Parent-Offspring Conflict in the Evolution of Vertebrate Reproductive Mode

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abstract: We propose and evaluate the hypothesis that parent-offspring conflict over the degree of maternal investment has been one of the main selective factors in the evolution of vertebrate reproductive mode. This hypothesis is supported by data showing that the assumptions of parent-offspring conflict theory are met for relevant taxa; the high number of independent origins of viviparity, matrotrophy (direct maternal-fetal nutrient transfer), and hemochorial placentation (direct fetal access to the maternal bloodstream); the extreme diversity in physiological and morphological aspects of viviparity and placentation, which usually cannot be ascribed adaptive significance in terms of ecological factors; and divergent and convergent patterns in the diversification of placental structure, function, and developmental genetics. This hypothesis is also supported by data demonstrating that embryos and fetuses actively manipulate their interaction with the mother, thereby garnishing increased maternal resources. Our results indicate that selection may favor adaptations of the mother, the fetus, or both in traits related to reproductive mode and that integration of physiological and morphological data with evolutionary ecological data will be required to understand the adaptive significance of interspecific variation in viviparity, matrotrophy, and placentation.

Keywords: viviparity, parent-offspring conflict, placentation, reproductive mode.

q1 Since Aristotle in his *Historia Animalium* divided animals into oviparous versus viviparous forms and forms nourished by yolk versus more direct means, analyses of the ecology, physiology, and evolution of reproductive mode have remained of considerable interest to biologists (Mossman 1937, 1987; Wourms 1977, 1981; Wourms et al. 1988; Blackburn 1992, 1999*b*, 1999*c*). Comparative and evolutionary studies have characterized the remarkable diversity in reproductive mode among animals (Luckett 1976*b*; Blüm 1986; Blackburn 1999*b*, 1999*c*) and have begun to consider the adaptive significance of prenatal mother-offspring interactions (Haig 1993, 1996*a*, 1996*b*). Ecological analyses of the evolution of viviparity have traditionally focused on the costs and benefits of oviparity in comparison with various forms of live birth (e.g., Tinkle and Gibbons 1977; Shine 1985, 1995) and the role of selection in optimizing parental investment (e.g., Clutton-Brock 1991). By contrast, physiological and morphological studies of the evolution of viviparity and placentation have concentrated on the description, ontogeny, and function of diverse structures and mechanisms for nutrient transfer (e.g., Stewart and Blackburn 1988; Wourms et al. 1988; Wourms and Lombardi 1992; Wourms 1993).

In this article, we integrate comparative, ecological, and physiological approaches to the evolution of reproductive mode and propose a new hypothesis that states that parent-offspring conflict (Trivers 1974) has driven the evolution of vertebrate reproductive mode. Several previous studies have provided evidence that parental-fetal relationships are subject to such conflict; however, these authors have focused on the adaptive significance of the current forms of parent-offspring interactions (Trivers 1974; Haig 1993, 1996*a*, 1996*b*) or the expected consequences of parent-offspring conflicts for the evolution of polyandry (Zeh and Zeh 2001) and speciation (Zeh and Zeh 2000; whereby viviparity-driven conflict between mother and fetus promotes antagonistic coevolution, genomic divergence, and increased postzygotic isolation). Here, we propose that parent-offspring conflict plays a fundamental, causal role in the evolution of viviparity and placentation and that it is responsible for much of the diversity in aspects of animal reproductive mode. We describe the evolutionary dynamics of parent-offspring conflict in this context, provide evidence for our viviparity conflict hypothesis, and suggest further tests using data from physiology, morphology, and phylogenetics.

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Parent-Offspring Conflict over Parental Investment

> How is the offspring to compete effectively with its parent? … Inside the mother the offspring is expected to employ chemical tactics. (Trivers 1974)

In all organisms where parents and their offspring are not genetically identical, conflicts of interest will arise between them over the level of parental investment (Trivers 1974). These phenotypic conflicts are mediated by patterns of gene expression. In mother-offspring interactions, genes of four sources and kinds may be involved: genes expressed in the mother, maternally derived genes expressed in the offspring, paternally derived genes expressed in the offspring, and genes expressed in the offspring regardless of their parental source (Trivers 1974; Haig and Westoby 1989; Haig and Trivers 1995; Haig 1997, 1999*b*, 2000; Ubeda and Haig 2003). Each of these types of gene exhibits its own optimal phenotypic effects for maximizing its representation in future generations with regard to how it influences the physiological interactions between the mother and developing embryos.

For the mother, each of her genes has an equal probability of being present in each offspring, so her best strategy involves allocating nutrients to each offspring over her lifespan to maximize the aggregate reproductive success of her descendants. For offspring, the effects of genes are expected to be more "selfish" such that offspring are selected to seek greater investment from the mother than she is selected to provide (Trivers 1974; Godfray 1995). This conflict arises because each offspring is more closely related to itself at $r = 1$ (and in the next generation to its sons and daughters at $r = 0.5$) than it is to any given full sibling at $r = 0.5$ (and its nieces and nephews, for which $r = 0.25$). Maternally derived and paternally derived genes in offspring may also exhibit different gene-expression strategies if such genes are "imprinted" as to their source (Haig and Westoby 1989; Haig 2000). Thus, to the extent that a mother's offspring derive from multiple paternity within or across broods, genes inherited from a particular father have a declining probability of being present in sibs (Haig 1999*b*). Such genes should therefore favor maternal investment in their bearers to an even greater extent than do maternally derived genes. Evidence for such imprinting effects on invasive ability of the trophoblast (fetal extraembryonic ectoderm; Mossman 1987, p. 315) and other aspects of maternal investment has been described in a variety of taxa (Cross et al. 1994; Bartolomei and Tilghman 1997; Haig 2000; O'Neill et al. 2000; Vrana et al. 2001; Tycko and Morison 2002).

Parent-offspring conflict is expected to result in offspring developing adaptations to extract more from parents than they are selected to provide and adaptations to compete with siblings over parental resources. The magnitude of such parent-offspring conflict can be measured by the difference between the brood size and degree of investment per offspring that is optimal for the parent versus what is optimal for an offspring (Trivers 1974; Godfray and Parker 1991; Parker 1995). Conflict is predicted q2 to be most intense when only one parent invests, when the coefficient of relatedness between siblings is low, when brood size is small, when there is the possibility of intrabrood competition, and when the benefits of care are nondepreciable (do not decline with increasing brood size; Parker 1985, 1995; Godfray and Parker 1991). However, q3 parent-offspring conflict is constrained by the genetic relatedness and mutual dependency of the interactants such that it often involves a tug-of-war over resource allocation, with signs of conflict remaining more or less covert unless the interactions between parties are perturbed in some way (Moore and Haig 1991; Haig 1993, 1996*a*, 1996*b*).

