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Placental Evolution in Therian Mammals

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Introduction

One of the great transformations in the history of vertebrates involves the origin and early diversification of the mammals. Mammals are distinguished from other vertebrates by almost countless aspects of their anatomy, physiology, behavior, reproduction, and life history. Many of these features appear to have arisen as an integrated complex during the early evolution of mammals. An exceedingly detailed fossil record has aided our understanding of this transition, and decades of work have led to an understanding of many of the unique adaptations of this group. In particular, the intimate interdependence of reproduction, anatomy, and physiology in mammals and their roles during the transition to the mammalian condition has presented a fascinating puzzle to vertebrate biologists (e.g., Crompton 1980; Crompton and Jenkins 1973; Crompton et al. 1978; Farmer 2000; Guillette and Hotton 1986; Hopson 1973; Jenkins 1984; Kemp 2006, 2007; Koteja 2012; McNab 1978; Pond 1977; Ruben 1995).

While the origin of mammals has provided one set of puzzles, the diversification of mammals is also ripe with questions. Three extant major groups of mammals exist. Monotremes retain many primitive features and are generally considered to have diverged from the therians in the Triassic to Jurassic periods (e.g., O'Leary

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et al. 2013, Luo 2007). The therians comprise the eutherians¹ or placentals and the metatherians or marsupials; these groups diverged sometime in the Jurassic to early Cretaceous periods (e.g., O’Leary et al. 2013, Luo 2007). Among the living mammals differences in reproductive strategies are perhaps the most intriguing. By definition all mammals nourish young postnatally by maternal provision of milk; however, other aspects of reproduction differ. Monotremes are **oviparous**² and the hatching is **altricial**. Both therian groups are **viviparous**, but differ in other aspects of reproductive strategy. Marsupials give birth to highly altricial young after a short period of maternal nutrition via a **placenta**. Eutherian newborns are all born after a relatively long or intensive period of intrauterine development with a well-developed placenta and may be altricial or **precocial**. These differences in reproductive strategy are among the most consistent defining characteristic of these clades. Although these differences had been recognized for well over a century, in the late 1970s and early 1980s a particularly lively debate on the potential reasons for and consequence of these differences arose.

Much of this debate was stimulated by Lillegraven (Lillegraven 1969, 1975, 1984, 2004; Lillegraven et al. 1987) who sought the causes and consequences of the “marsupial-placental dichotomy.” Lillegraven proposed that the critical elements differentiating the two clades arose from the differences in the capacities of the placenta. He maintained that the eutherian placenta differed from all other vertebrates in allowing “intimate apposition of fetal and maternal tissues and circulatory systems” with “sustained, active morphogenesis” accompanied by immunological protection of the fetus from the mother. Lillegraven proposed that this capacity was due to the **trophoblast**, which he believed was a unique “invention” of eutherians. He argued that because marsupials lacked a trophoblast they were unable to maintain a prolonged, active intrauterine gestation and therefore were constrained to a primitive state of reproductive capacity. Lillegraven further hypothesized

that this reproductive limitation imposed constraints on the subsequent development and evolution of marsupials. Finally he argued that the eutherian placenta was a key innovation and the ultimate source of many of the characteristics that have led to the great diversification and relative dominance of eutherians today (Lillegraven et al. 1987).

This view was countered by several authors (e.g., Hayssen et al. 1985; Kirsch 1977a, 1977b; Low 1978; Parker 1977) who believed that it was unlikely that marsupial biology was the result of being stuck at an intermediate stage of evolution or was fundamentally constrained. Instead, they proposed, the marsupial mode of reproduction should be thought of as an alternative strategy that provided greater maternal control of reproductive resources. Additionally, these authors argued that although marsupials exhibit less overall diversity than eutherians, they exhibited a large range of anatomical, ecological, and physiological adaptations, casting doubt on the hypothesis that their evolution was fundamentally constrained. Tyndale-Biscoe and Renfree (e.g., Renfree 1983, 1993, 1995, 2010; Tyndale-Biscoe 2005; Tyndale-Biscoe and Renfree 1987) portrayed reproduction in monotremes, marsupials, and eutherians as a continuum, with underlying similarity but differing emphases on maternal nutrition via the placenta or lactation. They emphasized that marsupials, by placing emphasis on lactation, lacked some of the adaptations of eutherians for intrauterine gestation, but also possessed a number of distinct adaptations of their own, particularly for specialized lactation. Examination of the consequences of the reproductive differences has continued to the present time with a large number of recent studies exploring comparative development in marsupial and eutherian mammals and its evolutionary consequences (e.g., Bennett and Goswami 2011; Cooper and Steppen 2010; Goswami et al. 2009, 2012; Kelly and Sears 2011; Keyte and Smith 2010, 2012; Sánchez-Villagra 2013; Sánchez-Villagra et al. 2008; Sánchez-Villagra and Maier 2003; Sears 2004, 2009; Smith 1997, 2001, 2006; Vaglia and Smith 2003; van Nievelt and Smith 2005; Weisbecker 2011; Weisbecker and Goswami 2010; Weisbecker et al. 2008; Weisbecker and Sánchez-Villagra 2007).

While there have been a number of studies that have addressed hypotheses on the development, adaptations, and diversity of marsupials, there has not been as much focus on the hypothesis that the trophoblast and placenta are unique innovations of eutherians. In

1. The terms marsupial and eutherian will be used in an informal sense throughout this paper. Properly the crown group of extant eutherians should be termed the Placentalia (Rougier et al. 1998; Asher and Helgen 2010), equivalent to the crown group Marsupialia. However, as this paper is on the evolution of the placenta, the term eutherian will be used for the crown group to avoid awkward constructions such as “the placenta in placentals”.

2. Terms in bold are defined in table 12.1.

recent years a great deal of new data on the basic biology of reproduction in mammals has emerged. These data provide new insight into the anatomy, physiology, and phylogeny of the placenta within mammals and in nonmammalian amniotes and allow evaluation of this fundamental hypothesis. In addition, in the last several decades, entirely new research areas arising from the discovery of genomic imprinting and the proposal of the theory of maternal-fetal conflict have emerged. Therefore the time is ripe for a fresh look at the issues surrounding the evolutionary patterns and significance of reproductive strategies in mammals.

In this review I will examine data on the function and evolution of the placenta in therian mammals. My intent is not to revisit the original debate or to provide a detailed critique of past discussions, but instead I will focus on the evolution of the placenta. I will summarize new data on the variation in placental morphology in both marsupials and eutherians, the relation between placental form and development, and new phylogenetic analyses of placental form. I will then discuss comparative aspects of reproduction in marsupials and eutherians with particular focus on maternal-fetal conflict and maternal control of reproductive effort. My hope is to shed new light on the significance of variation in reproductive patterns in therian mammals and ultimately on the role that reproduction may have played in the origin and diversification of mammals.

The Placenta: A Brief Overview

In vertebrates **viviparity** has evolved many times. In some taxa this includes the evolution of a specialized interface, the placenta, between fetal and maternal tissues for the transfer of nutrients. In others it consists of retention of the egg or embryo with little or no nutrition provided by the mother beyond the initial yolk. In a few taxa viviparity involves adaptations for embryonic consumption of maternal tissues, specialized eggs, or littermates (reviewed in Blackburn 2006; Shine 1995; Wake 1993). In amniotes viviparity is common in squamates, where it has evolved independently at least 100 times, and characteristic of therian mammals. In most viviparous squamates nutrition is still largely provided by the yolk, but in many, fetal membranes are specialized for gas, water, and mineral exchange (reviews in Blackburn 2006 and Blackburn and Flemming 2009;

Flemming and Blackburn 2003; Stewart and Thompson 2003; Thompson and Speake 2006). In all mammals and many squamates the mother provides nutrition beyond the yolk. This nutrition can be provided in two major ways: **histotrophically**, where specialized uterine secretions are absorbed by extraembryonic or placental tissues, and **hematrophically** where nutrients, waste products, and gas are exchanged between maternal and fetal blood supplies.

In therian mammals and many squamates the **placenta** facilitates the transfer of maternal provision to the fetus. Placentae are by most definitions structures consisting of the apposition of specialized maternal and fetal tissues for physiological exchange (e.g., Mossman 1937). In mammals and other amniotes the fetal side of the placenta generally develops from the specialized extraembryonic membranes of amniotes (the primitive **yolk sac** along with the **chorion**, **amnion**, and **allantois**) while the maternal side involves specializations of the endometrium. It is important to note that a specialized placenta is not a eutherian or even a mammalian invention, but instead is seen in many vertebrates. In squamates the convergence is “astonishing” (Blackburn and Flemming 2009) and can exist on the morphological, physiological, and genetic level (e.g., Brandley et al. 2012). The anatomy and function of the placenta in mammals have been well studied; these studies reveal extraordinary morphological and functional variability. Comprehensive reviews of placental morphology may be found in many sources (e.g., Carter 2001; Carter and Mess 2007, 2008; Carter et al. 2004; Enders and Carter 2004, 2012a, 2012b; Freyer et al. 2001, 2003, 2007; Freyer and Renfree 2009; Luckett 1977; Mess and Carter 2006, 2007; Mossman 1937; Wooding and Burton 2008 and references therein). Here I briefly introduce terminology important for the remaining discussion.

