels of time period

Table 20.4 Variance components and ratios for death in the first month of life at Cayo Santiago

Variance	Component±SE	Ratio	<i>P</i>
V_A	0.000±na ^b	$h^2_{anim} = 0.000$	na
V_M	0.131±0.029	$m = 0.116$	<0.001
V_R^a	1.000±na		

^aVariance of the probit link function requires this fixed at $V_R = 1$

^bNot estimated

are less active, spend more time in contact with their infants, and have smaller infants. Whether individual mothers differ in these age-related patterns of somatic and behavioral change that translate into mortality risks for their infants is a more difficult question beyond the scope of this analysis, but it can be addressed with random regression models used by animal breeders and ecologists (e.g. Meyer 2001; Brommer et al. 2007). Because all models of the evolution of senescence predict increasing genetic variance with age, we would predict that mothers become more heterogeneous in their effect on infant survival as they age (Hughes et al. 2002).

A further question about the maternal variance component is what it is actually measuring. The average environment provided by a mother is a large combination of behavioral and physiological characteristics. Some of these certainly have a genetic basis themselves, such as milk composition and yield or even responsiveness to infant solicitation (Nickerson 1995; Maestripieri 2003). This means they can evolve through direct selection on mothers or indirectly through selection on the survival of their infants. Conversely, infant traits can evolve through direct selection on infants or indirectly through selection on traits of mothers (Cheverud and Moore 1994). Slightly more elaborate quantitative genetic models for infant traits allow separating the maternal identity variance into genetic and nongenetic components. Alternatively, simple models for particular maternal traits like milk phenotypes or style of care can demonstrate a genetic basis for maternal variation directly (Bijma 2006).

This vignette makes the counterintuitive point that quantitative genetics is a very useful way for studying environments. I mean this in two ways. The first comes from the fact that partitioning variance into genetic and environmental

sources requires a good understanding, data, and statistical model of factors in the environment that affect phenotypes (e.g., maternal age). Second, when important environments are those provided by the phenotypes of other population members (e.g. mothers), quantitative genetics is invaluable for understanding the genetics of those phenotypes and thinking through how they should evolve (Wolf et al. 1999; Cheverud and Wolf 2009).

20.3.3 *AFR Is Traded Off with Adult Survival*

The final vignette of this chapter returns to the problem of life history trade-offs discussed above. The example extends the quantitative genetic analysis of female AFR to explore its phenotypic and genetic relationships with later life events (Blomquist 2009d), which will be measured with phenotypic and genetic correlations (Stearns 1989; Bell and Kofoupanou 1986; Reznick 1985). This approach of looking for trade-offs between two traits is simplistic and potentially problematic when we know that life histories involve many more traits, such as infant survival described above (Roff 2002). However, this is still a good place to start; once bivariate relationships are better understood, then we can start adding in greater complexity.

The question to be answered is “What is the cost of early life reproduction?” For long-lived, slow-reproducing female mammals like primates, the greatest cost they can pay is in reduced later life survival, because the only way for females to have many offspring is to live many years (Fig. 20.6). This suggests there could be a trade-off between female AFR and later life survival. Females that mature earlier would pay a cost of reduced lifespan, while those that delay reproduction for one or more years would be rewarded by a longer lifespan. This would be reflected by *positive* phenotypic and genetic correlations between AFR and lifespan or survival rates. The genetic correlations are predicted by the antagonistic pleiotropy theory of senescence (Williams 1957). Under this model, aging is caused by alleles with positive fitness effects early in life offset by negative consequences at advanced ages.

I used individual survival rates to ages 11, 16, 21, and 26 to gauge later life survival. These are basically the ratio of lifespan and the age cutoff and offer some advantages over analyzing lifespan itself (Blomquist 2009d). Like AFR most all of these have heritabilities significantly greater than zero (range: 0.13–0.39). Their phenotypic correlations with AFR are all positive but very weak (range: 0.083–0.132). The largest of these correlations are for the younger survival rates (ages 11 and 16) and both are statistically significant or nearly so (Table 20.5). The implication of these small positive correlations is that any trade-off between early reproduction and survival is very weak and may only affect survival over the first decade after maturation.

However, the genetic correlations are all large and positive (range: 0.476–0.706), indicating a strong trade-off between AFR and later life survival (Table 20.5). None

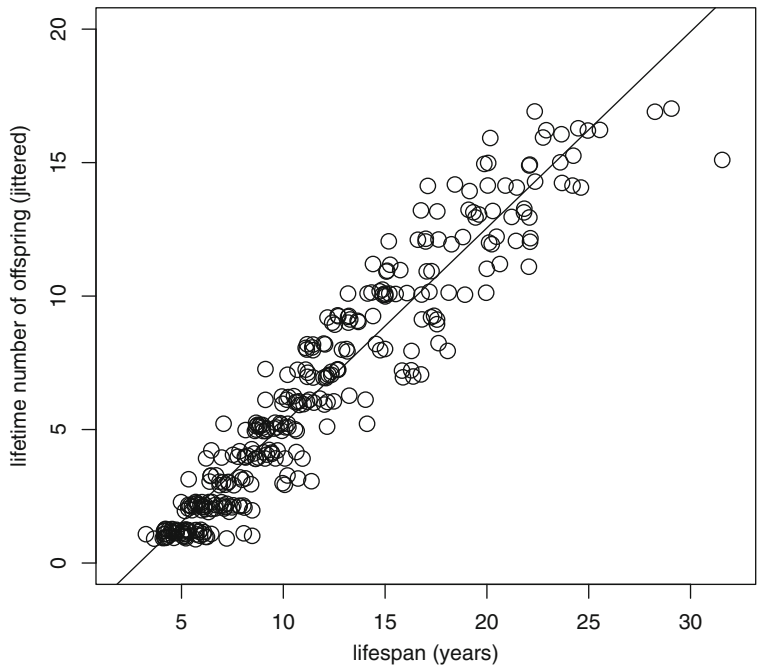


Fig. 20.6 Regression of lifetime number of offspring on adult lifespan for female rhesus macaques at Cayo Santiago ($P<0.0001$, $R^2=0.91$). Small random deviations (jittering) are added to number of offspring to expose overlapping points

Table 20.5 Phenotypic (r_p), genetic (r_A), and residual (r_R) correlations between female AFR and adult survival rates to age x (s_x)

	s_{11}	s_{16}	s_{21}	s_{26}
r_p	0.1094* <i>0.065</i>	0.1323** <i>0.032</i>	0.1008 <i>0.141</i>	0.0834 <i>0.288</i>
r_A	0.5900* (0.320) <i>0.067</i>	0.5945*** (0.215) <i>0.006</i>	0.4763*** (0.170) <i>0.006</i>	0.7062** (0.283) <i>0.013</i>
r_R	0.0229 (0.063) <i>0.716</i>	−0.0281 (0.068) <i>0.680</i>	−0.0234 (0.082) <i>0.775</i>	−0.0231 (0.076) <i>0.761</i>

Standard errors are given in parentheses and P -values in italics above the correlation * $P<0.10$, ** $P<0.05$, *** $P<0.01$

of the residual correlations between AFR and survival rates are significant, although most of them are weakly negative, implying that environmental effects that promote early maturation will raise later life survival. It is this combination of strong positive

genetic correlations and weak negative residual correlations that results in the weak positive phenotypic values.

The strong positive genetic correlations between AFR and adult survival identify an important genetically mediated constraint on the reproductive decision-making of female macaques. Heavy investment in offspring production early in life imposes a cost of reduced lifespan for female macaques. For example, if we use the estimated genetic variances and covariances for AFR and survival to age 16, the cost of maturing 1 year earlier is a loss of about 11 months of adult life (Blomquist 2009d). Of course, there is a cost to delaying reproduction because it increases the risk of dying before ever reproducing.

The weaker phenotypic pattern probably results from environmental variation that affects each trait in similar ways and drive the negative residual correlations. For example, abundant resources or reduced psychosocial stress may allow earlier maturation and elevated survival rates. This phenomenon is sometimes called “silver spooning” as individuals living in beneficial environments often have high survival and fertility, just like the wealthy in human populations can spend lavishly on their homes, cars, clothing, and entertainment simultaneously and seemingly avoid any trade-offs in allocating their income (Grafen 1988; van Noordwijk and de Jong 1986). The opposite is also true: bad environments that delay maturation will probably also reduce survival rates. Simple models of variation in resource acquisition and allocation show that trade-offs—which are about allocation variation—will often not be apparent phenotypically when there is a great deal of variation in the resources available to population members (Roff and Fairbairn 2007). Quantitative genetic techniques are one way around this problem because the genetic correlations should be unaffected by environmental “silver spooning” and reflect trade-off-related allocation decisions.