As in other situations with cooperative interactions entangled with conflict and conflict constrained by relatedness, the evolutionary outcome of parent-offspring interactions is difficult to predict (Parker 1983; Crespi 1992; Queller 1994; Godfray 1995; Brown et al. 1997; Zeh and Zeh 2000; Parker et al. 2002*b*). Such outcomes can depend on evolutionary starting points, genetic mechanisms, mating systems, sequences of mutation, the arsenal of traits in parents and offspring that can be modified by selection in this context, and the fitness costs and benefits of winning versus losing in relation to the costs of investing in adaptations for conflict (Haig 1993; Arnqvist and Rowe 2002; Rowe and Arnqvist 2002; Chapman et al. 2003). In parent-offspring interactions, conflicts of interest can be resolved with one side "winning" (at its optimum) at some more or less stable intermediate point, or conflicts may generate arms races of variable duration (Parker 1983, 1985; Godfray and Parker 1991; Godfray 1995). Although parents are usually expected to have an advantage that derives from size, physical power, and control of resources, offspring may engage in any number of strategies to manipulate parents into increased investment; examples include the release of hormones and other compounds into the maternal bloodstream (Haig 1993, 1996*b*) and the loud begging of nestlings in many species of birds (e.g., Parker et al. 2002*a*).

Thus far, most studies of parent-offspring conflict have focused on behavioral interactions, such as soliciting and siblicide (Trivers 1974; Clutton-Brock 1991; Mock and Parker 1997). More recently, evidence of physiological conflicts has been described between mothers and preparturition offspring, most notably during human pregnancy (Haig 1993). As described by Haig, these maternal- q4 fetal conflicts manifest themselves in the current form of matrotrophic (direct resource provisioning) viviparity in

humans. We argue here that such conflicts also reach back to the origins of maternal investment in vertebrates and thus should be instrumental in the evolution and diverse forms of viviparous reproduction itself. By our viviparity conflict hypothesis, the evolution of viviparity has been driven in part by parent-offspring conflict, whereby offspring are under continual strong selection to increase the level of maternal investment that they accrue. Mothers, in turn, are selected for reproductive modes involving egg retention and increased investment under appropriate ecological conditions (e.g., Tinkle and Gibbons 1977; Wourms et al. 1988; Shine 2002) and for increased physiological efficiency in nutrient provision (e.g., Wourms 1993; Tyndale-Briscoe and Renfree 1987), but they are still expected to favor levels of investment below the optimum for individual offspring. The main alternative hypothesis to ours is that the evolution of reproductive modes involving increased investment in individual offspring is driven by changes in reproductive ecology in the context of how the physiology and morphology of different lineages can be modified by selection. This hypothesis is not mutually exclusive to the viviparity conflict idea because ecological conditions and maternal-fetal interactions are expected to select sequentially or jointly on reproductive mode. Assessing the degree of support for each hypothesis requires analysis of the mechanisms and selective pressures driving evolutionary changes in viviparity and placentation.

Vertebrate Reproductive Modes

> Living embryos were exceedingly active in utero. They dashed about, open mouthed, inside the oviduct, snapping at whatever they encountered, including the investigator's hand. In this case, there was only one embryo in each oviduct. (Wourms 1977)

In oviparous species, preparturition conflict is unlikely because the quantity of yolk and other materials received by the developing embryo presumably cannot be influenced by genes expressed in the offspring. As a result, the origin per se of direct maternal investment in developing embryos and the initial stages of egg retention are presumably driven by ecological selective pressures. However, as soon as such investment has evolved, there is potential for conflict if the amount and duration of care received can be influenced by genes expressed in the offspring.

Two main nutritional patterns typify the transfer of maternally derived nutrients in viviparous vertebrates: lecithotrophy, in which energy for development is derived from the yolk of the ovum, and matrotrophy, in which nutrients are directly supplied by the mother during gestation (Wourms 1981; Blüm 1986; Blackburn 1999*b*, 1999*c*). These nutritional forms are not mutually exclusive, and the embryos of most viviparous vertebrates are nourished by some combination of yolk and direct maternal contribution (Wourms et al. 1988; Blackburn 1999*c*). Matrotrophic provision of nutrients provides the widest scope for parent-offspring conflict because postzygotic investment can be substantial, with the developing embryo in intimate contact with the mother throughout development. Matrotrophy can be categorized into three main forms on the basis of the nutrients supplied to offspring and how they are delivered (Wourms et al. 1988; Hamlett 1990).

The first form, oophagy, whereby the developing fetus feeds on sibling ova, or adelphophagy, the intrauterine cannibalism of embryos, is found in some amphibians, sharks, and teleost fishes (Wourms 1977; Wourms et al. 1988; Blackburn 1992; Gilmore 1993). This reproductive mode presents opportunities for parent-offspring conflict in that optimal brood sizes may differ between the mother and offspring (Godfray and Parker 1991, 1992). Because the offspring are active and in control of cannibalism levels, they may be able to achieve the brood size that maximizes their inclusive fitness, and indeed in the sharks and rays exhibiting oophagy or adelphophagy, only one embryo develops in each of two uterine compartments.

Cannibalistic brood reduction has been described in other viviparous forms, including some marine snails, caecilians, and other salamanders (Baur 1992; Mock and Parker 1997, pp. 324–333). Although sibling conflict typifies many such cases of this reproductive mode, the degree to which the interests of mothers and offspring differ remains unclear because it is difficult in theory and practice to specify optimal numbers and sizes of offspring for both parties (Parker et al. 2002*b*).

The second form, histophagy, involves the ingestion of maternal secretions by embryos and is characterized by the absorption of such secretions (Wake 1977; Wourms 1977; Blackburn et al. 1985; Wourms et al. 1988). These reproductive patterns are found in some sharks and rays, one anuran, and some caecilians; in addition, monotreme mammals exhibit an unusual combination of histotrophy and oviparity because eggs absorb considerable maternal secretions before deposition (Blackburn 1999*c*).

Maternal secretions are normally produced from the uterine epithelium, and the mother is presumably able to control their constitution and quantity more or less free of offspring influence. However, developing offspring may, in theory, increase the rate of histotroph production in at least three ways. First, in some amphibians, embryos abrade the uterine lining with specially adapted prenatal teeth, apparently to stimulate additional maternal secretions (Wake 1977; Guex and Chen 1986). Like begging calls in nestlings, such behavior may be partially maladaptive for the parents and may lead to investment beyond

their optimum (Godfray and Parker 1991). Second, oviductal secretions are under hormonal control in some amphibians (e.g., Xavier et al. 1970) such that offspring may be able to stimulate increased secretion via release of the same hormones (Haig 1996*b*). Third, the fetuses of some rays develop large supranuclear vesicles believed to function as storage depots for continually ingested secretions (Hamlett 1999). Such sequestering of maternal resources may elicit increased investment if it reduces the mother's information about offspring's level of need; indeed, it is otherwise unclear why a developing ray fetus would store resources unless they are retained until after parturition. Similarly, human fetuses sequester unusually high levels of fat in the last few weeks of pregnancy, after they have reached full term and are able to survive well postparturition. (Haig 1993, 1999*a*). Whether such an apparent adaptation indeed involves conflict requires further data.