As mentioned above the placenta is a structure that depends on the interaction of fetal and maternal elements. The fetal elements arise from the extraembryonic membranes of amniotes, the **chorion**, the **allantois**, and the **amnion**. Together with the yolk sac these membranes combine to form the membranes of the egg in egg-laying species, or the fetal contribution to the placenta in animals with a placenta. In both egg-laying and placental amniotes the amnion surrounds the embryo, while the chorion may fuse with either the yolk sac (vitelline membrane) or allantois to form the

choriovitelline or **chorioallantoic** membrane, respectively. In animals with placentae, these membranes are closely apposed to maternal epithelium to form chorioallantoic or choriovitelline placentae (table 12.1; fig. 12.1). In many egg-laying amniotes, including most squamates as well as monotremes, the chorioallantoic and choriovitelline membranes are both well developed; the chorioallantois thought to be largely responsible for gas exchange and the choriovitelline membrane for nutrition.

A yolk sac or **choriovitelline placenta** is present in early development in both marsupials and eutherians (Freyer and Renfree 2009). In addition to serving as an early site of nutrient exchange, it is important in production of growth factors, binding proteins, and receptors, as well as hematopoiesis, cholesterol production, and transfer of nutrients in all mammals. It forms the final functional placenta in most marsupials. In most eutherians, the yolk sac is reduced, and the **chorioallantoic placenta** is the final functional placenta.

Chorioallantoic placentae are found in several marsupials as well, at least transiently, and in peramelids the chorioallantois contributes to the final functional placenta.

In therians there is also significant variation in the degree that fetal tissues invade the uterine lining. This trait is independent of the specific fetal membranes contributing to the placenta (table 12.1; fig. 12.2). The least invasive type, the **epitheliochorial placenta**, involves contact between the epithelia of the chorion and the uterus. There is no erosion or invasion of the uterine lining by fetal tissues, and nutrients diffuse through several cell layers. In **endotheliochorial** placentae embryonic tissues invade the uterine lining and are in contact with the endothelium of the maternal blood vessels. Finally, in the most invasive condition, the **hemochorial placenta**, fetal tissues have eroded maternal blood vessels, so that maternal blood accumulates in spaces within the **chorioallantois**. These categories are often further subdivided. Tremendous variation and also

TABLE 12.1 A glossary of important terminology

General characteristic	Important terminology	Functional notes
Reproductive type	Viviparous	Female gives birth to live young. This term includes a wide range of conditions from ovoviviparity, where eggs are retained within oviduct or uterus with no provision of nutrients beyond initial yolk, to placental viviparity where elaborate adaptations exist for maternal nutrient provision. Many intermediate forms exist.
	Oviparous	An egg is laid and no further nutrition provided by mother before hatching.
Form of newborn young	Altricial	Young is small and poorly developed at birth. In general eyes are closed, and minimal thermoregulation and locomotion capacity exist. Requires a long period of postnatal care by parents.
	Precocial	Young is relatively independent at birth: eyes open, generally capable of locomotion. May be provisioned for variable period by parent.
Placenta		A structure composed of fetal and maternal tissue adapted for physiological exchange. May have many specific forms and may be responsible for many kinds of exchange.
Type of intrauterine provision of nutrients	Histotrophic	Secretions from the uterine lining are absorbed by vasculature in fetal membranes.
	Hematrophic	Placental adaptations exist for fetal blood supply to interact with maternal blood supply and absorb nutrients and gasses directly from it.
Precursor to extraembryonic membrane	Trophectoderm or trophoblast	Portion of blastocyst that gives rise to ectodermal portions of the chorion. Two terms generally considered to be homologous (for further information see table note).

TABLE 12.1 (continued)

General characteristic	Important terminology	Functional notes
Extraembryonic membrane (primitive)	Yolk sac membrane	Initially formed by enclosure of yolk (or hollow blastocyst) by mesodermal cells from embryonic disc; migration of endoderm forms bilaminar yolk sac. Primitive function nutritive.
Extraembryonic membrane (derived in amniotes; their presence defines the cleidoic egg)	Chorion	Develops from trophoctoderm and extraembryonic mesoderm. Generally nonvascular. Primitive function gas exchange.
	Allantois	Forms from extraembryonic endoderm and mesoderm. Readily vascularizes. Primitive function waste removal.
	Amnion	Forms either from the chorion or extraembryonic ectoderm. Forms protective cavity around developing embryo.
Membrane/placental type	Choriovitelline	Membrane is formed from the yolk sac membrane and chorion. In some species/some regions a second invasion of mesoderm vascularizes the yolk sac to form trilaminar yolk sac. When this membrane forms the embryonic contribution to the placenta, it is called a choriovitelline placenta.
	Chorioallantoic	Membrane is formed from chorion and allantois. Vascularization is via allantois. When this membrane forms the embryonic contribution to the placenta, it is called a chorioallantoic placenta.
Fetal-maternal interface	Epitheliochorial	No layers removed; epithelium of uterus in contact with epithelium of chorion.
	Synepitheliochorial (syndesmochorial)	Syncytium of maternal-fetal cells at interface (a subdivision of epitheliochorial placentation).
	Endotheliochorial	Erosion of uterine lining by trophoctoderm so that chorion is in contact with the endothelium of maternal blood vessels.
	Hemochorial	Maternal blood in direct contact with chorion and placental tissues derived from fetus.
Nature of interdigitation	Villous	The geometry of the contact between maternal and fetal tissues in the placenta. The categories listed represent increasing surface area of contact between maternal and fetal tissues. Many intermediate conditions.
	Folded trabecular	
	Lamellar trabecular	
	Labyrinthine	
Shape of placenta	Diffuse	Maternal-fetal interface scattered on surface of chorion.
	Cotyledonary	Areas of contact limited to distinct cotyledons.
	Zonary	Fetal portion of placenta contacts uterus in a central band.
	Discoid	Distinct disc for contact between fetus and uterus.
Cell fusion	Syncytium	Fusion of cells into a multinucleate tissue. May be fusion of fetal (chorional) cells only, or fusion of fetal cells with maternal cells. Appears to require capture of retroviral gene syncytium by host genome.

Note: Major terms and features of reproductive biology and placental morphology used in this paper. See Wooding and Burton (2008) and references in text for more information on placental types. The terminology for the trophoctoderm/trophoblast deserves particular note. Although Lillegraven (2004) has continued to argue that the trophoblast of eutherians is unique, virtually all workers on early development consider the trophoblast and the trophoctoderm, a more general term, to be homologous (e.g., Johnson 1996; Johnson and Selwood 1996; Moffett et al. 2006; Renfree 2010; Selwood and Johnson 2006; Taylor and Padykula 1978; Wooding and Burton 2008). Indeed, Hubrecht, who first coined the term trophoblast, explicitly includes the extraembryonic membrane of marsupials in his definition of the trophoblast (Pijnenborg and Vercruyse 2013).

homoplasy exists within this simple scheme (e.g., Enders and Carter 2012a, 2012b; Wooding and Burton 2008). It is important to note that hematrophic nutrition does not require a hemochorial placenta.

In addition to the degree of tissue invasion there is variation in the way maternal and fetal tissues interdigitate as well as in the overall shape of the placenta (table 12.1). For example, the specific geometry of contact between maternal and fetal tissues may be **villous**, **trabecular**, or **labyrinthine** (table 12.1). These different arrangements of interdigitation change the relative surface area in contact between maternal and fetal tissues and may be of major significance in placental

function (Capellini 2012). The three features of placental morphology—degree of invasiveness, type of interdigitation, and general shape—show some phylogenetic correlation, but also independent evolution (e.g., Capellini 2012; Elliot and Crespi 2009; Wildman et al. 2006).

A final feature of interest is the formation of **syncytia** within placental tissues. A syncytium is the fusion of cells to form a multinucleate tissue. In many species syncytia form in placental tissues, and in a few (e.g., eutherian ruminants, marsupial peramelids) a syncytium of maternal and fetal cells forms (Wooding and Burton 2008). It is thought that this acellular tissue allows more efficient transfer of nutrients. In recent years it has been