20.4 Conclusions

These three vignettes offer a small taste of the sorts of questions mammalian and avian ecologists have addressed with quantitative genetic methods in recent decades (Kruuk et al. 2008). It may have been obvious that these techniques are “data hungry,” requiring large numbers of phenotyped individuals linked up by extensive pedigrees. This is likely to prohibit their use with wild primate populations until/unless sufficient numbers of individual measurements become available from long-term research projects to achieve adequate statistical power (Jones et al. 2010; Quinn et al. 2006). It also emphasizes the extraordinary value of these projects and need for proper archiving and sharing of data (Strier et al. 2010).

The situation in captive primate colonies is quite different. Large numbers of primates in extensive pedigrees are being kept around the world (Rogers 2005), but, with some notable exceptions (e.g. Gagliardi et al. 2010; Ha et al. 2002; Martin et al. 2002; Jaquish et al. 1997, 1996; Williams-Blangero and Blangero 1995), they have rarely been used for quantitative genetic studies of phenotypes relevant to research on primate life history evolution and reproductive biology.

While estimating heritabilities or other quantitative genetic statistics has some value in itself for considering evolutionary dynamics of traits (Roff 1997), they become especially valuable when they identify new questions or can be used testing theoretical predictions about primate infants and their (allo)maternal caretakers. The examples above emphasize how life histories are a complex of genetically entangled traits (Rice 2004). Maturing early costs females reductions in later life survival. Maternal characteristics, many of which likely have a genetic component, drive variation in infant death rates and they change as mothers age. Dealing with this complexity quickly goes beyond our familiar adaptive logic of selection on individual traits. The benefit of an evolutionary quantitative genetic perspective, then, is to integrate studies of different parts of the life cycle, and potentially disparate aspects of behavior and physiology, by linking them in explicit models (Lynch and Walsh 1998).

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Chapter 21

Cultural Evolution and Human Reproductive Behavior

Lesley Newson

Keywords Cultural evolution • Reproductive behavior • *Homo* • Social learning • Family identity • Parenting

21.1 Introduction

There is much that is “typically ape” about the way humans go about living their lives and building their babies (e.g., Chapais 2008; Smith and Tompkins 1995). Among mammals, apes and humans are characterized by low lifetime fertility, a slow pace of reproduction, and a large investment in each offspring. Many of the differences between apes and humans can be considered differences of degree and not kind. For example, like other apes, humans have a large brain in comparison to our body size. The human brain is extreme, however, being about three times the size of the chimpanzee brain. Since brain tissue is “expensive” to maintain and build (Aiello and Wheeler 1995; Isler and Van Schaik 2009a), humans have an even bigger problem providing our developing babies with sufficient nutrition. Much of what is *not* typically ape about humans is a consequence of the fact that human populations share a complex culture. In this chapter, I will describe the role of culture in human reproduction and suggest how the motivations and abilities that maintain culture could have coevolved with human life history and parenting behavior.

In both primates and birds, larger-brained species are more innovative and better able to cope in environments that change unpredictably (Lefebvre and Reader 2004). Chimpanzees and humans are both excellent learners, but humans are unique in the extent to which we benefit from and rely on social learning (Whiten et al. 2009). Social learning is learning that is influenced by the presence of other individuals

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(Heyes and Galef 1996). For example, observing or smelling more experienced conspecifics gives young animals information about what is safe to eat and may help them learn how to acquire food items that are difficult to extract (Galef 1996; Terkel 1995). Humans have evolved a suite of behaviors, preferences, and cognitive capacities which facilitate social learning. An obvious example is language. By using symbols (i.e., words), humans can communicate complex ideas and information from more experienced to less experienced minds (Deacon 1997). The use of language requires a number of cognitive capacities such as word learning (Bloom 2000) and the ability to understand and to share behavioral and communicative intentions (Tomasello 2008). The use of language also relies on behaviors and preferences which motivate individuals to communicate useful information to others and to decide (consciously or unconsciously) what information to communicate and which communications to pay attention to and remember (Richerson and Boyd 2010).

When members of a group learn from one another, they inevitably share a body of information, or “culture.” A number of social animals can be considered to be cultural (i.e., they exhibit group-specific behaviors, preferences, and technology), but the exceptional sociality of humans and our capacity for social learning create culture of far greater complexity (Boyd and Richerson 1996). The intergenerational transfer of information in human populations results in the accumulation and change of culture over time. In the 1970s, it was recognized that this cultural change is analogous to the genetic change that occurs in a population over time (Cavalli-Sforza and Feldman 1981; Boyd and Richerson 1985). This led to the development of theories of “cultural evolution” based on Darwinian theory. It was proposed that human behavior is best understood as the result of two inheritance systems, genetic and cultural (Richerson and Boyd 1978). Over the years, increasing numbers of scholars in a variety of disciplines have made use of this “dual inheritance” approach (e.g., Bowles and Gintis 2011; Laland and Brown 2011; Mesoudi 2011; Whiten et al. 2011). According to dual inheritance theory, each human child is heir to a vast body of cultural information but the acquisition of this information is more complex than the acquisition of genetic information. A child’s genetic information is randomly assembled from the genetic information of its parents and set at the moment of conception. By contrast, the child will have many cultural parents because human social networks transcend biological relationships. She will acquire new cultural information throughout her whole life and will actively adopt this information rather than just passively receive it. She will forget or ignore much of the information she is exposed to, and she will sometimes modify the information she adopts. These modifications may be intentional, based on her experiences, or she may just misremember something. The selective remembering and modification of cultural information by members of a population causes their culture to change. This is not random change. The culture of a population at any one time has evolved from the culture that existed at a previous time. Useful and appropriate new variants are adopted more often than inferior ones. These are therefore observed more frequently and thus spread more quickly. Cultural change is often directed but change is not dictated by a single individual. Humans can talk about ideas and this allows

us to socially process the information they contain. Groups of people formally or informally reach a consensus about how things are or how they should change.

Human reproductive behavior, like all human behavior, can only be fully understood if the role of culture is considered. However, simply describing cultural influences yields limited insight without an appreciation of how and why members of a population generate and maintain the cultural information that they share (Richerson and Boyd 2005). Dual inheritance theory suggests that the shared cultural information evolves alongside a population's genetic information. In humans, changes in genes and culture both influence the phenotypes on which natural selection works, and so the gene pool and the pool of cultural information coevolve. In this chapter, I will use a gene–culture coevolutionary approach to consider the unique aspects of human reproductive behavior and life history and their divergence from that of the great apes. Section 21.2 looks at links between human life history, our cooperative style of raising offspring, and increasing brain size during the last two million years of human evolutionary history. Section 21.3 describes the heterogeneous and unstable habitats occupied by our ancestors and discusses the adaptations which made cooperative care of young beneficial in such environments. Section 21.4 describes the cultural mechanisms used by human groups to organize cooperation in the care of young. Section 21.5 discusses the role played by social learning and cultural evolution in the evolution of cooperative breeding in hominins and how a gene–culture coevolutionary process led to the emergence of a social psychology that supports the complex culture and widespread cooperation we see in humans. Finally, Sect. 21.6 looks at the reproductive behavior of modern humans. How might the rapid changes in reproduction we are currently experiencing be explained in terms of a reaction of our evolved psychology to a novel social environment?

21.2 The Coevolution of Life History, Cooperative Parenting, and Brain Size

Like great apes, humans have a slow life history and a long period of dependency after birth (Charnov and Berrigan 1993), only more so (Walker et al. 2006b). Chimpanzee females are usually over the age of ten when they give birth to their first offspring, about a third of the way through their entire lifespan (Wallis 1997). Most human females are considerably older than this when we begin to reproduce (Walker et al. 2006a) but we also live longer. Birth and weaning occur at an earlier stage of development in humans than in apes, which means that our children require more care and protection at these life events. One life history feature that is probably unique to humans is the period of active good health, often more than two decades long, which many women enjoy after their last child is born (Caro et al. 1995; Gurven and Kaplan 2007).

The longer nonreproductive periods that occur at each end of human life history result in human groups having a higher proportion of nonreproductive members.