The third form, placental viviparity, involves transfer of materials via "any intimate apposition or fusion of the fetal organs to the maternal (or paternal) tissues for physiological exchange" (Mossman 1937). Placental viviparity involves nutrient transfer via cell secretions (i.e., histotrophic exchange), via blood constituents (hemotrophic exchange), or by both routes. This reproductive mode is found in many chondrichthyan and some osteichthyan fishes, some squamate reptiles, some amphibians (caecilians, frogs, and salamanders), and all therian mammals (Blüm 1986; Blackburn 1999*c*). The placenta develops from fetal membranes (the amnion, chorion, allantoic sac, and yolk sac) and other tissues, and transfer of nutrients to developing young by this means may be more efficient physiologically than other methods, although the evidence for such efficiency is meager (Seal et al. 1972; Tyndale-Briscoe and Renfree 1987, p. 323; Wourms 1993). The prolonged and intimate contact between mothers and offspring engendered by this form of viviparity should provide offspring with considerable opportunities to influence maternal physiology to their own benefit and vice versa (Zeh and Zeh 2000). The origins and evolution of placental forms thus provide the clearest context for testing the assumptions and predictions of the viviparity conflict hypothesis, especially because viviparity and placentation appear to evolve in concert rather than sequentially (Blackburn 1995, 1998*a*, 1999*c*).

Assumptions of the Viviparity Conflict Hypothesis

The main assumptions of the viviparity conflict hypothesis are that relatedness between mothers and offspring is less than unity (the intensity of conflict then increases with multiple paternity within and across broods; Haig 1999*b*), that the evolution of viviparity and matrotrophy involve increased benefits to individual offspring and may also engender increased costs to mothers, and that offspring exhibit the ability to manipulate maternal investment in viviparous and incipiently viviparous forms.

Levels of genetic relatedness between mothers and offspring and between offspring are conducive to strong selection for parent-offspring conflict over prenatal investment. Thus, clonal reproduction is rare, and multiple paternity is virtually the rule among sexual organisms (Eberhard 1996, p. 413; Birkhead and Parker 1997; Jennions and Petrie 2000; Zeh and Zeh 2001; e.g., in viviparous taxa; Baker et al. 1999; Garner et al. 2002; Saville et al. 2002). Indeed, multiple paternity may be favored by one of the same traits that facilitates the evolution of viviparity, internal fertilization (e.g., Wourms et al. 1988). The possible resultant decrease in paternal investment may increase the offspring's optimal level and thus lead to a higher degree of conflict (Parker 1985); multiple paternity may also generate increased offspring demands through its effects on the evolution of genomic imprinting (Haig and Westoby 1989; Haig 1999*b*, 2000).

Perhaps the most pervasive theme in the literature on the evolution of viviparity is that it engenders clear benefits to individual offspring and may impose increased reproductive costs on mothers. Benefits to offspring include increased survivorship via avoidance of the egg stage, increased size at birth, and increased offspring vigor (e.g., Wourms 1977; Shine 1985, 1989, 1995, 2002; Crespi 1989; Compagno 1990; Guillette 1991; Wourms and Lombardi 1992; Gilmore 1993; Stewart and Thompson 1993; Qualls and Andrews 1999; Goodwin et al. 2002). These benefits contrast with numerous costs of reproducing via viviparity, most of which accrue to mothers; these encompass reduced foraging ability and higher susceptibility to predation while pregnant, total brood loss upon death, higher energetic costs, and lower fecundity (e.g., Wake 1977; Renfree 1983; Shine 1985, 1989; Compagno 1990; Wourms and Lombardi 1992; Heulin et al. 1994; Blackburn 1995, 2000; Schwarzkopf 1996; Goodwin et al. 2002; but see also Qualls and Shine [1998*b*], who showed that costs of reproduction apparently did not differ between conspecific viviparous and oviparous forms in a lizard). Phenotypic benefits to mothers of viviparity appear to be relatively few, and they may include increased energetic efficiency in placental forms (Wourms 1993) and greater flexibility in adjusting investment level under varying food supplies (Parker 1977; Low 1978; Renfree 1983; Hayssen et al. 1985; Stewart 1989; Trexler 1997; Jerez and Ramírez-Pinìlla 2001; but see Reznick et al. 1996). Taken together, these considerations imply that benefits to offspring increase substantially during the evolution of viviparity and that reproductive costs to mothers may increase as well.

We suggest that in viviparous and inchoate viviparous forms, offspring abilities to manipulate the mother are

even higher before than after birth as a result of the intimate, prolonged physiological contact between interactants. Offspring-parent manipulation should first become possible at the point when fetal tissues can release compounds that reach the mother; this may sometimes occur early in the evolution of viviparity from oviparity, and the initial effects may be as simple as slightly prolonged egg retention or embryo-induced changes in osmolarity gradients that contribute to uptake of materials through the egg capsule (Lombardi et al. 1993; see also Renfree 1977 on concentration gradients across the yolk sac placenta of a marsupial). Indeed, transfer of materials from mother to offspring appears common even in the incipient stages of viviparity (Blackburn 1998*b*; Stewart and Thompson 2000) such that physiological mechanisms for transfer in the other direction should not be unexpected on physiological grounds.

The abilities of preparturition human offspring to manipulate maternal investment are showcased by Haig (1993, 1999*a*). As he describes, human fetuses and their associated tissues secrete myriad factors (e.g., hormones, steroids, cytokines, and growth factors); these serve, in humans and other mammals, to signal the presence of the conceptus, facilitate invasion of the uterine lining, stimulate angiogenesis, locally modulate the mother's immune response in the uterus, maintain the early stages of the pregnancy, and control gestation length (see also Renfree 1977, 1983; Pavia et al. 1979; Hayssen et al. 1985; Clemens 1991; Arcuri et al. 1998, 1999; Lin et al. 2000).