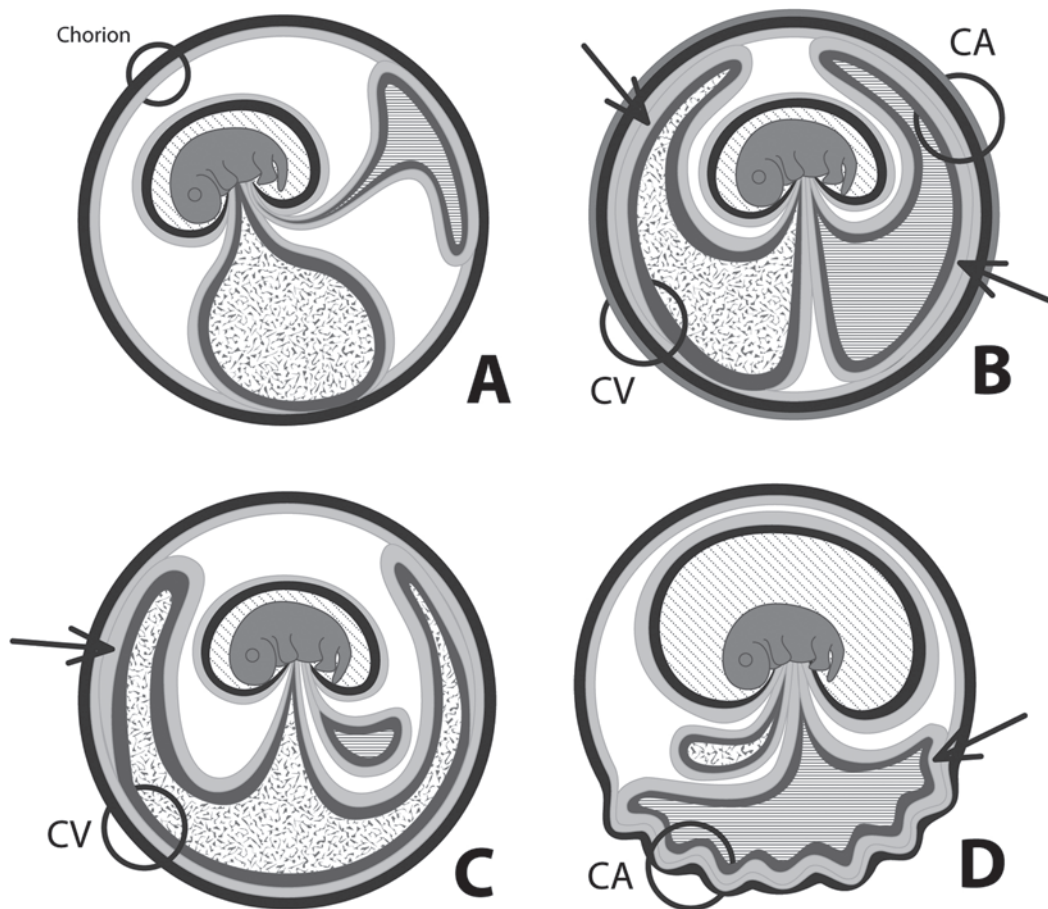


FIG. 12.1 Schematic views of extraembryonic membranes and placentae in A, the amniote “morphotype”; B, monotremes (a similar arrangement is seen in squamates); C, most marsupials; and D, eutherians. The primitive amniote condition with both chorioallantoic (CA) and choriovitelline (CV) membranes are also seen in most squamates and also monotremes. In these animals the chorioallantoic membranes are largely respiratory while the choriovitelline membranes are important in nutrition. In marsupials and eutherians (and some squamates) these extraembryonic membranes join with the uterine lining to form placentae. In many marsupials the chorioallantoic membrane is present for part of gestation and is replaced by the choriovitelline membrane as the final placenta. In all illustrations the darkest gray represents membranes derived from ectoderm, medium gray from endoderm, and light gray from mesoderm. The cavity with stippled lines is the amnion, irregular stippling is the yolk sac, and solid lines indicate the allantois. The chorion forms the outermost layer in all forms. The arrows point to regions where a second layer of mesoderm has invaded, providing vascularization and contributing to a trilaminar placenta. Redrawn from Ferner and Mess (2011).

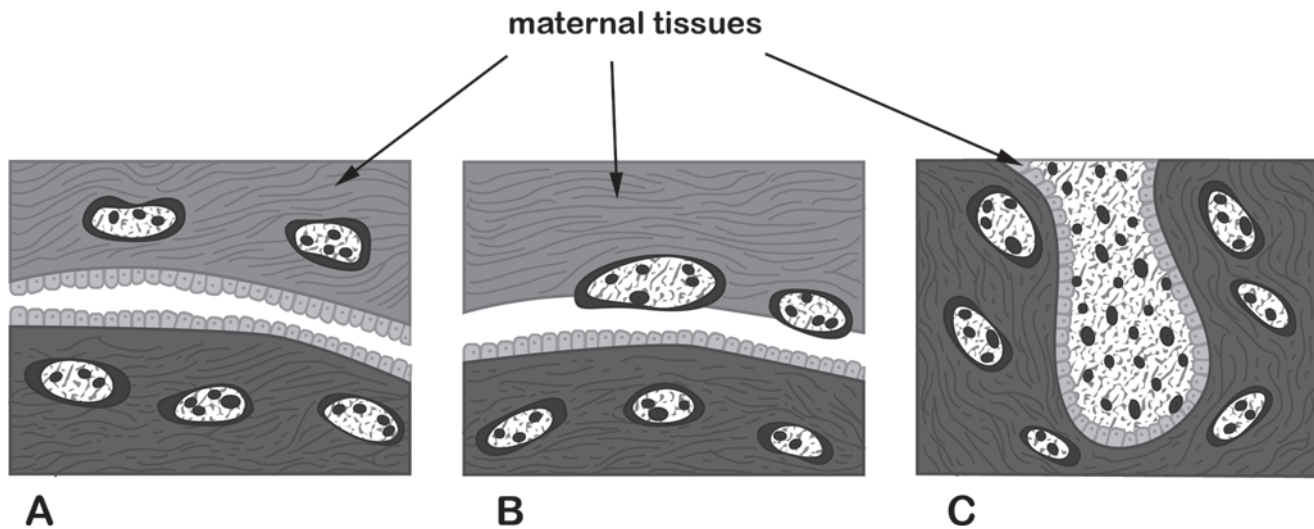


FIG. 12.2 Schematic view of the layers of maternal and fetal tissue in placentae. A, Epitheliochorial placentae, where the epithelium of the maternal (uterine lining/decidua) and fetal tissues (chorion) are in contact; B, endotheliochorial placentae, where the fetal tissue (chorion) is in contact with the endothelium of the maternal blood vessels; C, hemochorial placentae where maternal blood circulates in spaces within the fetal tissue. In all illustrations, small cells represent the epithelial layer; light gray, the tissue the maternal placenta/decidua; and dark gray, the fetal/placental tissue. The circular forms are red blood vessels or blood cells. Redrawn from Ferner and Mess (2011).

shown that in several eutherians the formation of syncytia depends on the presence of the retroviral gene syncytin. Interestingly, retroviral syncytin genes seem to have been independently captured by primates, rodents (mice), lagomorphs, and carnivores, and it is presumed that they will be present in all mammals with placental syncytia although they have not yet been identified in marsupials (e.g., Blaise et al. 2003; Cornelis et al. 2012; Harris 1998; Heidmann et al. 2009; Mi et al. 2000). The capture of retroviral genes has been proposed to have a general role in the evolution of the placenta (e.g., Chuong 2013; Haig 2012).

Evolutionary Patterns: Marsupials

The marsupial constraint hypothesis claims that marsupials are limited to a short intrauterine period, an inefficient yolk sac placenta, and altricial young because they are unable to develop the critical adaptations for intimate and prolonged gestation seen in eutherians. It is almost impossible to confirm or refute a claim of evolutionary constraint; however, one may look at the corollaries of this hypothesis to see if they are supported by variation in existing organisms. In particular, an implication of this hypothesis is that more “eutherian-like” conditions are derived, while the primitive condition in marsupials would reflect the constraints of

short gestation, highly altricial young, and simple placentae. More specifically, we can make the following predictions:

- 1) in marsupials, highly altricial young would be the primitive condition and more precocial young the derived condition.
- 2) close maternal-fetal interaction (i.e., invasive, syncytial placentae) would be a derived condition within marsupials.
- 3) increased invasiveness of the placenta would correlate with a more precocial young, as would elaboration of mechanisms for hematrophic, as opposed to histotrophic, nutrition.

The Altricial Precocial Spectrum in Marsupials

When compared to eutherians, the marsupial neonate appears highly altricial and relatively invariant. Nonetheless, variation exists. Hughes and Hall (1988) define three grades of marsupial newborns that they termed G₁, G₂, and G₃ (table 12.2; fig. 12.3). These three grades correlate with the time between primitive streak formation and birth and also neonatal size. They represent distinct levels of development, with external features, musculoskeletal elements, and internal organs (e.g., lungs, digestive

TABLE 12.2 Major characteristics of grades 1, 2, and 3 in marsupial neonates

	Grade 1	Grade 2	Grade 3
Examples	Dasyuridae <i>Tarsipes</i> (?)	Peramelids Didelphids <i>Trichosurus</i>	<i>Macropus</i> species
Neonatal weight	3–20 mg	100–300 mg	300–900 mg
Eye	No retinal pigmentation, no visible eye primordial or lids	Pigmentation, visible primordial	Prominent primordial, pigmented ring
Manus	Metacarpals just differentiating	Intermediate	Phalanges and metacarpals separated by joint capsules
Hind limb primordial	Undifferentiated paddle	Some digit differentiation	Early digital separation
Lung	Few partitions, superficial capillaries	Intermediate	Enlarged lung, highly subdivided, rich vascularization
Tongue muscles	Multinucleate tubes; immature striations	Striations	Mature striations
Metanephric kidney	Ureteric bud	Primitive ureter, secondary branching	Terminal branching, collecting ducts

Sources: Characters from Hughes and Hall (1988); body weight from Tyndale Biscoe and Renfree (1987).