This has led a number of scholars to suggest that these differences coevolved with differences in parenting style (Hawkes and Paine 2006). In contemporary human populations, the young receive a considerable amount of parental care from “allo-mothers,” i.e., individuals other than their mother, which suggests that humans can be considered “cooperative breeders” (e.g., Gurven and Hill 2009; Hill and Hurtado 2009; Hrdy 1999, 2009; Mace 2000; Sear and Mace 2008). Our ape relatives are not cooperative breeders, so independent mothering is likely to be ancestral in the hominin line. It is reasonable to conclude, therefore, that at some point, since the chimpanzee and hominin lineages diverged about six million years ago, hominin mothers began to rely on others for help in raising their offspring.

Humans grow more slowly than apes during the juvenile stage of development, between weaning and sexual maturity (Bogin 2006; Kramer 2005; Kramer and Ellison 2010; Walker et al. 2006b). Though unable to reproduce, juveniles can increase their inclusive fitness by helping to care for their siblings, cousins, and nieces and nephews. Human juveniles are still dependent on adults during this stage but studies of human foragers have shown that in some environments boys and girls can acquire up to 50% of their daily calories as well as performing work, including caring for infants and younger children. This allows adults to work at more skilled and complex tasks. The length of nonreproductive childhood is variable; the age at which puberty occurs is influenced by the health, nutrition, and activity of the child (Cameron 1996). Thus, during times of relative abundance, when the help of carers is less necessary, human females may begin their reproductive careers earlier (Gluckman and Hanson 2006; Walker et al. 2006a). While some nonhuman primates have been observed to experience menopause toward the end of their lives (Walker and Herndon 2008; Caro et al. 1995), it is common for women, even women in foraging populations, to enjoy vigorous good health for a decade or two after they cease to ovulate (Gurven and Kaplan 2007). These older women cannot reproduce but they can continue contribute to their inclusive fitness by increasing the survival of their children, grandchildren, and other relatives (Hawkes et al. 1998; Sear and Mace 2008). Because relatives and other members of their community provide help provisioning and caring for their children, human mothers can have shorter interbirth intervals than apes even though their babies are born at an earlier stage of development than apes, are more helpless at birth, and take longer to mature. Human mothers often have several dependent children at the same time (Robson et al. 2006).

Mother apes are protected from having to care for more than one offspring at a time because ovulation is suppressed by the hormone prolactin, which is released in response to the physical action of the infant sucking on the nipples (Konner and Worthman 1980; McNeilly 2001). When sucking is reduced below a threshold, either because her infant is dead or dying or because it is mature enough to gain sufficient nutrition from its own foraging, a female ape begins to ovulate. Similar ovulation suppression mechanisms are present in humans (Konner and Worthman 1980) and the metabolic load of meeting the nutritional demands of the suckling infant has also been found to inhibit ovulation (Valeggia and Ellison 2001). But if

resources are sufficient, interbirth intervals can be shorter in humans than in apes because of another feature of human parenting: humans tend to wean their infants earlier. Infants are given food to supplement breast milk, often starting at about six months of age (Hawkes and Paine 2006; Sellen 2007). The proportion of the infant's diet that is made up of these complimentary foods increases until its suckling is below the threshold that allows ovulation to commence. Thus, a human mother can begin to gestate her next child many years before the previous one can support itself by its own foraging (Robson et al. 2006).

The fossil evidence of hominin evolution provides little help in describing how and why human parenting behavior and life history diverged from that of the apes. It may, however, contain clues about the timing of the changes. A comparison of life history variables and encephalization (brain mass in relation to body mass) of a range of primates shows that greater encephalization is associated with a longer slower life history (Barrickman et al. 2008). The rate of growth is limited by the speed at which nutrients can be supplied to support brain growth. The costs of growing a larger brain appear to be compensated for by a longer and/or more efficient reproductive lifespan. The fossil evidence suggests that the encephalization of hominins assigned to the *Australopithecus* genus was about the same as that of the chimpanzee (Foley and Lee 1991). It is some time after the appearance of *Homo*, in fossils dated to about 1.8 million years ago, that evidence of encephalization considerably greater than that of chimpanzees is found (Rightmire 2004). To grow this larger brain, infants would have needed nutrients to be supplied more rapidly than apes and earlier hominins. Isler and Van Schaik (2009a, b) argue that a mother's foraging alone could not have supplied nutrients fast enough and suggest that the mothers must have been receiving help from others. More rapid brain growth and a longer period of brain growth may have also necessitated giving unweaned infants supplementary food (Kennedy 2005; Sellen 2006). If Isler and Van Schaik are correct, hominin females have been receiving help with provisioning their young for at least 1.8 million years. Two million years BP also roughly coincides with the appearance of more complex stone tools and the appearance of hominin fossils outside Africa (Klein 2009).

It may be reasonable to conclude that extra provisioning from alloparents allowed the evolution of larger brains. However, it is misguided to try to nominate a single change in behavior, physiology, or anatomy which triggered a cascade of changes leading to modern humans. The evolutionary process consisted of incremental and concurrent changes in many elements of hominin biology. As one change occurred, it allowed, necessitated, or was accompanied by other changes. For example, the association between brain enlargement and lengthening of hominin life history suggests a way that these changes could have helped to drive the evolution of cooperative breeding. A lengthening of life history would have increased the supply of alloparents by creating a semi-independent juvenile stage when youngsters were unable to forage well enough to support themselves but strong enough to carry a baby and relieve a mother of some of the burden of protecting it. But the argument for causation in the other direction is just as strong. Semi-independent juveniles

would not have been available to help if adult alloparents were not already acquiring food in excess of their own requirements and sharing it with the juveniles.

21.3 Flexible Parenting for Chaotically Variable Environments

One independent factor in the interconnected cascades of change described above was the climate. During the last two and a half million years, the Earth's climate has been extremely unstable with recurrent ice ages (Ditlevsen et al. 2002; GRIP 1993; Lehman 1993). The appearance of the earliest fossils assigned to the *Homo* genus coincides with the Plio-Pleistocene, a period when moist woodland and rainforest habitats of Africa were retreating and being replaced with areas that had a more arid, heterogeneous, and unstable climate (Passey et al. 2010; Trauth et al. 2005). Fossil evidence suggests that these expanding habitats were exploited by members of the *Homo* genus but not Australopithecine hominins whose residence in Africa overlapped with that of *Homo* for half a million years or more (Bobe and Leakey 2009; Kingdon 2007). It has been inferred from this that *Homo* had evolved adaptations not present in Australopithecines and hominoids which allowed them to exploit arid, seasonably variable habitats with a patchy distribution of resources (Potts 1998; Reed 1997). Such adaptations may well have also preadapted *Homo* to dispersal and colonization of other habitats (Wells and Stock 2007).

Cooperative breeding could have been one of the adaptations which allowed hominins to exploit the variable and unstable Plio-Pleistocene habitats. Many of the cooperatively breeding birds in Africa and Asia exploit such habitats, and some employ the nomadic lifestyle commonly seen in human foragers (Emlen 1984). The slow life history and low fecundity of apes are adaptive in the moist wooded habitats which are occupied by contemporary apes because a strategy of investing in a small number of slow growing infants is effective in an environment where predation risk is low and resources are sparsely but evenly distributed over space and time. The ape lifestyle much less suited to habitats with high predation risk in which levels of resources fluctuate and/or sources of food are widely and unevenly distributed (Wilbur et al. 1974). Cooperative breeders have adaptations which allow them to cope with variation. By adjusting the proportion of mothers to allomothers in response to resource fluctuations and predation risk, cooperative breeders can be flexible in the number of offspring produced and increase the chances of giving sufficient care to each one (Clutton-Brock 1991; Emlen 1984).

Deciding which of the females in a group will conceive at any given time and which will not reproduce and instead exert effort to help raise the young of other females is a problem of coordination but it can also be viewed as cooperation between females who are competing for limited breeding opportunities (Bergmüller et al. 2007). Cooperative breeding has independently evolved in many families of mammals and birds, including callitrichine primates (Solomon and French 1997; Stacey and Koenig 1990). Solutions to the coordination problem have emerged in

each evolutionary trajectory. The cooperative breeding seen in human groups is of the less common “plural” type in which more than one of the adult females in a group produces offspring (e.g., banded mongooses: Cant 2000; Cant et al. 2010), compared to singular breeders in which there is a single breeding female per group (e.g., callitrichine primates: French 1997; Puffer et al. 2004). In plural cooperative breeders, solving the coordination problem of who breeds and who helps is more complex. In banded mongooses, for example, it has been found to involve intra-group and intergroup aggression, infanticide, and abortion (Cant 2000).