Considerable evidence indicates that abilities of fetuses to influence development are not restricted to humans. Thus, steroid regulation of reproduction by mothers is present in all vertebrates (Blüm 1986; Guillette 1987), and fetal offspring of elasmobranchs, amphibians, and reptiles can produce the same or similar compounds as do mammals, apparently with comparable physiological roles in affecting maternal investment. Guillette (1989) presented evidence that viviparous nonmammalian vertebrates also secrete steroids and prostoglandins as pregnancy recognition signals and that embryonic factors influence maternal uterine development in various ways apparently beneficial to the fetus. Hamlett (1999) noted that the placenta of some sharks secretes steroid hormones and that the yolk sac placenta (the simplest form of placentation) exhibits tissues that also appear to produce steroids, and Callard and Koob (1993), Callard et al. (1993), and Koob and Callard (1999) provided additional evidence for steroid regulation of elasmobranch reproduction, with potential effects from the fetus. Even under the seemingly simplest form of viviparity, histophagy, as expressed in a species of salamander, antagonistic maternal immune reactions (rejection and facilitation) toward the embryo have been found, along with immunosuppressive factors in the pregnancy serum thought to originate from the embryo (Chateaureynaud et al. 1979; Badet 1984). A range of cytokines and other hormones, which regulate immune responses, fetal growth, and differentiation in mammals, has also been identified at the maternal-fetal interface in a species of placental reptile (Paulesu et al. 1995; Paulesu 1997; Jones et al. 2003). Painter and Moore (1999) reported the production of progesterone and corticosterone from the reptilian fetal adrenal gland and suggested that the fetal placenta metabolizes steroid hormones, and Bonnet et al. (2001) reported that progesterone plays an important role in the pregnancy of a viviparous snake by stimulating vascularization of the oviducts. Endocrinological studies of a placental skink and a review of other reptiles (Guarino et al. 1998) have shown that when the corpus luteum begins to degenerate after the middle of pregnancy, the placenta can become an endocrine organ, and, as in some mammals, it begins to replace and maintain the high levels of progesterone circulating in maternal blood. Moreover, young embryos of the reptile *Lacerta vivipara* produce a compound that extends the life of the corpus luteum (and thus gestation length; Xavier et al. 1988), and embryos of other lizards release a variety of compounds, often early in development (see Guillette 1992). Callard et al. (1992) noted that oviparous groups (e.g., skates, turtles, and birds) exhibit a predominantly preovulatory pattern of progesterone production, whereas those groups in which viviparity has evolved (e.g., sharks, snakes, and lizards) exhibit mainly a postovulatory pattern. Finally, Shine and Guillette (1988) present evidence that in reptiles, increased duration of progesterone secretion prolongs egg retention, which may serve as a simple mechanism for the initial stages in the evolution of viviparity. Their model is of special importance for the viviparity conflict hypothesis, given that progesterone can also be secreted by reptile fetuses. Offspring of oviparous and viviparous reptiles may also benefit from delaying birth, potentially beyond the maternal optimum in viviparous forms, and they may thus control this important aspect of development (Shine and Olsson 2003).

These cases indicate that preparturition offspring of all major vertebrate groups exhibiting viviparity demonstrate abilities to or the potential to manipulate maternal reproductive physiology. Thus, the assumptions of the viviparity conflict hypothesis appear to be satisfied. The hypothesis makes three main predictions that can be evaluated with the available data: multiple origins of viviparity and forms of placentation, extreme diversity in traits related to fetal-maternal interactions among vivparous forms, and evidence of fetal-maternal conflict over levels of investment, which may lead to arms races.

Multiple Origins of Viviparity and Forms of Placentation

> Once egg retention exists, maternal oviductal and ovarian function could be modified by responding to embryonic factors. (Guillette 1989)

One of the hallmarks of strong selection is parallel or convergent evolution (Schluter and Nagel 1995; Losos et al. 1998; Madsen et al. 2001; Nosil et al. 2002). This evolutionary pattern implies first that selection, rather than the chance effects of drift, has given rise to a particular trait and second that diverse lineages have been similarly transformed, overcoming lineage-specific constraints on many occasions. Multiple origins of viviparity, matrotrophy, and more invasive placentation may be explicable by both the viviparity conflict and reproductive ecology hypotheses, and they provide indirect support for viviparity conflict to the degree that they cannot be explained by variation in ecological conditions. In addition, more or less unidirectional trends from oviparity to viviparity and to increased investment in viviparous forms suggest either that such transitions are irreversible due to their genetic or physiological architecture (Bull and Charnov 1985; Lee and Shine 1998) or that strong selection on offspring can prevent them.

Striking parallelism and convergence are found in the origins of viviparity itself, the origins of placentation, and the forms of placentation most conducive to offspring control over parental investment. Among vertebrates, viviparity has evolved more than 120 times; there are more than 100 inferred transitions in reptiles, 12 in teleost fishes (including patrotrophic viviparity in some seahorses; Blackburn 1999*c*; Wilson et al. 2003), nine to 10 in sharks and rays, five in amphibians, and apparently two in mammals (Hayssen et al. 1985; Dulvy and Reynolds 1997; Zeller 1997, 1999; Blackburn 1999*b*, 1999*c*; Goodwin et al. 2002; Reynolds et al. 2002). Matrotrophy has also evolved readily (23–24 times), with at least three inferred origins in reptiles, 12 in teleost fishes, four to five in sharks and rays, three in amphibians, and one in mammals (Dulvy and Reynolds 1997). In some lineages, viviparity is characteristic of higher taxonomic categories (e.g., eutherian and metatherian mammals and some elasmobranch groups); however, in other taxa, it varies among closely related species or even among populations (e.g., Blackburn 1992, 1993, 1995, 1998*a*; Heap 1994; Qualls et al. 1995; Surget-Groba et al. 2001). The transitions between oviparity and viviparity appear to be virtually unidirectional because there is evidence of shifts from viviparity back to oviparity in only a few cases, and even these are ambiguous (de Fraipont et al. 1996, 1999; Dulvy and Reynolds 1997; Lee and Shine 1998; Blackburn 1999*a*; Surget-Groba et al. 2001; Reynolds et al. 2002; Douady et al. 2003).

Viviparity has been linked more or less closely to environmental factors in several taxonomic groups. Thus, in reptiles, viviparous forms are most common in relatively cold climates (Tinkle and Gibbons 1977; Shine and Bull 1978; Shine 1985, 2002 and references therein), and in elasmobranchs, viviparity and matrotrophy are found most often in tropical and subtropical waters (Wourms 1977; Clutton-Brock 1991; Dulvy and Reynolds 1997), where utilization of yolk by embryos may be energetically inefficient (Dulvy 1998). By contrast, reproductive mode is apparently not associated with ecomorphotype in sharks (Compagno 1990), and Wourms et al. (1988) noted that for teleost fishes, "it is difficult to correlate viviparity … with specific ecological parameters." Indeed, Shine and Berry (1978), Shine (1985, 1987), and Packard et al. (1989) stressed that the current ecology of viviparous forms provides only indirect evidence for the role of specific environmental factors in the origins of this reproductive mode. Thus, although viviparity itself is clearly adaptive in harsh environments for eggs among some taxa, the selective advantages of transitional stages in the origin of viviparity are often unclear (Shine and Bull 1979; Shine 1985; Smith and Shine 1997; see also Blackburn 1982), and the ecological adaptive significance of the different forms of viviparity or matrotrophy has been difficult to elucidate (Wourms et al. 1988; Guillette 1991; Stewart and Thompson 2000).

Blackburn (1995, 1998*a*) provides evidence that intermediate transitional stages in the evolution of viviparity and placentation are rarely found among extant forms such that they appear to evolve rapidly. His hypothesis is also supported by the finding of Reynolds et al. (2002), who used phylogenies to infer that evolutionary changes in elasmobranch viviparity often proceeded directly from egg laying to matrotrophic viviparity and the emphasis by Rothchild (2003) on the great gap between metatherian and eutherian reproductive modes. Moreover, Mossman (1987, p. 146) points out that little morphological change in fetal membranes is required for the transition to viviparity because most of the changes are mediated by physiological shifts. By the viviparity conflict hypothesis, ecological factors need not drive transitions to viviparity and matrotrophy in isolation because an advantage will always be present for offspring to accrue additional investment up to their optimal level. Moreover, selection on offspring and mothers is apparently strong enough to cause rapid microevolutionary change, which has led to accelerated among-population divergence and speciation in some taxa such as mammals (Zeh and Zeh 2000).