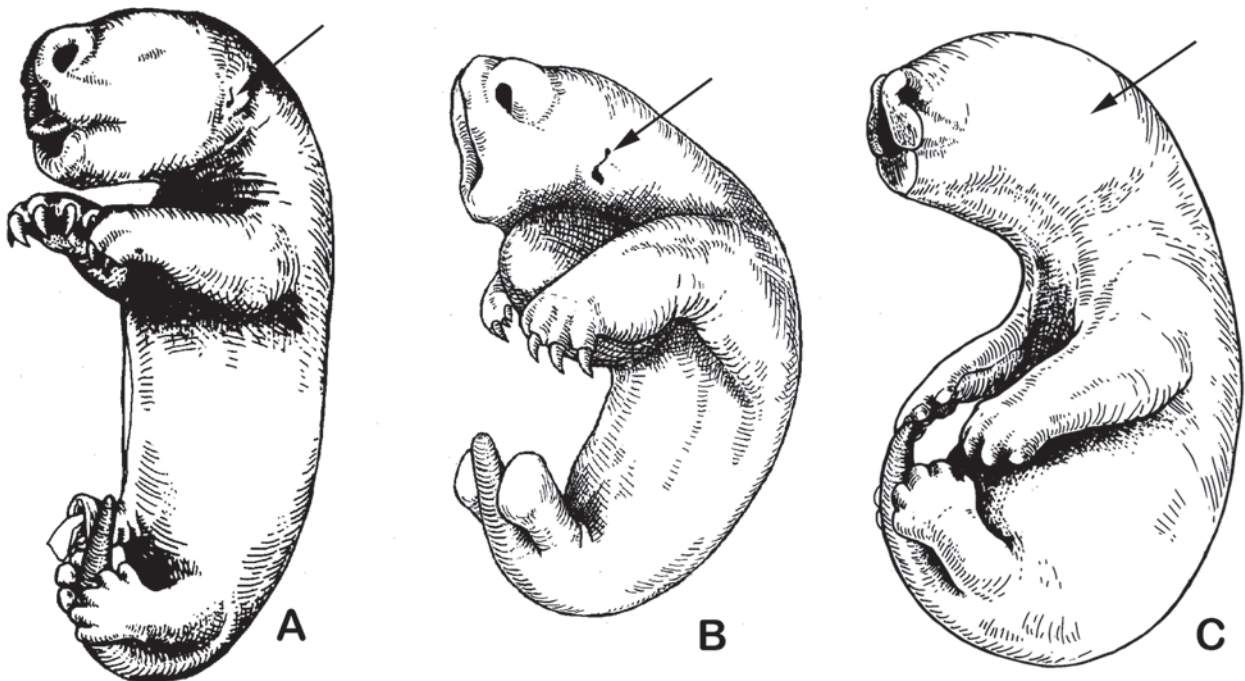


FIG. 12.3 Neonates representing the altricial precocial spectrum in marsupials. A, Precocial marsupial, *Macropus eugenii*; B, ultra-altricial marsupial neonate, *Dasyurus viverrinus*; C, “intermediate” marsupial, *Monodelphis domestica*. These are not drawn to scale, but illustrate the relative differentiation of cranial and limb structures at birth in each taxon. The arrows represent the ear opening; note the lack of features between the ear and the nasal opening in the dasyurid. Also note the extreme difference in development of the fore- and hind limb in the ultra-altricial dasyurid.

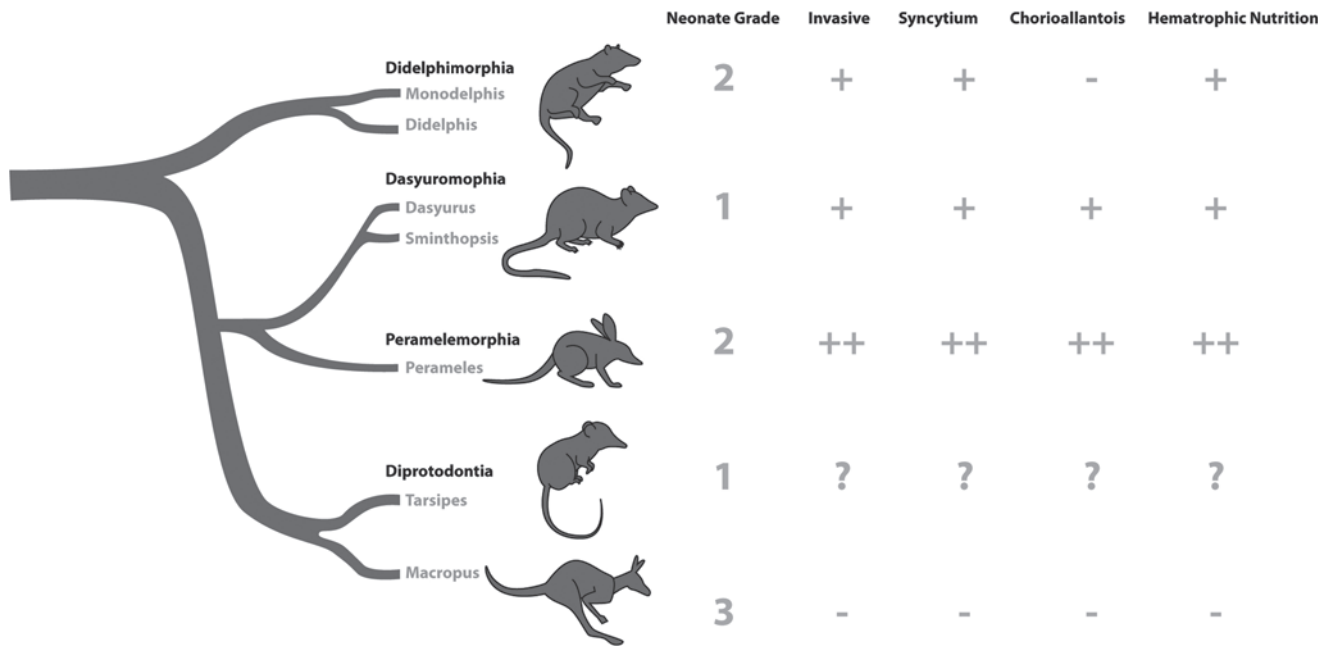


FIG. 12.4 Major characteristics of marsupial development and placenta form plotted on a phylogeny (redrawn from Nilsson et al. 2010). The cladogram of marsupials is highly reduced, with many clades missing. Neonatal grade represents the altricial precocial spectrum as shown in figure 12.3, with 1 representing the most altricial neonates, and 3 the best developed. The other columns represent invasive placentae (i.e., evidence of an endotheliochorial placenta), the presence of syncytium, the presence (at least transiently) of a chorioallantoic membrane. A plus sign (+) represents a character that is closer to the eutherian condition (with ++ representing much closer), while a dash (-) represents a character that is further from the condition seen in eutherians. The final category represents whether or not evidence exists for hematrophic nutrition, again a condition thought to be primitive for eutherians. This illustration demonstrates that the most precocious neonates develop with placentae least like the primitive eutherian condition.

tract, and UG systems) at differing levels of functionality at birth. At one end of the spectrum are ultra-altricial species such as *Sarcophilus* (the Tasmanian devil) and other dasyurids. These animals often weigh significantly less than 20 mg at birth and are born after an extremely short gestation. Anatomical systems are minimally developed. At the other end are many macropodids, weighing between 300 and 900 mg at birth, with relatively long periods of development and relatively well-developed anatomy and physiology. The intermediate grade is most common and includes peramelids, most phalangers, didelphids, and representatives of many other taxa. These neonates are generally intermediate in developmental time, morphological development, and weight (table 12.2).

These three grades of altriciality do not represent an evolutionary gradation within marsupials. The “intermediate” condition appears to be primitive (fig. 12.4). It is found consistently in the didelphids, the basal group of marsupials, and is also widespread across the marsupials. Both the relatively precocial grade and also the ultra-altricial state are derived. The ultra-altricial

condition appears to have evolved twice as it is seen in dasyurids and also in the honey possum, *Tarsipes rostratus*. This latter species is embedded within the clade that includes the macropodids (Kavanagh et al. 2004). Newborn *T. rostratus* weigh 3–6 mg (about the weight of a single, dry grain of rice), with an unknown, but “very brief” period of active gestation (Renfree et al. 1984). The fact that an extremely short gestation period and an ultra-altricial young is derived within marsupials, more than once, strongly suggests that ultra-altriciality is of evolutionary advantage, the result of selection, and not simply the result of primitive constraints due to an inefficient placenta.

Placentation in Marsupials

Although elements of the anatomy of the placenta in marsupials have been studied since Hill in the early 1900s, recent work has added considerably to our understanding and allows a deeper and more comprehensive view of placental evolution in marsupials. This

work has shown that in marsupials although the placenta is functional for a relatively brief time, it shows a wide range of variation in morphology and function and is well developed in many species.

A **choriovitelline** or yolk sac placenta is present at least as a transitory structure in both marsupials and eutherians (Freyer and Renfree 2009). In most marsupials the choriovitelline placenta forms the functional placenta throughout gestation. In bandicoots, dasyurids, and wombats a **chorioallantois** is also present at least transitionally (Freyer et al. 2003; Freyer and Renfree 2009; Hughes 1974; Tyndale-Biscoe and Renfree 1987). The broad phylogenetic distribution of a chorioallantois as well as its importance in monotremes and viviparous squamates has led Freyer et al. (2003) to speculate that a chorioallantoic contribution to the placenta may have been primitively present in marsupials and subsequently lost in many.