Anatomically modern humans have physiological and behavioral mechanisms which help to solve the coordination problem of which group members reproduce and which help them raise their offspring. Postmenopausal women and prepubescent children cannot be parents. People who are undernourished, exhausted, and severely stressed are less fertile (Cameron 1996; Vallengia 2009; Vallengia and Ellison 2001) and may also be less inclined to mate. These rather blunt mechanisms are fine-tuned with social mechanisms. Like many other cooperative breeders, humans are sensitive to social cues when deciding whether to reproduce now or to postpone reproduction. The cues are much more complex and varied in humans than other cooperative breeders, and many of them are part of the cultural information that populations share.

21.4 The Role of Culture in Human Reproduction

Behaviors associated with reproduction are more diverse in humans than any other animal species (e.g., Hrdy 1999; Low 2000). Mating systems observed in humans range from polygyny to monogamy to polyandry. The kinds of help mothers receive and who provides that help are also highly variable (Vallengia 2009), and variability between groups is much greater than the variability within groups (Hrdy 1999). To some extent, the intergroup variability can be explained by the tendency for people to behave like their friends and family members. The influence of culture is more complex than this, however. Many of the social cues which individuals use to determine when to reproduce are bound up in cultural institutions—rules, customs, beliefs, and rituals—which members of a population share.

Despite the vast diversity in reproductive behavior, human behavioral ecologists have found consistencies which suggest that humans match their rate of reproduction to the availability of both physical resources and the social resources mothers must draw on for help in raising her offspring (reviewed in: Cronk 1991; Low 2000; Volland 1998). For example, all populations have culturally evolved kinship institutions which recognize that certain kinship relationships (biological and fictive) imply an obligation to provide help when needed (Brown 1991). Marriage and marriage-like institutions link public recognition of a sexual relationship with a woman to an understanding that children born by the woman are related to this partner (or partners) and his (their) kin. This suggests that these norms and customs are culturally evolved by populations to adjust reproductive rate in response to fluctuating

resource availability and to solve the coordination problem of who is a parent and who is an alloparent.

The details of marriage-like institutions tend to differ in systematic ways. When land is inherited down the female line, as is the case with many African horticulturists, marriages tend to be unstable and men are more likely to invest in their nieces and nephews than in their own offspring (Mace 2000; Scheider 1961). By contrast, when greater strength is needed to defend or exploit heritable resources, they are likely to be passed down the male line. In such cultures, norms prescribe strong stable marriages with extensive investment by the father and his kin. The reproductive behaviors seen in foraging cultures are the most diverse. For example, before contact with Westerners, the Aché and related small-scale cultures in central South America had “partible paternity” institutions (Beckerman and Valentine 2002; Mesoudi and Laland 2007). These institutions were based on the belief that the paternity of a child is shared among all the men who had had sex with its mother at about the time of its conception. Children with several fathers were believed to be stronger than children with only one or two fathers. This may have been the case because a child with several “fathers” had more relatives who took an interest in his or her welfare.

Control of reproduction through cultural norms inevitably demands that individual members of a group make reproductive decisions that conform to behavior the group deems to be appropriate (Newson et al. 2005). For example, young adults may be obliged to accept the spouse their older relatives have chosen (Apostolou 2007). It might be expected that relinquishing control of reproductive decisions will reduce an individual’s fitness, but this appears not to be the case, at least not in pre-industrial societies. Human behavioral ecologists studying such societies have found that the reproductive decisions made by individual members are consistent with Darwinian prediction that each will strive to maximize his or her inclusive fitness given the availability of resources. Individuals who achieve greater cultural success, who control more resources and/or have more social influence, have greater reproductive success (e.g., Borgerhoff-Mulder 1988; Cronk 1989, 1991; Hill and Hurtado 1996; Irons 1979; Low 1999, 2000; Low and Heinen 1993; Mace 1996; Voland 1998; Wang et al. 1995). This suggests that reproductive norms do not eliminate competition in human populations. They may instead make competition less costly by reducing hostility and aggression among competing group members and kin groups and reducing the risk of children being born that cannot receive adequate care (e.g., Henrich 2012).

21.5 Learning and Culture in the Coevolutionary Mix

The anatomically modern humans that make up contemporary and historical populations are very different from the much more ape-like hominins living more than 1.8 million years ago. The fossil record contains no clues to the mechanisms which our ancestors might have used to solve the coordination problem of which females

are mothers and which are allomothers. However, techniques have been developed for inferring the age and stage of development of the small number of hominins whose bones and teeth have been found (Bogin 2006; Gibbons 2008). They suggest that the expansion of the childhood period, when sexually immature individuals could provide alloparental care, had begun by about two million years ago.

Hrdy (2009) argues that a cooperatively breeding group provides the selective environment which encourages the evolution of “prosocial” inclinations, i.e., the tendency of individuals to choose to behave in ways that benefit fellow group members. She points out that behaviors such as food sharing, teaching, and shared attention (the tendency of interacting pairs to pay attention to the same thing), which are rarely seen in apes, are commonly observed in groups of cooperatively breeding species. Burkart (2009) suggests that when an animal with the cognitive skills of an ape evolves the prosocial behaviors associated with cooperative breeding, information sharing will become more efficient and culture can become more complex. Groups of chimpanzees can be said to possess shared cultural information, but individuals have rarely been observed to actively share information by teaching the young or correcting their behavior.

If early *Homo* individuals learned parenting and foraging techniques from one another, it is reasonable to speculate that cultural evolution contributed to the coevolutionary processes that changed parenting behavior, hominin life history, and brain size. Cultural changes would influence and be influenced by genetic changes (Richerson et al. 2010). For example, in harsh environments, adults who behave in ways that encourage juveniles to protect and help provision their younger relatives are likely to have more surviving offspring. This encouragement could take the form of adults behaving aggressively to juveniles when they hurt or threaten a younger child and affiliatively when they help a younger child. Such simple operant conditioning would bring short-term benefits, but it would also bring selection to bear on the genes influencing behavior (Laland 1994; Laland et al. 2010; Richerson et al. 2010). Juveniles who were better at avoiding punishment and gaining approval would have been more likely to survive, so the genes associated with more docile and obliging behavior would have been selected. Children subject to a regime of punishment and reward would be more likely to employ such methods themselves when they become parents. If they migrate to other groups when they mature, this parenting behavior would likely spread around the local population.

Socially learned behaviors would have helped to drive the evolution of cooperative breeding, but cooperative breeding would have also driven the evolution of better social learning skills. Improved social learning skills will only be favored by natural selection when it is more efficient to learn by observing others than by learning individually (Boyd and Richerson 1996; Laland et al. 1996; Van Schaik and Burkart 2011). In groups that breed cooperatively, social learning is more efficient because youngsters have the opportunity to observe several different experienced individuals. A chimpanzee spends the first four years of its life in constant contact with its mother, and she is the only experienced individual it can observe closely (Henrich 2010). When novices can observe several experienced individuals, the most successful learners will be those who can most efficiently decide *who* and

what to copy. Ideally, they should be able recognize when an old familiar technique is less efficient than a new one and consider switching to the new technique. One observation of social learning in chimpanzees suggests that they lack this ability. Chimpanzees who learned by observing a technique for obtaining a reward from an experimental “artificial fruit” continued to use this technique even after observing a different technique which yielded a much larger reward (Whiten et al. 2009).

As hominins became better at recognizing superior behaviors and techniques, superior cultural variants would build up more rapidly in the population (Boyd and Richerson 1985; McElreath et al. 2008; Mesoudi 2011). The increasing usefulness of the shared information would strengthen selection of individuals who were good at learning it. In such a group, the success of each individual depends on the behavior of his or her groupmates. Greatest success would be achieved in the groups whose members were the best learners and most prepared to allow others to learn from them (Csibra and Gergely 2011). The increased cleverness and cooperation may require an even larger and more expensive brain, but if culturally acquired foraging techniques make it possible to gain sufficient resources to support a larger brain, then brains can get larger (Boyd et al. 2011).