Placentation has evolved concomitantly with viviparity among vertebrates (Blackburn 1995, 1999*b*, 1999*c*), and it

exhibits the same pattern of multiple evolutionary origins, with many striking cases of convergence and parallelism (e.g., Wourms 1977; Blackburn et al. 1984; Wourms et al. 1988; Wourms and Lombardi 1992; Blackburn 1993, 1999*b*, 1999*c*; Meyer and Lydeard 1993; Reznick et al. 2002; also Wourms and Cohen 1975 on trophotaeniae, a placental analogue in some fishes). There are three main forms of placentation with regard to one of its most fundamental aspects, the functional morphology of the maternal-fetal interface: epitheliochorial placentation, which involves proliferation of the trophoblast and uterine epithelium with little or no invasiveness of the trophoblast into maternal tissue; endotheliochorial placentation, whereby the trophoblast invades maternal tissue but does not penetrate into the bloodstream; and hemochorial placentation, in which the trophoblast invades far enough for the developing placenta to gain direct access to maternal blood (e.g., Luckett 1976*b*; Mossman 1987; King 1992). Hemochorial placentation entails the greatest opportunities for offspring to manipulate the mother toward increased investment; offspring have direct access to maternal nutrients in the blood, they may release compounds into her bloodstream, and they can distinguish between maternal versus fetal sources of hormones and other substances, while mothers may remain ignorant of this important information (Haig 1991, 1993, 1999*a*; Kurz et al. 1999).

Hemochorial placentation has apparently originated at least eight times in mammals, among flying lemurs, bats, rodents and lagomorphs, primates, anteaters and armadillos, hyraxes, tenrecs and elephant shrews, and hedgehogs (King 1992; Carter 2001); only in some rodents has hemochorial placentation apparently been lost, given rise to an endotheliochorial form (Mess 2003). Similarly, a species of shark has evolved a unique form of hemochorial placenta (Wourms 1993), the placentae of some reptiles may approach (though not reach) the hemochorial state (Luckett 1976*b*; Mossman 1987 p. 146; Blackburn 1993), and some metatherians (e.g., bandicoots and fat-tailed dunnarts) exhibit an invasive placenta that has evolved convergently with that of eutherians (Luckett 1976*b*; Renfree 1983; Hayssen et al. 1985; Tyndale-Briscoe and Renfree 1987; Roberts and Breed 1994*a*, 1994*b*; Zeller 1999). Blackburn et al. (1985) comment on the "convergent trends toward reduction of the distance between fetal and maternal bloodstreams in numerous placental groups" (see also Wourms and Lombardi 1992), which ultimately results in hemochorial forms. Finally, Pijnenborg et al. (1981) describe the convergent evolution, in rodents and humans, of invasion into the maternal spiral arteries of trophoblast cells, which modify the arteries such that blood flow cannot be restricted (see also Haig 1993).

Carter (2001) remarks that in hemochorial forms, the "prime function of the trophoblast is to adapt maternal circulation to the needs of the placenta and growing fetus." They stated that "the advantage of reducing the number of layers in the interheme membrane is clearly great enough for such adaptations to have been selected many times." But if such an advantage exists, presumably it should be more common among mammals rather than distributed so sporadically. By contrast, Mossman (1987, pp. 152–153, 296) notes that there is no clear selective advantage associated with variation in trophoblast invasiveness, and Pijnenborg et al. (1985) state that it is difficult to attach any adaptive advantage to the differences among the three forms of placentation. Leiser and Kaufmann (1994) describe how neonatal/placental weight ratios are uncorrelated with the number of tissue layers separating maternal and fetal blood but are apparently associated with the geometry of maternal-fetal blood flow interrelationships; moreover, high daily fetal growth rates per placental weight appear to require a relatively efficient placenta (hemochorial or endotheliochorial). These findings suggest that placental form influences aspects of fetal development related to maternal input, although the ecological disparities among the mammals with hemochorial placentation argue against the presence of ecological correlates.

According to the viviparity conflict hypothesis, there may indeed be no ecologically based selective difference among the three placental forms. Thus, such differences arise because only in some lineages have fetuses been able to gain access to the maternal bloodstream; the current outcomes of conflict vary among taxa, depending on differences in physiological and morphological starting points, sequences of mutational events, strengths of selection on the interacting parties, and the presence and form of other adaptations. Consistent with this hypothesis, hemochorial placentation is reached by quite different developmental pathways across these mammal groups (Carter 2001).

Rampant Diversification of Viviparity and Placentation

> There is no other mammalian organ whose structure and function are so species diverse as those of the placenta. This is curious since the "purpose" of the placenta, presumably, is the same in all species. (Faber et al. 1992)

The viviparity conflict hypothesis implies antagonistic coevolution between parents and offspring in traits that influence prenatal investment. Thus, after microevolution toward viviparity and matrotrophy has begun, these traits are expected to evolve rapidly and in a manner that may be difficult to predict from comparative or ecological data, exhibiting similar evolutionary dynamics to those en-

countered in other cases of antagonistic coevolution, such as sexual conflict (Brown et al. 1997; Arnqvist and Rowe 2002; Rowe and Arnqvist 2002; Chapman et al. 2003) or host-parasite interaction (Hughes 1991; Haraguchi and Sasaki 1996; Buckling and Rainey 2002). Although parent-offspring strife is constrained by genetic relatedness, it should nonetheless generate high diversity in morphological, physiological, developmental, and genetic aspects of reproductive mode.

Forms of viviparity itself exhibit notable diversity within eutherian mammals (Rothchild 2003), squamate reptiles (Blackburn 1993), caecilians (Laurin et al. 2000), other amphibians (Wake 1977; Wake and Dickie 1998), and fishes (Wourms 1977, 1981; Wourms et al. 1988; Compagno 1990; Wourms and Lombardi 1992; Hamlett and Hysell 1998; Hamlett 1999). Such diversity extends across all taxonomic levels because closely related species, populations, or individuals within populations often differ substantially in fundamental aspects of reproductive mode (e.g., Guillette 1981; Packard et al. 1989; Blackburn 1992, 1993, 1995, 1998*a*; Heap 1994; Pinella and Laurent 1996; Meisner and Burns 1997; Smith and Shine 1997; Trexler 1997; Fairbairn et al. 1998; Stewart and Thompson 2000; Swain and Jones 2000; Thompson et al. 2000; Smith et al. 2001; Reznick et al. 2002).