In many marsupials the placenta is **epitheliochorial** as there is no loss of tissue layers between the chorion and the maternal circulation. However, in many marsupials there is erosion of the epithelium of the uterus by the fetal tissues, to produce at least a partial **endotheliochorial** placenta. Hill (1900) first described the invasive placenta of dasyurids (see also Hughes 1974 and Roberts and Breed 1994). In *Dasyurus viverrinus* placental cell processes grow to enclose the capillaries underlying the maternal epithelium. Fetal tissue is fused into a **syncytium**, and maternal blood is in close approximation to the yolk sac and chorion. The same condition of eroded maternal epithelium by placental tissues is also seen in the dasyurid, *Sminthopsis crassicaudata* (Hughes 1974; Roberts and Breed 1994). In *Monodelphis* the choriovitelline placenta is also invasive (Zeller and Freyer 2001); it penetrates the maternal epithelium at regular intervals, leading to close association of fetal tissues and maternal capillaries. In *Monodelphis* as in dasyurids, syncytia form in fetal tissues. Recent studies (i.e., McGowen et al. 2013) have shown that the placenta in marsupials such as *Monodelphis* expresses a wide range of genes and that it is metabolically active with many adaptations for the transfer of nutrients between maternal and fetal tissues.

Perameles has the most invasive placenta of any marsupial with a highly vascularized invasive **chorioallantoic** membrane. This **endotheliochorial chorioallantoic** placenta forms the functional placenta through to the final stages of gestation (Freyer et al.

2003; Hughes 1974; Padykula and Taylor 1976, 1982). As in some other taxa a syncytium forms, but, in *Perameles* the syncytium results from a fusion of maternal and fetal cells. This forms a single tissue layer, which provides intimate contact between fetal cells and maternal circulation.

In contrast to the above species, *Macropus eugenii* and other macropodids lack most of these adaptations for close maternal-fetal interaction (Freyer et al. 2007). The placenta is solely formed from a bilaminar choriovitelline membrane, is not invasive, and does not form syncytia.

Histotrophic versus Hematrophic Nutrition

In monotremes the egg receives **histotrophic** nutrition before being laid, and it is often assumed that histotrophic nutrition is primitive in therians. Indeed, Lillegraven (1969) asserted that with the possible exception of *Perameles*, marsupials were limited to histotrophic nutrition while in utero. It appears that initially there is significant histotrophic nutrition in all marsupial taxa. However, in *Monodelphis*, for example, histotrophic secretions are replaced by **hematrophic** nutrition as the trilaminar choriovitelline membrane invades the uterine lining and establishes close association between fetal tissues and maternal circulation (Zeller and Freyer 2001). It is likely that all marsupials with invasive, vascularized placentae such as peramelids, dasyurids, and some didelphids utilize significant hematrophic nutrition. In contrast in *M. eugenii* and other macropodids, hematrophic nutrition never develops, but instead, *M. eugenii* develops extensive and enhanced adaptations for increased histotrophic nutrition (Freyer et al. 2007). These include well-developed uterine glands for secretion and high levels of nutrients in the fluids of the uterus.

The phylogenetic distribution of these traits allows us to trace evolutionary patterns in marsupials and arrive at tentative conclusions about potential constraints. First, both chorioallantoic and invasive (endotheliochorial) placentae appear broadly in marsupials. This type of placenta has been thought to be characteristic of, and indeed limited to, eutherians, but it is possible that both a functional chorioallantois and an endotheliochorial placenta are primitive in marsupials (Freyer et al. 2003). Second, peramelids are uniformly recognized as

having the most “advanced” or eutherian-like placentae. However, they do not use their advanced placentae to produce precocial young, but instead the invasive placenta allows them to reproduce particularly fast. As pointed out by Russell (1982) the rapidity of reproduction in bandicoots is remarkable. Their gestation length is short (12–13 days); weaning time is early (50–60 days), and the delay between weaning and the birth of the next litter inconsequential (peramelids mate while lactating and give birth immediately after a litter is weaned). The possession of highly invasive placentae does not correlate with the supposed advantageous long gestation or precocial young but instead rapid reproduction. Third, invasive, syncytial placentae are also seen in dasyurids, whose young are ultra-altricial, again arguing against a relation between precociality and placenta type.

Finally, the most precocial marsupial young are produced by the placentae that least resembles the “eutherian condition” as envisioned by Lillegraven. Macropodids produce relatively large, relatively precocial, single young. The placenta is bilaminar, noninvasive, and does not form syncytia. Importantly, hematrophic nutrition never develops, and a sophisticated method of nutrient delivery via histotrophic means is present (Freyer et al. 2007). In addition, macropodids also appear to have the most advanced level of hormonal interplay between the placenta and the mother so that the “feto-placental unit is capable as in all eutherian mammals of redirecting maternal physiology” (Renfree 2010; see also Renfree 2000).

These patterns of placental function provide very little to support the view that there is an overriding or basic constraint on marsupial placental function. Marsupials exhibit a wide range of placental adaptations that appear related to variation in reproduction patterns that match complex life history requirements (Fisher et al. 2001). There is no correlation between neonate grade and any particular characteristic of placental function. Further, marsupials are clearly capable of developing sophisticated maternal-fetal contact via placental structure, significant histotrophic and/or hematrophic nutrition, and significant hormonal interplay between the fetus, placenta, and mother (reviewed in Bradshaw and Bradshaw 2011; Renfree 2010; Tyndale-Biscoe and Renfree 1987). All evidence points to a strategy of maternal-fetal interaction under selection rather than limited by fundamental constraints.

One more point often thought to be unique to eutherians is the immune protection of the fetus. Lillegraven (1975, 713) proposed that “the major barrier between the fetal antigens and maternal antibodies is an anatomical one, consisting of the placental trophoblast and its noncellular components.” Recent work suggests that such protection is not a unique feature of the trophoblast, but involves wide-scale modulation of the immune system and maternal physiology. It is impossible to directly test whether marsupials have the evolutionary capacity to develop mechanisms for immunological protection. Attempts to induce an immune reaction by multiple mating of a female to the same male produce no heightened immunological response, suggesting immune protection is not a current constraint (e.g., Rodger et al. 1985; Walker and Tyndale-Biscoe 1978).

There is some question about whether animals with epitheliochorial placentae (as in the majority of marsupials) face a large immunological challenge as contact is limited to an interface between epithelia. Embryos in such cases have been likened to “commensal bacteria in the gut,” provoking little or no immune response (Moffett and Loke 2006). It is a critical issue in mammals with hemochorial placentae; however, even in these cases, recent work demonstrates that such protection is due not only to characteristics of the trophoblast (chorion) but instead complex regulation and modulation of gene expression in the decidua of the uterus, the maternal immune system as well as placental tissues (e.g., Arck et al. 2007; Kumpel and Manoussaka 2012; Moffett and Loke 2004, 2006; Mor and Cardenas 2010; Nancy et al. 2012; Yoshinaga 2012). This multisystem response makes it unlikely that the eutherian chorion is an invention that is responsible for immune protection during gestation.

Placenta Evolution in Eutherians

The placenta in eutherian mammals is well developed and also highly variable (table 12.1). For many years it was thought that the epitheliochorial condition was primitive and that the more intimate connections of the endotheliochorial and hemochorial were derived in eutherians (reviewed in Luckett 1993). There were a number of reasons this hypothesis was appealing. It was thought that marsupials were limited to

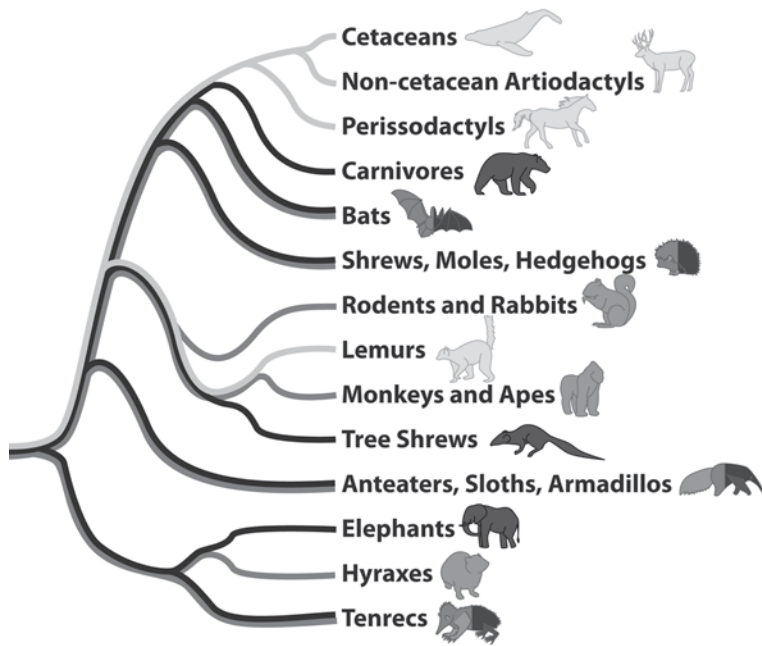


FIG. 12.5 Placental variation in the Eutheria. Light gray represents taxa with epitheliochorial placentae; medium gray, taxa with hemochorial placentae; and dark gray, taxa with endotheliochorial placentae. Taxa with two colors represent clades with significant variation within the clade. Far more variation exists than is represented here. For example, within the rodents there are taxa with endotheliochorial placentae (Heteromyidae); individual taxa with epitheliochorial placentae are found in the shrews and the clade Afrotheria; hyenas, within the carnivores, have hemochorial placentae, etc. The colors represent character states of terminal taxa; no attempt has been made to represent ancestral character states. Compiled from the more complete representations of several sources (Elliot and Crespi 2009; Mess and Carter 2007; Vogel 2005; Wildman et al. 2006).

epitheliochorial placentae and thus this type characterized the outgroup to eutherians. Further, the evolutionary transition from less elaborate maternal-fetal contact to more elaborate and intimate interchange appeared to be parsimonious as a functional scenario. Finally, and perhaps not incidentally, humans and other anthropoid primates exhibit an intimate hemochorial placenta; the condition in humans was assumed to be the advanced and not the primitive condition. Recently our understanding of the evolution of the placenta in eutherians has been reversed, largely because of new understanding of mammalian phylogeny. When modern phylogenies have been used to reconstruct patterns of placenta evolution, the most parsimonious reconstruction places the epitheliochorial (least invasive) condition as derived (fig. 12.5). Some models have reconstructed the hemochorial condition as primitive while others cannot resolve whether the hemochorial or endotheliochorial placenta is primitive (e.g., Elliot and Crespi 2009; Martin 2008; Mess and Carter 2007; Vogel 2005; Wildman et al. 2006).³ Thus, it seems almost certain that invasive placentae are primitive in eutherians, and the less invasive epitheliochorial condition is derived.