Complex culture not only provides humans with useful expertise; it also creates differences between human groups which can potentially lead to competition between groups. This is important because when competition occurs between groups of individuals, natural selection can begin to favor group-promoting behaviors on the part of group members (Wilson 1997). A larger body of cultural information can accumulate in groups with members who are inclined to share information more widely (Henrich 2004). Cooperation will be closer in groups that develop institutions for enforcing and/or rewarding behaviors that resulted in effort and resources being distributed more fairly (Boyd and Richerson 2006). The membership of successful groups would increase not only because of the increased survival and reproduction of its members but because successful groups would be more likely attract immigrants from other groups (Boyd and Richerson 2008). Much of the difference between groups would be cultural but, as group life began to demand closer cooperation, more trust, and greater trustworthiness, natural selection would favor genes which made individuals better communicators and more inclined to prosocial behavior (Richerson and Boyd 2001a).

Kaplan and Gurven (2005) have suggested that once human groups had evolved culture complex enough to include language, group members could “negotiate” norms that would facilitate cooperation by establishing locally agreed conditions for the distribution of resources and reproductive opportunities. Such norms could never please all group members and would therefore be subject to interpretation and continual renegotiation. In this way, human populations would use their unique capacities for culture to create and constantly recreate cultural mechanisms that solve the problem of who will be a parent and who will be an alloparent.

For over half a century social psychologists have observed the behaviors that underpin human sociality (e.g., Baumeister and Bushman 2008). This research has mostly comprised observation of people in economically developed Western countries and detailed conclusions about the way *all* humans behave cannot be drawn

from such culturally uniform samples (Henrich et al. 2010). The results demonstrate, however, that even in Western cultures, which are perceived to be highly individualistic, people are motivated to form and maintain interpersonal attachments (Baumeister and Leary 1995) and inclined to behave in ways likely to gain approval from those they are attached to. We categorize ourselves and others into groups, and we are inclined to behave in ways characteristic of the groups we identify with (Turner et al. 1994). The feeling of being excluded is painful (MacDonald and Leary 2005). In Western samples, a strong social identity, multiple social identities, and an ability to identify with new groups are associated with psychological health (Haslam et al. 2009; Iyer et al. 2009).

Social interaction within groups generates norms—behaviors, beliefs, and preference which are “normal” for the group (Postmes et al. 2000, 2006). These norms are internalized by the members so that they also seem “normal” to each individual group member. However, just as humans are selective about the cultural knowledge they acquire, they are selective and rather flexible in their application of social norms. They tend to conform to whatever social group they feel part of at the moment. The salience of different social identities can be manipulated experimentally and yield predictable responses not just in behavior but in cognition (Swaab et al. 2007). This research has led some social psychologists to conclude that social identity does not just supply rules of appropriate behavior; it provides members with a way of interpreting the environment and gives direction to their lives (Haslam et al. 2006). This is consistent with the idea that humans have an evolved psychology which adapts them to be part of closely cooperating groups (Richerson and Boyd 2001b; Sober and Wilson 1999). When group members interact, they develop a shared perception and group goals.

21.6 Low Fertility in Wealthy Societies: A Case of Mismatch?

Many people living today have access to resources far in excess of what was available to our ancestors during most of human evolutionary history. Yet the fertility of the wealthiest populations is very low. Currently, fertility is low or declining rapidly in almost all human populations (UNPD 2009). An explanation of the biology of human reproduction must include an explanation of this apparent abandonment of the pursuit of reproductive success.

The adoption of the idea that it is prudent to limit family size is part of a suite of changes in beliefs and values related to the family and reproduction (e.g., Inglehart and Baker 2000; Inkeles and Smith 1974). The adoption of family limitation by a population is easy to detect; the fertility of the population rapidly declines (see Fig. 21.1). Other changes are also dramatic. Beliefs about marriage and gender roles change. Children cease to be regarded as economic assets and are seen instead as financial responsibilities. These changes began in the last 300 years and accompany a change process often referred to as “economic development,” which includes the introduction of new technologies and changes in the structure of communities as

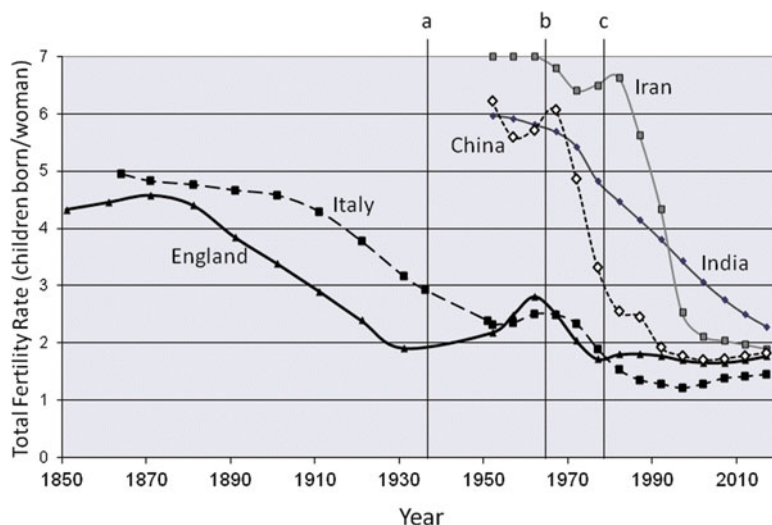


Fig. 21.1 A number of “folk theories” exist for the cause of fertility decline, such as that it is due to the introduction of contraceptive technology, the declining power of religion, or, in China, a “one-child policy” imposed by the government. However, the course of the decline in fertility in a few countries shows these causes to be implausible. The first advance in contraceptive technology, the rubber condom, only became available in 1935 (a), long after most European populations had experienced their fertility decline. Birth control pills did not become widely available until the mid-1960s (b). 1979 (c) was the year of the Iranian revolution when religious leaders came to power in Iran and also the year that China instituted the one-child policy, at a time when most Chinese had already adopted family limitation [demographic data from Coale and Watkins (1986) and the United Nations, Department of Social Affairs (http://esa.un.org/wpp/unpp/panel_indicators.htm)]

well as economic change. The phrase “economic development” implies the existence of some identifiable end point at when an economy can be considered “developed” and stable. This is clearly not the case with the change process humans are currently experiencing. Populations of European descent, which began the change process several generations ago in the seventeenth century, are still experiencing rapid cultural change.

Scholars trying to understand what is driving these changes are faced with a large array of collinear variables representing aspects of wealth, health, urbanization, employment, education, exposure to modern media, and much more. Changes in attitude are measured, but how accurately these reflect changing beliefs and values is difficult to ascertain. Objective analysis is hampered because the analysts are part of this change, and so they share modern beliefs and values. For example, it has long been part of Western culture to perceive premodern people as “primitive” or “irrational.” They are seen as being caught in the “Malthusian trap” in which technological improvement leads to a larger population and prevents “advancement” to a more comfortable and interesting life (e.g., Galor 2005). Darwinian theory encourages a more objective view; the Malthusian trap is an inevitable consequence of the

competition for reproductive success. If premodern beliefs are associated with greater fitness, they are easier to explain in Darwinian terms than those associated with the low fitness which is integral to our current “modern” way of life. Despite this understanding, contemporary Darwinists are culturally modern people, so we are likely to disapprove of fathers and husbands controlling young women or parents making their children go to work. Modern ethnocentrism makes it seem obvious why such practices must be abandoned, but a more objective and theoretically informed view reveals it to be a fascinating puzzle (Borgerhoff Mulder 1998).

Many social scientists who take an evolutionary approach have proposed some kind of environmental “mismatch” (Barkow et al. 1992) as an explanation for modern low fertility. They note that the adoption of family limitation occurs as a number of environmental factors diverge from those in which human reproductive behavior evolved and suggest that, due to a novel factor (or novel factors), evolved psychological mechanisms which maximized fitness in previous environments no longer operate. One novel factor is the availability of contraception (Perusse 1993). However, in many European populations the fertility decline was virtually complete before any contraceptive technology became widely available (see Fig. 21.1).

The cultural changes associated with “economic development” clearly affect the costs of raising children, and some human behavioral ecologists have considered this as a reason for declining fertility. As mentioned above, humans, like all primates, produce a small number of offspring and invest a great deal in each one (Charnov and Berrigan 1993). The greatest reproductive success will be enjoyed by those who produce not simply the most offspring, but the most offspring who are able to compete successfully against other members of their generation (Kaplan 1996; Lawson and Mace 2011). Parents must judge how much to invest in an offspring to give it a good chance of competing successfully. Gibson and Lawson (2011) provide ethnographic evidence suggesting that parents may be investing more because infant mortality decreases with economic development. Increased child survival increases the chance that investment in children will pay off. They found that parents in Ethiopian villages invested more in their children when they had access to a development project that improved child survival. The extremely high parental investment in wealthy societies could be the result of a runaway process occurring in the evolutionarily novel circumstances of high resources and high child survival. Parents may feel it best to produce a limited number of offspring so as to invest enough to give them a sufficiently high chance of success (Lawson and Mace 2011; Mace 1998, 2008).