Although the basic hormones involved in regulation of reproductive processes are highly conserved among vertebrates, the sources, functions, and targets of these hormones differ strikingly among taxa, sometimes between closely related species. Thus, Blüm (1986), Callard et al. (1992), Cross et al. (1994), and Roberts et al. (1999) describe the wide range of hormonal mechanisms vertebrate embryos use to help maintain pregnancy. Rothchild (1981) noted how among species of mammals, the regulation of preovulatory follicles has remained conservative, while the regulatory mechanisms for postovulatry follicles (after maternal-fetal conflict has begun; Haig 1993) differ widely. Guillette (1989) describes some of the profound differences among humans, pigs, and sheep in the chemical signals used for recognition of pregnancy (see also Freyer et al. 2003), and Heap (1994) describes how mammal species are remarkably dissimilar in the mechanisms whereby immunological rejection of the conceptus is achieved. Haig (1993) and Stewart and Allen (1995) describe the convergent evolution of chorionic gonadotropins in primates and horses, and Forsyth (1994) describes the convergent evolution of placental lactogens, which are involved in diversion of nutrients to the fetus, in primates, rodents, and ruminants. Finally, Amoroso (1981), Heap (1994), Meyer (1994), and Blackburn (2000) describe notable variation in the sources, levels, and profiles of progesterone during gestation; for example, progesterone appears to regulate reproduction differently even among closely related snakes in garter snakes (Highfill and Mead 1975; Whittier et al. 1987; also see Bonnet et al. 2001). These patterns imply strong divergent and convergent selection on the production levels, targets, and functions of reproductive hormones involved in maternal-fetal interaction (see also Haig 1996*b*), which appears difficult to attribute to ecological causes even though an absence of evidence cannot be interpreted unambiguously as the converse.

Trophoblasts of therian mammals differ profoundly even among closely related species in the chemical signals that they produce (Packard et al. 1989; Heap 1994); in their expression sites for growth factors (Carter and Han 1999); in the presence, density, and form of their "giant cells" (Mossman 1987, p. 298); and in their degree of invasiveness into the uterine lining (Hughes 1974; Luckett 1976*b*; Pijnenborg et al. 1981, 1985; Heap 1994; Carter 2001; Allen et al. 2003; Freyer et al. 2003). Moreover, in accordance with different resolutions of conflict over investment or ongoing conflict, the degree of invasiveness is determined in diverse ways among taxa "by properties of the trophoblast itself, by maternal factors such as decidualization, by pregnancy-induced change of other uterine tissues, and by maternal immune responses" (Pijnenborg et al. 1981). q14

The placenta exhibits greater interspecific variation in morphology than does any other mammalian organ (e.g., Benirschke 1983; Mossman 1987; Faber et al. 1992; Leiser and Kaufmann 1994). This remarkable variation among species in the development, physiology, and morphology of placentae has fascinated and puzzled biologists for more than 50 yr (Mossman 1937, 1987, p. 150; Luckett 1976*b*; Renfree 1977; Pijnenborg et al. 1985; Stewart and Blackburn 1988; Wourms et al. 1988; King 1992; Allen et al. 2003). The main source of such puzzlement is that the physiological and morphological vicissitude of placenta-based interactions is accompanied by simplicity of primary function: transfer of nutrients (Faber et al. 1992). Much of the variation in placental morphology is due to diversity in the definitive forms of homologous or analogous structures, but much is also generated via heterochronic shifts and the terminal addition of new stages (Luckett 1976*b*; Wourms et al. 1988; Wourms 1993; Stewart and Thompson 1996, 2003; Allen et al. 2003), which provides an additional dimension for diversification. Here, we propose that the striking interspecific diversity of placental physiology and morphology reflects a long evolutionary history of maternal-fetal conflict. Evaluating this hypothesis requires consideration of the mechanisms of interaction at the maternal-fetal interface.

Maternal-Fetal Antagonism at the Placental Interface

> One reason why the placenta and placental signalling molecules … are evolving so quickly may be because the placenta is the site of considerable genetic experimentation. If the relationship between the mother and the conceptus possesses elements of conflict, rather than being strictly nourishing, a change in one side of the placenta will in all likelihood be accompanied by a counter-move on the other side. (Roberts et al. 1999)

Roberts et al. (1999) anticipate the viviparity conflict hypothesis and one of the best means to test it: finding more or less direct evidence of maternal-fetal antagonism manifested in the genetics, physiology, and morphology of the placenta, the uterus (or analogous structure), and the hormones and other chemical factors that mediate their interactions. The conflict hypothesis makes several predictions regarding this fetal-maternal interface: the presence of placental and maternal structures and functions that reflect a tug-of-war of constrained reciprocal antagonism (Haig 1993, 1996*a*, 1996*b*, 1999*a*), a positive association between placental complexity and maternal investment, higher interspecific variation in the placental traits that are most closely related to resource transfer, and rapid evolution and positive selection on placentally expressed genes and maternally expressed genes that interact with the fetus.

Reciprocal maternal-fetal antagonism is manifested in the first stage leading to placentation, association of the trophoblast with the uterine lining. In mammals, increased fetal (trophoblast) invasiveness has apparently been countered over evolutionary time by three responses: maternal secretion of compounds to reduce its degree (Heap 1994), which includes a stronger maternal immune response (Pijnenborg et al. 1981; Leiser and Kaufmann 1994; Stewart and Allen 1995); the evolution of more developed maternal epithelial barriers (Pijnenborg et al. 1995); or the shedding of overly invasive trophoblasts with the uterine lining (Pijnenborg et al. 1981; Haig 1993, 1996*a*; Finn 1998). Moreover, as described by Pijnenborg et al. (1985), pigs exhibit noninvasive trophoblasts, but if a trophoblast is transplanted to an ectopic site, it invades maternal tissue, expressing cytolytic and phagocytic properties that are apparently suppressed by the mother in normal pregnancies (Pijnenborg et al. 1981). Similarly, a mouse trophoblast (which is normally mildly invasive) invades uncontrollably when transplanted to ectopic sites (see Cross et al. 1994). These findings suggest that invasiveness reflects a tug-of-war between mother and fetus, with adaptations on both sides to restrain the other; this hypothesis can be evaluated more directly by analyzing trophoblast invasiveness and maternal responses in a species-level phylogenetic context.