3. There is tremendous homoplasy in all characters of the placenta, and it is likely that the simple categories of epitheliochorial, endotheliochorial, and hemochorial are not adequate to fully describe character state evolution. For example, Enders and Carter (2012a, 2012b) present multiple examples of clear homoplasy and possible independent evolu-

Character state reconstructions of other aspects of placental morphology including the shape and nature of contact between maternal and fetal tissues also have reached the conclusion that more intimate maternal-fetal contact is primitive in eutherians and the derived condition represents evolution away from intimate contact. Most phylogenies reconstruct the **labyrinthine**, **discoid** placenta (see table 12.1) as primitive (e.g., Capellini 2012; Elliot and Crespi 2009; Wildman et al. 2006).

This somewhat unexpected result has stimulated a number of studies on the evolutionary and functional significance of differing placental morphologies. Lewitus and Soligo (2011) find two predominant “constellations” of placental morphology and life history characteristics in eutherians (table 12.3). Hemochorial, labyrinthine placentae are most often found in eutherians with small, altricial young, born after short gestations. These animals tend to have large litters, short times to weaning, and high reproductive turnover. In contrast, epitheliochorial (noninvasive), villous, or trabecular (less interdigitated) placentae are most often found in animals with long life spans, large precocial young, and long periods of gestation and lactation.

tion in both endotheliochorial and hemochorial placentae. Further, many taxa exhibit more than one condition through the course of pregnancy, so that the primitive condition for that taxon is difficult to reconstruct. Therefore it is likely that placenta evolution is more complex than appears in most phylogenetic reconstructions.

TABLE 12.3 Examples of the constellations of characters of placental morphology and life history traits in eutherian mammals identified by Lewitus and Soligo (2011)

	Type I	Type II
Placenta	Epitheliochorial	Hemochorial
	Villous to trabecular	Labyrinthine
	Diffuse	Discoid
Life history	Long lifespan	Short lifespan
	Precocial young	Altricial young
	Small litter	Large litter
	Long gestation	Short gestation
	Large neonate	Small neonate
	Late weaning and maturity	Early weaning and maturity
	High interbirth interval	Low interbirth interval

Capellini et al. (2011), who studied all therians including marsupials, reached a similar conclusion. They found that degree of placental invasiveness and interdigitation type correlated with gestation length and fetal growth rates. More interdigitated and more invasive placentae were associated with shorter gestation times, holding fetal brain and body mass constant. They found no correlation with placental type and either neonatal size or maternal size. Capellini et al. (2011) confirmed Elliot and Crespi's (2008) result that there is a positive relation between more invasive placentae and neonatal brain size; however, they state that this relation is "minimal." They concluded that the form of interdigitation was the critical factor in determining gestation time and not invasiveness as hemochorial and endotheliochorial placentae were similar (see also Capellini 2012). Several overall conclusions are important. Fast gestation is highly correlated with invasive placentae, and particularly placentae with a highly interdigitated interface between maternal and fetal tissues. Further, the production of large, fast developing litters, generally associated with altriciality is highly associated with labyrinthine (highly interdigitated) placentae.

Epitheliochorial placentae, with less interdigitation and less intimate contact between maternal and fetal placental layers, have independently evolved in several taxa (fig. 12.5). They are most often found in large-bodied species such as cetaceans or perissodactyls with long gestation times and large, precocial young. Such

taxa also appear to depend on increased histotrophic nutrition. This observation has led to the conclusion that less intensive placental types are advantageous in species with large young and long gestations because they protect the mother from excessive energy demands from the fetus (e.g., Capellini 2012; Capellini et al. 2011; Carter and Mess 2007; Klisch and Mess 2007; Wildman et al. 2006). Further, the switch to histotrophic from hematrophic nutrition may allow the female greater control of her reproductive resources, while allowing efficient and prolonged energy transfer between mother and fetus.⁴ There is no evidence that histotrophic nutrition is less efficient than hematrophic nutrition (Vogel 2005).

Thus, in eutherians there is tremendous variation in placental form and function. Further it appears that as in marsupials, in eutherians less invasive placentae are derived and more precocial young rely more on histotrophic nutrition. Highly invasive placentae

4. There are obvious exceptions to this broad overview. In particular the pattern seen in primates challenges this simple model. Hemochorial, highly invasive placentae are found in the anthropoid primates; the condition in the hominoids, and in particular humans, is among the most intimate of maternal-fetal interactions seen in mammals. On the other hand, the lemuriformes are the only major group of mammals outside the perissodactyl/cetartiodactyl clade to have epitheliochorial placentae. They do not appear to fit the general correlation of large highly precocial young. It has been proposed that the possession of hemochorial placentae in anthropoids is related to large neonatal brain size (Martin 1996, 2008), which requires high rates of nutrient transfer during gestation.

are generally correlated with the most altricial young and in particular animals with the fastest reproductive turnover. Why have we seen an evolution away from the highly invasive placentation types?

The Dark Side of the Placenta

In addition to new insight arising from our changing view of eutherian phylogeny and therefore the evolution of the placenta, our view of placental function has changed in the last 20 or so years with the development of new theories regarding maternal-fetal conflict and genomic imprinting.

These issues were first put forth clearly in a series of papers by David Haig (e.g., 1993). In short, the theory of maternal-fetal conflict states that a fetus is a hybrid of maternal and paternal genes. In any case where the fetus has direct access to maternal nutrient stores (as in placentation), a potential evolutionary conflict exists because the fetus (which is half paternal genes) and mother do not necessarily share the same long-term reproductive strategy. It is in the evolutionary interest of the fetal genes to consume the maximum maternal resources necessary for its own growth during its own developmental cycle. This is particularly true in cases where the mother mates with more than one male (in a breeding or over a lifetime). In contrast, it is in the evolutionary interest of the mother to allocate her energetic investment across the sum of all reproductive efforts to increase her lifetime fitness. This is particularly important in animals that produce multiple litters. This conflict of interest may be easily controlled by the mother in cases where she directly provisions the young through active feeding, or lactation (as long as she can control access to milk). However, when the placenta—whose tissues are largely produced by the embryo—is responsible for the nutritional interchange, the mother's ability to control her resources may be reduced.

Haig's hypothesis took the maternal-fetal conflict theory a step further when he proposed that it was an evolutionary explanation for the then newly discovered phenomenon of genomic imprinting (e.g., Haig 1996, 1998, 2000, 2004). Genomic imprinting was discovered about 25 years ago, and arose from the discovery that for some genes only one copy is expressed in the fetus. Depending on the gene, either the copy inherited from

the mother or father is expressed. Two observations bolster the hypothesis that gene imprinting is related to maternal-fetal conflict. First, it has only been seen in clades in which the embryo has access to maternal resources during development: some insects, angiosperms, and therian mammals. It has been documented in both marsupials and eutherians but not in monotremes or any other vertebrate (e.g., Renfree et al. 2012).

The second feature is that the specific genes exhibiting imprinting are often found in the placenta or are important in fetal growth (e.g., Coan et al. 2005; Cross et al. 2003; Ferguson-Smith 2011; Ferguson-Smith et al. 2006; Fowden et al. 2006; Frost and Moore 2010; Gootwine 2004; Haig 1996, 2008; Hemberger 2007; Jirtle and Weidman 2007; Reik et al. 2003; Renfree et al. 2008, 2009; Wang et al. 2013). Frequently when the paternal copy is the one that is expressed, fetal or placental growth is enhanced. The “canonical” example (e.g., Frost and Moore 2010) is the well-known *Igf2* (insulin growth factor) system. *Igf2* is a potent enhancer of fetal growth, and disruptions in its function have been shown to disrupt normal growth in fetal mice. In humans and mice (as well as many other mammals) the paternal copy of the *Igf2* gene is expressed, and fetal growth is enhanced substantially with higher levels of this product. The “tug of war” is made more complex in mice because the maternal copy of another gene is expressed, which functions to reduce the bioavailability of this protein. In humans there may be a parallel negative regulation of *Igf2*, but it is not as well characterized. *Igf2* has also been shown to be imprinted in marsupials as well as the other eutherians in which it has been studied (Ager et al. 2007; Killian et al. 2000).