It is also the case that in economically developed societies, more investment is likely to be necessary if parents want their children to succeed in a competitive job market, make good livings, and have children themselves (Kaplan 1996). Indeed, in a wage labor economy, investment in education can yield very high rewards in terms of income and prestige. Even in wealthy societies, people with fewer siblings have a slight health advantage as well as greater cultural success (Lawson and Mace 2011). This superiority is not reflected in their reproductive success, however. There is no evidence that people from small families enjoy greater fitness

than those from large families, at least not in their own lifetime and that of their children (Kaplan et al. 1995).

Gibson and Lawson's (2011) investigations in Ethiopian villages revealed that declines in family size coincide with parents' beliefs that their children require more investment. Further support for changes in beliefs about the cost of children is provided by interviews with men and women from Bangladesh (Caldwell and Barkat-e-Khuda 2000) and Britain (Fisher 2000) who were part of the first generation to limit family size. In general, they believed small families to be more economically prudent than large families. The interviews showed, however, that size of their own families was not decided through discussion between parents about the costs of having another child. Fisher says of the 107 elderly working class men and women she interviewed in the 1990s:

... respondents did not state simply that they could not recall any discussion, planning, or decision-making but emphatically insisted that there was none (page 312).

Fisher concluded that the lack of discussion about controlling births was due to norms which prevented husbands and wives discussing sex. Her male and female subjects agreed that men initiated sexual intercourse and played the dominant role in the use of the two forms of contraception available at the time, condoms and withdrawal. The actual decision that resulted in the family having another child was usually made by the husband alone, often during sexual intercourse.

The beliefs influencing parental investment are embedded in the complex web of beliefs, values, and customs that affect the behavior of people in a community. They can, nevertheless, change very rapidly. After interviewing the residents of a group of Punjabi villages where a program to introduce contraception had failed, Mamdani (1972) concluded that Indian villagers would never voluntarily use birth control. He quoted many interviewees to show that they could not perceive that their lives could be better if they had fewer children. One of his informants was a man who made a living as a water carrier. He was contemplating a life of leisure as his six sons increasingly took over his work and began to support him. He said to Mamdani, "You told me I was a poor man and couldn't support a large family. Now, you see, because of my large family, I am a rich man." Mamdani's conclusions were proved wrong within 10 years as the fertility of the Punjabi villagers began to decline, even in women who were not taking advantage of the birth control program (Nag and Kak 1984). The same water carrier, reinterviewed in the early 1980s, reported that his sons were complaining that their lack of education prevented them getting well-paid work and said, "These days one shouldn't have more than two children."

Our understanding of the recent rapid changes in human reproductive behavior will progress as we gain more insights into the cooperative nature of human reproduction and mechanisms human groups evolved to determine who will be a parent and who will contribute effort in other ways. As argued in Sect. 21.3, cooperatively breeding animals do not make reproductive decisions in social isolation. Because cooperatively breeding parents cannot supply all the effort necessary to raise their offspring, calculating whether or not this is a good time to have a baby cannot be made on an individual basis. We therefore have no reason to expect that natural

selection would have equipped humans with the ability to make reproductive decisions without regard to information they receive during interactions with others. Instead, as argued in Sect. 21.5, evolution equipped humans to participate in social interactions in which information about reproduction and parenting is exchanged. These interactions lead to group members reaching tacit agreements about the allocation of parenting effort to guide decisions about which group members should reproduce and which group members should help them raise their children. These agreements are somewhat flexible. Cultural norms evolve as environmental conditions change. Young group members learn about the current norms. The successful ones make decisions which conform closely enough to the group norms to gain approval, support, and offspring that thrive.

Economic development brings rapid environmental change and introduces many novelties, so it is not surprising that reproductive norms change. It is more surprising that in virtually all human populations they have evolved in a direction that encourages small families and extremely high parental investment. The explanation may lie in changes to the structure of populations. Prior to the industrial revolution, most humans spent all or most of their lives in small communities (Watkins 1990; Wilson 1976). They were largely illiterate so information was mostly communicated during face-to-face social interaction. Members of sedentary communities seldom traveled outside their regions. Nomadic people tended to travel in groups of family and friends. In these contexts, the extended family is the most important social institution (Davis 1937/1997). It is the main unit of production and the main provider of education and assistance in sickness and hardship.

Until very recently then, most human communities really were comprised of cooperatively breeding groups. People had practical reasons for working to keep their family strong and ensure its continuation in future generations. Supporting the reproduction of close relatives enhanced their inclusive fitness. The proximate mechanism encouraging family members to support one another is likely to have been identification with the family group. As argued in Sect. 21.5, social psychologists have found that identifying with a group causes its members to adopt the shared group purpose (Haslam et al. 2009). If family membership is a person's most important social identity, then she will adopt her family's goals as her own and it will seem normal and natural to see obligation to family as more important than her own interests and desires. If this is her belief, then it will seem reasonable to accept the marriage partner chosen by elder family members, as is the case in many premodern societies (Apostolou 2007), or to not get married at all and concentrate on helping relatives.

The introduction of employment, literacy, transportation technology, and many other novelties creates new kinds of communities and new social networks (Bongaarts and Watkins 1996; Kohler 2001). People may no longer live in close proximity to their kin. One consequence of this is that child-rearing will become more costly for the parents because they are less likely to be near people who have a genetic interest in serving as alloparents (Turke 1989), and even if they do live near their kin, their kin may be employed in wage labor or attending school. A second consequence will be a change in the information being exchanged during social

interactions. In the new social environment, people spend much more time in nonfamily groups, among workmates or schoolmates with whom they share interests but not family interests (Newson et al. 2005). People form new social identities. Influence from kin is diluted by influence from friends and colleagues and also by strangers communicating via mass media.

There is no reason to believe that the information exchanged in these nonfamily groups will generate or maintain norms that encourage behavior consistent with optimizing reproductive success. Norms will not change instantly, however. People moving into the new social environment from small kin-based communities will continue to maintain their family-promoting norms. Members of the first generation may have a large family and communicate family-promoting norms to their children. Their children will, however, be likely to adopt more “modern” norms which give lower priority to the pursuit of reproductive success and a higher priority to interests that compete with reproductive success. Thus, culture evolves as people adopt values which more closely reflect the shared interests of the new social groups. The inevitable time lag between the change in social environment and the adoption of new reproductive norms makes it difficult to test or investigate this mechanism of cultural change. More confusion is generated because a large number of reproductive norms change with modernization, and they change at different times (Buss et al. 2001; Cook 2004). For example, in populations of European descent, the adoption of the belief that adults should be free to marry the person they love preceded by several generations widespread acceptance of the belief that this freedom should extend to lovers who happen to be of the same sex.

21.7 Conclusion

All aspects of biology are better understood in the light of evolution, and this is certainly the case when our goal is to understand how the human primate builds its babies. However, because culture plays a role in the biology of humans far beyond that seen in other animals, we must consider cultural evolution along with biological evolution (Boyd et al. 2011; Whiten et al. 2011).

To compile this evolutionary account of human evolution, I have done my best to integrate evidence and theory from the work of scientists in many different disciplines and to try to show how they can inform each other. Nevertheless, I am sure readers will agree with me that this account is frustratingly incomplete. Our knowledge of our ancestors who lived millions of years ago or even a few hundred years ago will, of course, always be scanty, and our understanding of their lives and the changes they experienced will always rely on a lot of speculation. However, the development of many new techniques is allowing scientists to infer more and more about the past. Our speculation is becoming increasingly well informed.

By contrast, information about current human populations and the changes they have experienced in recent years is available in vast quantities and is being collected and studied by large numbers of scholars in many disciplines. The frustration and

incompleteness here arises from the limited dialogue between members of different disciplines who are studying roughly the same problem from different perspectives. In understanding human reproduction, the knowledge and insights of historical demographers are as important as those of primatologists. The data collected by anthropologists is as important as the data collected by psychologists. Human reproduction is not just a male and female producing offspring. It is the fusion, growth, and fission of families. Human families can, it seems, take many forms, and the rapid changes in social structure experienced by current human populations are challenging us to invent new kinds of families so we can continue to build healthy babies in new social environments.