Among eutherian and metatherian mammals studied to date, the trophoblast and developing placenta begin to secrete hormones early in ontogeny. Some of these hormones function as signals for maternal recognition of pregnancy (e.g., Heap et al. 1981; Guillette 1989; Allen and Stewart 2001), which may represent simple fetally derived hormonal signals to the mother that a fetus is present, serving to maintain the pregnancy but also perhaps functioning as a test of embryo quality imposed by mothers (i.e., ability to produce large amounts of gene product quickly; Haig 1999*a*). In either case, the developing conceptus should be under strong selection to manipulate the mother, given any degree of conflict over whether a particular incipient pregnancy will proceed and how much will be invested in the fetus. Such conflict apparently underlies the evolution and function of equine chorionic gonadotropin, which is produced in large quantities by a placental structure (the endometrial cups) unique to horses (Haig 1993; Stewart and Allen 1995). This hormone, which appears to be produced by a paternally imprinted gene (Allen et al. 1993; Lennard et al. 1995), exhibits low binding affinity to its maternal receptors, and analysis of experimental hybrid pregnancies between horses and donkeys provides evidence that the maternal receptors of horses have evolved to become recalcitrant to this fetal hormone to prevent overstimulation of the ovaries (Haig 1993; Stewart and Allen 1995). Moreover, analyses of hybrid and normal pregnancies show that equine chorionic gonadotropin is not essential for the completion of development, though its absence is associated with inadequate placentation and high levels of abortion (Stewart and Allen 1995; Allen 2001; Allen and Stewart 2001); the analyses also show that the development of the endometrial cups depends in part on the genotype of the uterus (Allen et al. 1993; Allen and Stewart 2001), suggesting that the mother has evolved some degree of control over their growth and that the mother's immune system destroys the endometrial cups about a month after they are formed (Allen 2001). During the second half of gestation, the horse fetus also undergoes a massive, temporary enlargement of the gonads, which produce large quantities of oestrogens; as with equine chorionic gonadotropin, production of this hormone by the fetus is not essential for development. However, fetuses with their gonads removed developed into smaller foals, apparently as a result of reduced uteroplacental blood flow (Allen 2001; Allen and Stewart 2001).

Haig (1993, 1996*b*) presents evidence from human pregnancy that antagonistic coevolution may explain the remarkably high levels of some products secreted by the placenta, the secretion by the placenta of some of the same hormones that mothers are also producing (thereby masking the source of the secretions), and the production of gene products that are rapidly inactivated by the mother.

Moreover, Painter et al. (2002) found that the placenta buffers the effects of experimental variation in maternal steroid concentration in a viviparous reptile and that maternal hormones may inhibit placental hormone secretion. These results hint at the presence of antagonistic interactions whereby each party can undermine the endocrine production strategies of the other. This evidence from horses, humans, and a reptile suggests that the evolution of endocrine hormone production has involved considerable conflict between mothers and fetuses, which can be resolved in diverse ways.

By our hypothesis, the striking interspecific variation in placental morphology (reviewed for mammals in Mossman 1987) also reflects the outcomes of maternal-fetal conflict over investment (see also Kurz et al. 1999; Zechner et al. 2004). Presently, our clearest prediction is that the placental traits that vary most among taxa will be those most closely associated with control over nutrient transfer because on these traits antagonistic selection has been strongest. The many origins among mammals of hemochorial placentation concord with this prediction, as does the presence of unique structures such as the equine endometrial cups. Moreover, among placental skinks, there is a positive association between placental complexity (which may reflect adaptations for conflict) and the extent of nutrient transfer (Thompson et al. 2000, 2002). However, this prediction is difficult to test because the functional morphology of placentation has been analyzed in sufficient detail to ascribe adaptive significance to taxon-specific placental structures in only a few taxa: humans (Haig 1993, 1999*a*), mice (Rossant and Cross 2001), horses (Allen 2001; Allen and Stewart 2001), and some other farm animals (Allen et al. 2003). Indeed, the byzantine complexity and puzzling details of placental development in humans and horses, two of the best-studied species, suggest that robust comparative analyses of the adaptive significance of variation in placental phenotypes must await further study directed toward clades such as primates, rodents, and artiodactyls, where much of the descriptive groundwork has already been laid.

Maternal-fetal conflict may also be expressed in the development of new fetal structures, some of which are analogous to the placenta. Thus, the appendiculae of some placental sharks, outgrowths of the umbilical cord that appear to function as an additional, secondary placenta (Wourms et al. 1988; Hamlett 1989, 1990, 1999; Wourms and Lombardi 1992; Lombardi et al. 1993; Wourms 1993), may also represent an effect of maternal-fetal coevolution if they originated in response to maternal limitations imposed on the original placental interface (Southwell and Prasad 1919). Appendiculae appear to have a secretory role in some species (Hamlett 1989, 1990, 1999), which the viviparity conflict hypothesis predicts will involve manipulation of the mother to increase nutrient provision (e.g., Haig 1996*b*). They also exhibit striking morphological diversity among species, and in at least one shark genus, they are present in some species but not others (Hamlett 1989). Some placental structures of therian mammals that may be comparable to appendiculae in apparently facilitating absorption of nutrients include "inverted yolk sacs, hematomes, areolae, arcade networks, and marginal folds of chorioallantois around the placentomes" (Mossman 1987, p. 297); these structures also vary notably among mammalian groups in their presence and forms (see also Allen 2001 on multiple sources of nutrient transfer in horses). By our hypothesis, some or all of these structures evolved in the context of offspring under strong selection to develop new routes for increased maternal investment. Similarly, the functional redundancy of diverse biochemical factors involved in mammalian implantation (Viganò et al. 2003) may reflect recruitment of new mechanisms for trophoblasts to successfully invade the uterine lining.

At the molecular level, numerous genes involved in mammalian maternal-fetal interactions evolve especially rapidly (Haig 1993; Chun et al. 1999; Roberts et al. 1999; Wallis 2000; Sol-Church et al. 2002; see also Kurz et al. 1999). However, imprinted genes analyzed thus far show no evidence of antagonistic coevolution (McVean and Hurst 1997; but see Paldi 2003; Verona et al. 2003), perhaps because they fulfill essential functions in contexts other than fetal development (Rossant and Cross 2001; Cross et al. 2003). Antagonistic coevolution may also be responsible for the strong positive selection detected in the evolution of numerous placentally expressed genes (Ohta 1993; Wallis 1993; Hurst 1994; Maiti et al. 1996; Xie et al. 1997; Garbayo et al. 2000; Hughes et al. 2000; Maston and Ruvulo 2002; Zhang and Rosenberg 2002; Zhang et al. 2002), dramatic escalations in rate of change of maternal hormones associated with the origins of placental hormones (Wallis 1981, 1993, 1994, 1996, 1997, 2000; Lioupis et al. 1997; Wallis et al. 2001), and the co-option of endogenous retroviruses for regulating the placental expression of genes involved in immunosuppression and trophoblast invasiveness (Harris 1998; Bièche et al. 2003). Joint analysis of such molecular evolutionary changes with the evolution of placental and maternal endocrine regulation and placental morphology may be especially useful for understanding how placental traits originate and evolve. Such analyses should also yield implications for human health and reproduction because miscarriages are frequently caused by disruptions of placental development (e.g., Rossant and Cross 2001), because trophoblast invasion of the uterine wall provides useful models for understanding immunology and carcinogenesis (e.g., Ohlsson 1989; Barnea and Brusato 2000), because parent-offspring and intra-

genomic conflict apparently favor the evolution of alleles that promote cancer (Summers et al. 2002), and because adult health increasingly appears to be programmed by the environment and epigenetics of fetal development (e.g., Godfrey 2002).

Considered together, the evidence from studies of implantation, hormone production, placental structure, evolution of accessory structures for matrotrophic exchange, and molecular evolution suggest that maternal-fetal arms races may be widespread, at least in elasmobranchs and placental vertebrates. Analysis of how and why these are resolved or continue unabated remains a challenge for future work.