We are still far from a complete understanding of the extent, function, and significance of imprinting for the vast majority of genes. The relation of imprinted genes to maternal-fetal conflict is still somewhat controversial (e.g., Ashbrook and Hager 2013; Moore 2012), and not all imprinted genes discovered so far fit easily into the model of maternal-fetal conflict. For example, Keverne (2013) portrays some imprinted genes as being involved in a complex process of coadaptation between the mother and fetus. But both theoretical and empirical work suggests that in animals with close maternal-fetal exchange, genetic conflict should, and in fact does, exist. Many workers believe that both the tremendous variability in placental type seen in eutherians and the

overall evolutionary trend toward reduced intimacy of interaction in many mammals is in part maternal responses to this conflict (e.g., Capellini et al. 2011; Elliot and Crespi 2009; Enders and Carter 2012a; Garratt et al. 2013; Vogel 2005; Wildman et al. 2006).

These hypotheses and data then allow us to examine the evolution of reproductive strategies of therian mammals in a new light. Previous workers (Hayssen et al. 1985; Kirsch 1977a, 1977b; Low 1978; Parker 1977; Tyndale-Biscoe and Renfree 1987) emphasized that the advantage of the marsupial strategy is that it allows the female more control of her reproductive efforts. This hypothesis was largely couched in the context of ecology and overall energetics. Specifically it was argued that in the face of highly unpredictable resources the marsupial reproductive strategy would be strongly advantageous because a female could adjust her litter size or terminate her investment more easily during lactation than during internal gestation. The evolutionary significance of this hypothesis was criticized (e.g., Morton et al. 1982; Lee and Cockburn 1985), but there has been no real refutation of the statement that a female marsupial does retain greater control of litter size and her ability to allocate resources during a reproductive bout than do eutherians. The emergence of the maternal-fetal conflict theory in the past 20 years suggests that the control of resources by the mother during gestation is a general issue in therians and not dependent on specific reproductive conditions. The maternal-fetal battle is a potential cost of prolonged active, intrauterine gestation, which may have had significant impact on the evolution of both marsupial and eutherian reproductive strategy.

Discussion and Summary

I started this review by revisiting the debate on the marsupial-placental dichotomy of the 1970s. However, our understanding of many aspects of mammalian reproduction has changed since that time. Marsupials were characterized as having minimal development of the placenta and, with the possible exception of peramelids, were thought to be largely dependent on histotrophic nutrition. Histotrophic nutrition was thought to be a primitive means of nourishing the young and generally less efficient. Marsupials were assumed to produce uniformly highly altricial young and, because of limitations arising from the lack of a trophoblast, to be

unable to increase the complexity, length, or intensity of the maternal-fetal interface. Eutherians, on the other hand, were seen as initially having effective epithelio-chorial and endotheliochorial placentae and eventually evolving an intense hemochorial placentation, which provided efficient nutrition for rapid development of precocial, large-brained young. It was thought that eutherians were able to protect the fetus from allograft rejection and also to establish hormonal communication from the placenta to the mother while marsupials could not.

Many years of work by a large number of workers have turned this simple model on its head. In both marsupials and eutherians the structure and function of the placenta is complex and variable. In both, variation is influenced by life history strategy (as the rate of reproduction and relative altriciality of the neonate is determined by ecological and evolutionary contexts in both groups). There is little evidence that marsupials are fundamentally constrained in their placental structure and function.

Instead as emphasized by many, it appears that short intrauterine gestation is a specific evolutionary strategy that has been paired with exceptional adaptations for lactation. Likewise, in eutherians, although there is a much more intense intrauterine interaction, a great deal of the variation in placental form and function is also best interpreted in the light of the need for maternal control of her reproductive resources and reduction of direct fetal access to maternal circulatory supply. In many eutherians there has been evolution away from a strategy that emphasizes a highly intensive maternal-fetal interface and returns control of resources to the mother (e.g., Klisch and Mess 2007). In short, this new perspective allows new appreciation for the issues surrounding maternal control of reproductive resources in all therians, and lends support to hypotheses that it may be of fundamental importance in the evolutionary choices made by marsupials.

The degree of difference in the two strategies should not be minimized. They do not represent a continuum but are quite distinct strategies. Some of the best evidence for the distinctness of the strategies comes from the study of early development, where it can be clearly shown that marsupial development is modified from the earliest stages of differentiation to meet the needs of the highly altricial young (e.g., Keyte and Smith 2010,

2012; Smith 1997, 2001, 2006; Vaglia and Smith 2003). These studies further show that the marsupial neonate is not just embryonic at birth, but exhibits a very elaborate complex of adaptations that allows it to survive after an exceedingly short gestation. The adaptations of the marsupial neonate are derived, and unlike that seen in any other amniote, including monotremes (Smith 1997, 2001; Weisbecker 2011).

It is undeniable that the placenta in eutherians consistently develops far beyond any stage seen in marsupials. Internal gestation is prolonged, and we see many unique adaptations of the uterus, decidua, and hormonal and immune system (e.g., Carter 2012). As just one example, Lynch et al. (2008) have demonstrated that the regulatory gene *HoxA-11* has taken on a unique role in eutherian mammals as a regulator of prolactin expression in the uterus in eutherians. One function of this prolactin expression is the silencing of expression of several genes involved in the inflammatory response. This suppression of the inflammatory response in eutherians is hypothesized to help maintain pregnancy. Prolactin is not expressed in the uterus of *Monodelphis*, and presumably other marsupials. On the other hand, just as it is clear eutherians have developed a number of adaptations that allow prolonged intrauterine gestation, marsupials exhibit adaptations for lactation not seen in eutherians, as has long been argued by Renfree (1983, 2010). For example, recent comparative genomic studies demonstrate more milk-specific proteins in the milk of marsupials than either monotremes or eutherians. Further, these studies reveal complex changes over time in the expression of specific milk proteins uniquely in marsupials, to meet the changing nutritional needs of the young through the very long gestation (Lefèvre et al. 2010).

There is little data to support the hypothesis that reproductive strategies in marsupials are simply the retention of a primitive pattern. But, if the differences we observe do not grow out of constraints, why do we see such differences in the two taxa? Ultimately, the question of why a clade does or does not take a certain evolutionary path is virtually impossible to answer, especially when dealing with a single case or comparison and with events long in the past that leave little or no trace in the fossil record.

One of the most important points summarized in this paper is that internal gestation via a placenta places significant potential costs on a mother. Evolutionary

theory predicts that selection should favor those embryos that develop greater capacity to extract disproportional resources from the mother for the current pregnancy even at the cost of her lifetime fitness (Haig 2000). Early mammals were small, homeothermic, and nocturnal and likely to be under considerable energetic stresses. Viviparity evolved in this context, and it is likely that it placed significant additional energetic stresses on the mother in early marsupials and eutherians. But it appears that the response to these energetic stresses led to two different paths. In marsupials control of reproduction was strongly biased toward the mother. Gestation was kept short, and intense maternal-fetal intrauterine contact limited. Reproductive effort was largely devoted to lactation, during which the mother maintained greater control of duration of a given reproductive effort and the number of young raised to weaning. In addition this mode extended maternal energetic output over a longer time period lessening the energy demands at any given time. While this basic point has been made by Renfree, Parker, Low, and Hayssen, it is generally in the context of highly fluctuating resources such as those faced by many extant Australian marsupials. Here I argue that internal gestation via a placenta in and of itself may be a significant energy constraint. Supporting the idea that marsupials evolved away from intense maternal-fetal contact is the evidence that more intense maternal-fetal contact was primitive in marsupials. Additionally, it is clear that ultra-altriciality is a derived state in the group, and not a primitive condition for marsupials, again suggesting selection away from maternal investment in utero in some taxa.

In eutherians, if current reconstructions are correct, a very intense form of maternal-fetal contact—hemochorial, labyrinthine placentae—evolved early. Today we see such placentae for the most part in animals with very fast reproductive turnover: rapid production of large litters with short gestations. Although these young are often altricial by eutherian standards, they are relatively well developed, and can have a very rapid time to weaning. Subsequently, within eutherians we see evolution away from this intense form of placentation, in particular as mammals entered environments in which it was necessary for the young to be precocial, and highly independent at birth.

These scenarios leave the question of “why” unanswered. Did early marsupials and placentals face slightly

different ecological conditions so that rapid turnover was favored in eutherians, and longer, less intense investment favored in marsupials? Did chance events early in the evolution of the lineages lead to different paths? Were there particular adaptations toward improved lactation early in the marsupial line, or did particular innovations appear in early eutherians for internal gestation? Understanding of the full complexity of the patterns of form and function, of phylogeny and variation allows us to ask, and perhaps someday answer, questions of intricacy beyond a simple hypothesis of constraint.