Gaining a better understanding of “family member” as a social identity will help in the cultural evolution of new family forms. How flexible can a human family be? Social psychologists have found that many Westerners are able to maintain several social identities and gain a feeling of belonging to many groups. Is this an ability all humans have or can acquire? Can we be helped to maintain the feeling of belonging when our social environment demands mobility and flexibility? Is “my family” a special social identity bringing special emotions and responsibilities? If so, is this something we learn in our natal families or is part of our genetic or cultural endowment? Social scientists from many different disciplines can contribute theory and evidence to help provide answers to these questions. Working together, we may be able to help in the creation of social policies that will help parents and their children to successfully cope with continuing rapid change.

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Part VII

Conclusion

Chapter 22

Conclusion: The Ontogeny of Investigating Primate Ontogeny

Robert D. Martin

Keywords Immunological paradox • Developmental programming • Suckling • Brain • Weaning • Evolution

22.1 Introduction

The development of offspring in primates, including humans, provides the focus for *Building Babies: Primate development in proximate and ultimate perspectives* (nobly edited by Katie Hinde, Kathryn Clancy, and Julianne Rutherford). The volume has corralled historically disparate fields into a cohesive whole with the aim of generating a synthetic cross-disciplinary survey of the various proximate mechanisms and evolutionary processes involved in primate development.

The focus of this book begs the question “What is so special about primates?” All mammals suckle their infants, so this remarkable form of parental behavior dates back to the origin of mammals, some 200 million years ago (mya). The origin of vivipary in mammals can be traced back to the common ancestor of marsupials and placentals, perhaps 165 mya (Luo et al. 2011). The truly ancient emergence of both adaptations demands respect. Because both placentation and suckling have exceedingly long evolutionary histories, accompanying adaptations are necessarily deeply embedded in the biology of extant placental mammals, including primates. Building on this ancient heritage, investment in individual offspring is typically prolonged in primates. Compared to other mammals, they have relatively long gestation and lactation periods, contributing to drawn-out life histories that have been aptly described as “life in the slow lane” (Charnov and Berrigan 1993; Martin 1990, 2003, 2007). Because of this extension of maternal investment, the relationship

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between the developing primate and the providing mother is likely to be crucial for understanding primate reproduction, growth, and development. Thus, adaptations for placentation and suckling as investment strategies are particularly important in primates, especially for humans.

Beyond physiological strategies of investment, the complexity of neurological function and sociobehavioral adaptation across primates requires special attention when tackling offspring development. For instance, alloparenting—care provided by adults other than the individual's biological parents—and paternal care are both exceptionally common among primates, as reviewed by Tecot et al. (2012) and Huck and Fernandez-Duque (2012). The sociobehavioral and cognitive milieu experienced by a developing primate is extremely complex in comparison to most other mammals (see chapters by Bezanson, Meredith, MacKinnon, Lonsdorf, and Newson for various manifestations of this complexity in primates).

Thematic reviews serve a valuable function in bringing together separate threads that can be woven into a general synthesis as a launching pad for promising new lines of research. At the same time, such reviews may highlight certain enigmas that emerge from accumulated knowledge and require resolution. Indeed, the preceding collection of chapters is no exception. By its very nature, the study of primate development is multidisciplinary. Anthropologists, embryologists, ethologists, evolutionary biologists, geneticists, medical scientists, microbiologists, primatologists, psychologists, veterinarians, zoologists, and others have all contributed to our current understanding of development in nonhuman primates and humans. This volume has integrated empirical information from comparisons among primates (both in captivity and in the wild), results of targeted experimental studies, and a biomedical framework for human reproduction, frequently in an explicitly evolutionary framework (i.e., merging the proximate and ultimate of the title), to generate a comprehensive overall picture. In what follows, I synthesize some of the prevalent issues explored in detail in individual chapters in the context of what I see as two main organizing themes: (1) maternal investment in primate brain development and (2) the conflict and cooperation inherent to the maternal–offspring relationship both pre- and postnatally. In closing, I comment on how the innovative findings and perspectives presented here light the way for future research into primate development.

22.2 Investing in the Primate Brain: A Life History Perspective

From the outset, emphasis on the brain has been a key feature of studies of primate evolution (Martin 1990; Allman 1999). And development of the brain both prenatally and postnatally is intimately connected to reproduction, as explicitly recognized in the maternal energy hypothesis (Martin 1981, 1996; Martin and Isler 2010), which proposes that resources provided by the mother have provided a guiding constraint in the evolution of the mammalian brain. The brain achieves its adult size relatively early in life, and in mammals generally most of brain growth has taken

place by weaning. Moreover, the maternal energy hypothesis has recently received convincing support from a penetrating phylogenetic analysis (Barton and Capellini 2011). Among primates, humans have by far the largest relative brain size, about three times larger than for the average condition among higher primates. Because of the pelvic constraint at birth, the brain in a human neonate is unusually small for a primate, approximately a quarter of adult brain size. As a special adaptation in humans, the rapid fetal rate of brain growth continues for about a year after birth (Martin 1983; Milligan 2012).

The fetal brain is supported by flexible transport of nutrients across the placenta (Rutherford 2012). Suckling is the postnatal continuation of early maternal provision of nutrition through the placenta, so it is reasonable to propose the concept of “lactational programming” as the postnatal counterpart of “fetal programming” (Hinde 2012). Variation in milk yield between rhesus macaque mothers greatly exceeds variation in milk energy density, and yield is therefore the most reliable indicator of available milk energy (Hinde et al. 2009). The same applies to baboons and also to human mothers. So clearly particular attention should be directed to factors that influence milk yield in primates, but very little data are currently available. Blomquist (2012) suggests that population genetics analysis may contribute to a better understanding of variation in milk yield and other physiological and behavioral phenotypes among primate mothers. New data suggest that the maternal gut biota will normally find its way into milk and colonize the infant gut, offering a promising new vision of how postnatal programming of growth could take place (Martin and Sela 2012).

Another aspect of particular interest is postnatal development of the brain and the degree to which it depends upon the quantity and composition of the milk provided by mothers. To that end, Milligan asks in her chapter whether bigger brains require better milk. The logical expectation is that a more plentiful supply of appropriate milk constituents is required for growth of the larger human brain than for brain growth in apes or early hominids (Martin 1981, 1983). It is also possible that, prior to birth, the human placenta possesses unique anatomical or functional features that increase the availability of maternal nutrients to the fetal brain (Rutherford 2012). As noted by Martin (1983): “Continuation of the foetal pattern of brain and body growth into the first year of postnatal life in human beings also poses special problems with respect to lactation, since it is quite clear that a pattern of early postnatal brain growth that is unique among mammals must require a unique milk to supply the needs of the developing human infant.”

In spite of considerable advances in knowledge, we still do not know how a human infant receives all of the nutrients it requires for brain growth after birth. It seems that humans may be unusual in having an extended period of mixed feeding (Hawkes and Paine 2006; Sellen 2007), lasting for two years or more prior to definitive weaning. In fact, it has become widely, but somewhat uncritically, accepted that the duration of suckling is naturally shorter in humans than in great apes. The suggestion is that “early weaning” emerged as an adaptation during human evolution, despite the fact that our infants are born at an earlier stage of development and take longer to mature. But this introduces a largely unrecognized paradox: the clear

prediction from exceptional brain enlargement, greatly delayed sexual maturity, and unusually long life spans in humans is that we should have *late*, not early weaning. Many authors seem to have made the assumption that early weaning will necessarily be favored by natural selection because it shortens inter-birth intervals. However, the central tenet of life history theory is that rate of reproduction is an inherent part of an overall strategy involving multiple trade-offs (Clancy laces an elegant discussion of life history trade-offs throughout her chapter). One concomitant of the characteristic drawn-out life histories of primates is that they typically have a very low intrinsic rate of reproduction in comparison with other mammals with faster life histories. Evolution of earlier weaning in humans would therefore break a well-established primate pattern. As yet, no resolution of this paradox has been forthcoming; indeed, the paradox has barely been recognized.