Alternative Hypotheses

> Tentatively, the most reasonable general hypothesis (for the evolution of placental diversity) seems to me to be that the genotypes of each group differently limit the directions evolution can take. (Mossman 1987, p. 293)

q22 The diverse forms of viviparity and placentation may also represent multiple adaptive peaks structured by ecological
q23 selective pressures in the context of different morphological and physiological starting points. Testing this hypothesis requires drawing comparative connections between aspects of ecology and the physiological details of reproductive mode. Similarly, the role of disparate physiological and morphological evolutionary starting points for the evolution of viviparity among the major vertebrate groups in generating diversity requires further study. The amniote egg is, however, fundamentally similar among vertebrates (e.g, Luckett 1976*b*; Mossman 1987), and the profound differences in reproductive physiology between closely related or conspecific forms argue strongly against the primacy of diverse starting points in producing adaptively similar but diverse extant forms. Indeed, the problem of matrotrophic viviparity appears to be considerably more complex than efficient nutrient transfer to developing offspring; to the extent that the viviparity conflict hypothesis holds true, the reproductive strategies of mothers and offspring are mutually problematic because physiological efficiency serves as both a constraint on conflict and a selective pressure itself.

Further evaluation of the viviparity conflict hypothesis, in relation to alternatives, may best proceed along several fronts. First, Haigian analyses of physiological mechanisms of maternal-fetal interaction and genomic imprinting effects in nonhuman mammals and other viviparous vertebrates (Haig 1993; Haig and Trivers 1995) would demonstrate the generality of conflict. Such studies would be especially useful in species that are presumed or inferred to be plesiotypic for their forms of viviparity or placentation because they would show the potential role of conflict in the early stages of transition between reproductive modes. Second, the fetal-maternal arms race hypothesis requires phylogenetically based tests, which would most directly demonstrate effects of antagonistic coevolution. A phylogenetic perspective on the evolution of the placenta is already available (Luckett 1976*a*, 1976*b*, 1993; Mossman 1987; Carter 2001; see also Thompson et al. 2002; Mess et al. 2003) and may serve as a template for such analyses. However, the high diversity of placental traits urges caution in the use of such traits to infer phylogenies themselves (e.g., Luckett 1976*a*; Mossman 1987) and in the use of animal models for understanding human placentation (e.g., Faber et al. 1992; Rossant and Cross 2001). Third, given that conflict over reproductive mode may affect evolutionary trajectories, it may have important macroevolutionary consequences. For example, might metatherians have evolved in the context of mothers winning in most aspects of conflict over control of investment via short gestation and long lactation (Hayssen et al. 1985; Renfree 1977, 1983)? Did the allantois itself originate in viviparous forms as a result of the evolution of this reproductive mode (Mossman 1987, pp. 118, 124–126)? Given that fetal membranes and placental structure are relatively uniform within mammalian families but extremely different among them (Mossman 1987, p. 122, 288–290), might they be involved in the origin of higher mammalian taxa? Fourth, Zeh and Zeh (2000) provide evidence that viviparity-induced conflicts have led to accelerated speciation in mammals via rapid divergence of traits involved in maternal-fetal interactions (see also Wilda et al. 2000); are viviparous clades of vertebrates more or less speciose than their oviparous sister taxa (Slowinski and Guyer 1994)? Finally, tests for ecological differences between closely related species or populations that differ in aspects of viviparity, matrotrophy, and placentation may reveal unforseen adaptive linkages or evidence that the differences reflect divergent outcomes of conflict. Given that antagonistic coevolution is expected in the evolution of traits related to viviparity and matrotrophy, analyses of their adaptive significance may often be misled by genetic conflict in the guise of ecological maladaptation. Moreover, changes in reproductive mode as a result of maternal-fetal conflict may also affect the ecology of a species (J. Reynolds, personal communication) such that differentiating causes from effects becomes difficult.

Our main goal has been to provide a new perspective on the diversification of vertebrate reproductive modes. Most generally, we have shown that analysis of reproductive mode provides a novel opportunity for analysis of how conflicts are resolved or ongoing between parties that are mutually dependent (e.g., Crespi 1992; Brown et al. 1997; Choe and Crespi 1997). Our perspective should

compel evolutionary ecologists to incorporate physiological mechanism more deeply into analyses of selection on reproductive ecology (e.g., Shine and Guillette 1988; Shine 1995; Blackburn 2000), and physiologists should likewise entertain the possibility that mechanisms represent more or less maladaptive compromises rather than manifestations of optimized function subject to the particularities of constraint. The forms of traits associated with viviparity, matrotrophy, and placentation should be largely adaptive, but the question becomes not just how but also for whom.

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1 Please provide publication information for Aristotle's *Historia Animalium* to add this reference to the literature cited.

2 Please see throughout manuscript: Parker 1995 is not listed in the literature cited. Please provide reference information or delete from text.

3 See query 2

4 Please provide a citation for Haig in the sentence that begins "As described by Haig ..."

5 Please provide a page number for direct citation of the quote from Mossman 1937.

6 Please note: Throughout the manuscript, you seem to go back and forth between using the past tense (here, "Hamlett noted") and the present tense (later, "Koob and Callard provide"). I wanted to bring this to your attention. It is not required that you are consistent one way or the other, except maybe when a shift occurs in the same sentence. Please review throughout.

7 Shine and Bull 1978 is not listed in the literature cited. Did you intend to cite Shine and Bull 1979? If not, please provide reference information or delete from text.

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9 Haig 1991 is not listed in the literature cited. Did you intend to cite some other Haig reference? If not, please provide reference information or delete from text.

10 In the sentence that begins "Hemochorial placentation ...," would it be OK to change "given rise to an endotheliochorial form" to "giving rise to ..."? This phrasing seems a bit unclear as is.

11 Please provide a page number for citation of the direct quote from Blackburn et al. 1985.

12 Please provide a page number for citation of the direct quote from Carter 2001.

13 Who are "They" in "They stated that ..."? Are you referring again to Carter? Also, please provide a citation and a page number for citation of the direct quote.

14 Please provide a page number for citation of the direct quote from Pijnenborg et al. 1981.

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19 See query 16

20 See query 16

21 Does the direct quote beginning "inverted yolk sacs ..." come from Mossman 1987? I moved it closer to the quoted material, which is our style.

22 In the quote from Mossman that begins "Alternative Hypotheses," is it OK that I changed the brackets around "for the evolution of placental diversity" to parentheses? Do the brackets appear in how the text was originally published?

23 Is it OK that I changed the hyphen in "morphological-physiological starting points" to "and"?

24 In Carter and Han 1999, please spell out IGF in the journal title.

25 Please verify that W. C. Hamlett was the author of the 1999 reference "Placental and analogs in elasmobranchs."

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27 Is the spelling of the second author's name Prasad or Prashad?

28 Please verify the spelling of the author's last name for Xavier et al. 1988. Is it Xavire or Xavier?

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