22.3 The Immunological Paradox, Inflammation, and the Stress Response in Primate Pregnancy

A fundamental question relating to pregnancy in mammals is the “immunological paradox,” first clearly identified by Medawar (1953). A mother and her fetus are genetically distinct organisms that somehow manage to coexist without triggering immunological rejection (Sterner et al. 2012). Pregnancy does not simply involve acceptance or rejection like a transplant. Instead, it depends upon checks and balances that ensure nurturing of the fetus by the mother without runaway invasion. So the maternal–fetal relationship has elements of symbiosis as well, and the interface between fetal trophoblast cells and maternal leukocytes in the placenta is unique. Despite numerous findings and new hypotheses, the immunological paradox remains essentially unresolved to this day (Moffett and Loke 2004, 2006). The concept of the immunological paradox of pregnancy was eventually joined by the notion of maternal–fetal conflict (Sterner et al. 2012). Because mother and fetus have different needs, conflict between the two seems very likely (Haig 1992, 1993, 2002). The notion of maternal–fetal conflict has been investigated in relation to specific medical conditions in human pregnancy such as preeclampsia (Yuan et al. 2005). Although various forms of maternal–fetal conflict undoubtedly exist, however, it is important to remember that cooperation between mother and fetus is essential for successful pregnancy.

Clancy (2012) points out that early pregnancy depends upon a mild inflammatory response and is threatened if the response is either lacking or too pronounced. In Clancy’s words, the inflammatory environment needs to be “just right.” In humans, elevated maternal C-reactive protein (CRP) concentrations are detected by 4 weeks after conception and subsequently maintain the higher levels throughout pregnancy. The raised maternal CRP level may contribute to protection against pregnancy loss, particularly after the first trimester. If the initial inflammatory response after implantation is too weak, invasion by the trophoblast may be too shallow, resulting in

preeclampsia or full-blown eclampsia. The hypertension that characterizes preeclampsia then leads to an exaggerated systemic inflammatory response to pregnancy, which may result in intrauterine growth restriction and pose serious risks to both fetus and mother.

Another pervasive concept relevant to maternal–offspring interactions is that of “stress” during both pregnancy and postnatal development. Unfortunately, the notion of stress has been invoked in many different contexts and often rather loosely, such that its usefulness has been widely questioned. However, complete abandonment of the stress concept would be a prime example of “throwing out the baby with the bathwater.” While it is clear that discipline must be exercised in defining and assessing stress in any particular study (e.g., are mechanisms of intrauterine nutritional “stress” comparable to traditionally defined HPA dysregulation?), numerous important findings have emerged. Examples are provided by Nyberg’s chapter discussing the HPA (hypothalamus–pituitary–adrenal) axis and Rutherford’s discussion of the relationship between the placental enzyme 11B-HSD2 and cortisol production. In another example, the chapter by Tardif et al. reviews some of the fascinating aspects of reproductive biology in marmosets, including the tendency to “cut bait,” i.e., abort a pregnancy, when faced with even minor nutritional restriction. Whether this extraordinary physiological response is related to increased maternal stress or, specifically, to HPA axis activation, is not yet known, but studies reviewed by Nyberg (2012) and Clancy (2012) suggest promising avenues for future inquiry. Potts (2012) relates population variation in reproductive output among female chimpanzees to nutritional ecology, and this relationship may well be mediated by stress pathways related to maternal energetics.

22.4 The Biobehavioral Matrix

Particularly with respect to primates, the paradigm of “social stress” (relating to interactions with conspecifics in social groups) has actually served us quite well. It is notable that short-lived, “acute” stress may have positive benefits, whereas long-term, “chronic” stress usually has negative consequences (Kinnally 2012). Such adverse effects figure prominently in human health, and primate models, such as baboons, have yielded valuable information. For instance, social rank can greatly influence physiology and health, often with adverse effects in reproduction and immunology (Sapolsky 2005).

It has now become widely accepted that inadequate fetal development can give rise to health problems later in life, sometimes across generations, as described by the “fetal programming paradigm” or “Barker hypothesis” (Barker et al. 1990; Barker 1995, 1998; Nathanielsz 1999; Nathanielsz and Vaughan 2001; see also Rutherford 2012). However, it has not been so clearly recognized that postnatal events can have similar effects. Yet the scope for disruption of developmental patterns is actually far greater in postnatal life, particularly during

the period of suckling, complementary feeding, and early sociobehavioral learning. In all primates, the mother–infant relationship is a very important early component of an individual’s social environment (see chapters by Lonsdorf 2012; Hinde 2012; Fairbanks and Hinde 2012; Kinnally 2012).

There has been extensive research into the effects of complete or partial deprivation of maternal care on the development of social behavior, notably in rhesus macaques following the initial studies conducted by the Harlow group (Winslow 2005). Inadequate mother–infant interaction during early postnatal development may significantly modify the brain of the growing infant, and this may result in abnormal social behavior and poor emotional control later in life. In adult female rhesus macaques, maternal care or abusiveness is tightly linked to the quality of care received in infancy (Maestripieri 2005; Kinnally 2012). In humans, stress in early postnatal life, including abuse, neglect, and nutritional deficiencies, increases the risk of mental and physical ailments. Machado’s chapter focuses on two brain structures most often linked to normal emotional and social behavior in primates—the amygdala and the orbitofrontal cortex. He points out that abnormal behavior patterns displayed by isolated or peer-reared rhesus macaques resemble those of monkeys with lesions of the orbitofrontal cortex, suggesting that early developmental environments can literally be traumatic.

Studies of rhesus macaques in the breeding colony at the California National Primate Research Center (Davis, CA) have revealed connections between milk and behavioral phenotype (Hinde 2012). Cortisol concentrations in milk were higher for mothers rearing sons. Moreover, the higher the milk cortisol concentration at the time of testing, the more male infants were characterized as “confident.” This suggests that glucocorticoids ingested during development may have a stress inoculation effect, at least in males. In her chapter, Hinde points out that the relationship between milk cortisol and infant temperament appears to work in opposite directions in humans and macaques, posing yet another unresolved paradox. Nonetheless, in the words of Glynn et al. (2007), “Biologically active components in breast milk may represent one avenue through which the mother shapes the development of the human infant during the postnatal period.”

Development and postnatal behavior in primates can also be influenced by prenatal steroids, such as androgens, and disorders in androgen production can adversely affect fetal development (Smith et al. 2012). An excess of androgens may masculinize the external genitalia of a female fetus, while an inadequate supply of androgens can feminize male external genitalia. Here, marmosets and tamarins constitute an interesting test case because the customary twins are dizygotic and yet share a single placental circulatory system. In line with this, it does not appear that prenatal androgen affects normal development of female genitalia (Smith et al. 2012). However, fetuses of both sexes exposed to elevated levels of maternal androgens in the first trimester are born at lower birth weights than those exposed to normal levels. This has intriguing intergenerational consequences, considering that birth weight is an important predictor of adult weight and that adult weight in female marmosets is an important predictor of litter size produced (Tardif et al. 2012).

22.5 Evolutionary Perspectives on Development

In her chapter, Bezanson makes the important point that the juvenile primate is not merely a young adult but instead a very specific entity. All of the chapters in this volume subscribe to this fundamental vision of development as a constitutive and informative unit of analysis in its own right. A rich platform of innovative research and conceptual approaches has been revealed, and yet a number of puzzles remain for future exploration. A valuable function of overviews is to provide signposts for future research. The Barker hypothesis regarding fetal programming has revolutionized our understanding in the role played by developmental history in the emergence of disease conditions late in life. Having overcome considerable opposition at the outset, the hypothesis has become accepted wisdom. But *Building Babies* shows that events during postnatal development can be equally far-reaching with respect to influencing the adult state. So fetal programming has now been joined by postnatal programming in an overarching view of developmental consequences for later life. Given that the scope for culture-driven intervention is far greater in human postnatal development, this is clearly an area of great concern for future research. Another cause for concern is the mounting evidence that both fetal and postnatal programming can exert influences across generations.

Building Babies has also highlighted a number of unresolved issues that require additional, focused research for their resolution. Despite the fact that it was explicitly recognized some 60 years ago, the immunological paradox of pregnancy is still in need of resolution. It is far from clear how a genetically distinct fetus is able to escape rejection by the mother and is, instead, nurtured in the most remarkable fashion. In one striking recent development, it has become clear that syncytin genes have been recruited from retroviral sequences as part of the adaptation of invasive placentation to evade the mother's immune response. The evolutionary context has recently been clearly documented for carnivores (Cornelis et al. 2012; Malik 2012). Another issue is the enigma of nutrient supply for development of the greatly enlarged human brain, particularly during its particularly rapid growth during the first year of life. Yet another is the paradox that the emergence of early weaning has been widely seen as a specific adaptation in the human lineage, whereas the expectation from life history theory is surely that weaning should occur even later than in the great apes. In sum, identification of specific problems for future research is a beneficial outcome of any effective review, and *Building Babies* admirably serves that purpose.

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