Finally, the evolutionary consequences of the “marsupial-placental dichotomy” in reproductive choice continue to puzzle biologists. Eutherians are more diverse phylogenetically and evolutionarily, having produced radiations in the air and the sea never utilized by marsupials. It has tempted biologists for many years to attribute this difference in evolutionary diversity to the differences in reproductive strategy. However, as

pointed out recently by Sánchez-Villagra (2013), the factors determining the evolution of major lineages are complex, and include many aspects of ecology, geology, biogeography, and perhaps chance. It might be argued, for example, that “eutherian” diversity is really nested within the Boreoeutheria (Asher et al. 2009), and that all other mammalian clades, eutherian and marsupial, are far less diverse taxonomically and morphologically. It is interesting that these other clades (Afrotheria, Xenarthra, Marsupialia, as well as early radiations of South American mammals) all evolved on smaller southern continents rather than the large Laurasian mass, which gave rise to the bulk of eutherian diversity. The fact remains that after long years of study we still have not resolved many of the most interesting issues concerning evolutionary patterns in therian mammals. The origin and early diversification of the Mammalia remains one of the great stories of transformations in vertebrate evolution, ripe for future study.

* * *

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References

- Ager, E., S. Suzuki, A. Pask, G. Shaw, F. Ishino, and M. B. Renfree. 2007. Insulin is imprinted in the placenta of the marsupial, *Macropus eugenii*. *Developmental Biology* 309:317–328.
- Arck, P., P. J. Hansen, B. M. Jericevic, M. P. Piccinni, and J. Szekeres-Bartho. 2007. Progesterone during pregnancy: endocrine-immune cross talk in mammalian species and the role of stress. *American Journal of Reproductive Immunology* 58:268–279.
- Ashbrook, D. G., and R. Hager. 2013. Empirical testing of hypotheses about the evolution of genomic imprinting in mammals. *Frontiers in Neuroanatomy* 7:1–6.
- Asher, R. J., N. Bennett, and T. Lehmann. 2009. The new framework for understanding placental mammal evolution. *BioEssays* 31:853–864.
- Asher, R. J., and K. M. Helgen. 2010. Nomenclature and placental mammal phylogeny. *BMC Evolutionary Biology* 10:1–9.
- Bennett, C. V., and A. Goswami. 2011. Does developmental strategy drive limb integration in marsupials and monotremes? *Mammalian Biology* 76:79–83.
- Blackburn, D. G. 2006. Squamate reptiles as model organisms for the evolution of viviparity. *Herpetological Monographs* 20:131–146.
- Blackburn, D. G., and A. F. Flemming. 2009. Morphology, development, and evolution of fetal membranes and placentation in squamate reptiles. *Journal of Experimental Zoology Part B—Molecular and Developmental Evolution* 312B:579–589.
- Blaise, S., N. de Parseval, L. Benit, and T. Heidmann. 2003. Genome wide screening for fusogenic human endogenous retrovirus envelopes identifies syncytin 2, a gene conserved on primate evolution. *Proceedings of the National Academy of Sciences USA* 100:13013–13018.
- Bradshaw, F. J., and D. Bradshaw. 2011. Progesterone and reproduction in marsupials: a review. *General and Comparative Endocrinology* 170:18–40.
- Brandley, M. C., R. L. Young, D. L. Warren, M. B. Thompson, and G. P. Wagner. 2012. Uterine gene expression in the

- live-bearing lizard, *Chalcides ocellatus*, reveals convergence of squamate reptile and mammalian pregnancy mechanisms. *Genome Biology and Evolution* 4:394–411.
- Capellini, I. 2012. The evolutionary significance of placental interdigitation in mammalian reproduction: contributions from comparative studies. *Placenta* 33:763–768.
- Capellini, I., C. Venditti, and R. A. Barton. 2011. Placentation and maternal investment in mammals. *American Naturalist* 177:86–98.
- Carter, A. M. 2001. Evolution of the placenta and fetal membranes seen in the light of molecular phylogenetics. *Placenta* 22:800–807.
- Carter, A. M. 2012. Evolution of placental function in mammals: the molecular basis of gas and nutrient transfer, hormone secretion and immune responses. *Physiological Reviews* 92:1543–1576.
- Carter, A. M., A. C. Enders, H. Kunzle, D. Oduor-Okelo, and P. Vogel. 2004. Placentation in species of phylogenetic importance: the Afrotheria. *Animal Reproduction Science* 82–83:35–48.
- Carter, A. M., and A. Mess. 2007. Evolution of the placenta in eutherian mammals. *Placenta* 28:259–262.
- Carter, A. M., and A. Mess. 2008. Evolution of the placenta and associated reproductive characters in bats. *Journal of Experimental Zoology Part B—Molecular and Developmental Evolution* 310B:428–449.
- Chuong, E. B. 2013. Retroviruses facilitate the rapid evolution of the mammalian placenta. *BioEssays* 35:853–861.
- Coan, P. M., G. J. Burton, and A. C. Ferguson-Smith. 2005. Imprinted genes in the placenta—a review. *Placenta* 26:S10–S20.
- Cooper, W. J., and S. J. Steppan. 2010. Developmental constraint on the evolution of marsupial forelimb morphology. *Australian Journal of Zoology* 58:1–15.
- Cornelis, G., O. Heidmann, S. Bernard-Stoecklin, K. Reynaud, G. Veron, B. Mulot, A. Dupressoir, and T. Heidmann. 2012. Ancestral capture of syncytin-Car1, a fusogenic endogenous retroviral envelope gene involved in placentation and conserved in Carnivora. *Proceedings of the National Academy of Sciences USA* 109:E432–E441.
- Crompton, A. W. 1980. Biology of the earliest mammals. Pp. 1–12 in K. Schmidt-Nielsen, L. Bolis, and C. R. Taylor, eds., *Comparative Physiology: Primitive Mammals*. Cambridge: Cambridge University Press.
- Crompton, A. W., and F. A. Jenkins. 1973. Mammals from reptiles: a review of mammalian origins. *Annual Review of Earth and Planetary Sciences* 1:131–153.
- Crompton, A. W., C. R. Taylor, and J. A. Jagger. 1978. Evolution of homeothermy in mammals. *Nature* 272:333–337.
- Cross, J. C., D. Baczyk, N. Dobric, M. Hemberger, M. Hughes, D. G. Simmons, H. Yamamoto, and J. C. P. Kingdom. 2003. Genes, development and evolution of the placenta. *Placenta* 24:123–130.
- Elliot, M. G., and B. J. Crespi. 2008. Placental invasiveness and brain-body allometry in eutherian mammals. *Journal of Evolutionary Biology* 21:1763–1778.
- Elliot, M. G., and B. J. Crespi. 2009. Phylogenetic evidence for early hemochorial placentation in Eutheria. *Placenta* 30:949–967.
- Enders, A. C., and A. M. Carter. 2004. What can comparative studies of placental structure tell us? a review. *Placenta* 25:S3–S9.
- Enders, A. C., and A. M. Carter. 2012a. The evolving placenta: convergent evolution of variations in the endotheliochorial relationship. *Placenta* 33:319–326.
- Enders, A. C., and A. M. Carter. 2012b. Review: the evolving placenta; different developmental paths to a hemochorial relationship. *Placenta* 33:S92–S98.
- Farmer, C. G. 2000. Parental care: the key to understanding endothermy and other convergent features in birds and mammals. *American Naturalist* 155:326–334.
- Ferguson-Smith, A. C. 2011. Genomic imprinting: the emergence of an epigenetic paradigm. *Nature Reviews Genetics* 12:565–575.
- Ferguson-Smith, A. C., T. Moore, J. Detmar, A. Lewis, M. Hemberger, H. Jammes, G. Kelsey, C. T. Roberts, H. Jones, and M. Constancia. 2006. Epigenetics and imprinting of the trophoblast—a workshop report. *Placenta* 27:S122–S126.
- Ferner, K., and A. Mess. 2011. Evolution and development of fetal membranes and placentation in amniote vertebrates. *Respiratory Physiology and Neurobiology* 178:39–50.
- Fisher, D. O., I. P. F. Owens, and C. N. Johnson. 2001. The ecological basis of life history variation in marsupials. *Ecology* 82:3531–3540.
- Flemming, A. F., and D. G. Blackburn. 2003. Evolution of placental specializations in viviparous African and South American lizards. *Journal of Experimental Zoology Part A—Comparative Experimental Biology* 299A:33–47.
- Fowden, A. L., C. Sibley, W. Reik, and M. Constancia. 2006. Imprinted genes, placental development and fetal growth. *Hormone Research* 65:50–58.
- Freyer, C., and M. B. Renfree. 2009. The mammalian yolk sac placenta. *Journal of Experimental Zoology Part B—Molecular and Developmental Evolution* 312B:545–554.
- Freyer, C., U. Zeller, and M. B. Renfree. 2001. Placentation in marsupials: contribution to the marsupial stem species pattern. *Journal of Morphology* 248:231.
- Freyer, C., U. Zeller, and M. B. Renfree. 2002. Ultrastructure of the placenta of the tammar wallaby, *Macropus eugenii*: comparison with the grey short-tailed opossum, *Monodelphis domestica*. *Journal of Anatomy* 201:101–119.
- Freyer, C., U. Zeller, and M. B. Renfree. 2003. The marsupial placenta: a phylogenetic analysis. *Journal of Experimental Zoology Part A—Comparative Experimental Biology* 299A:59–77.
- Freyer, C., U. Zeller, and M. B. Renfree. 2007. Placental function in two distantly related marsupials. *Placenta* 28:249–257.
- Frost, J. M., and G. E. Moore. 2010. The importance of imprinting in the human placenta. *Plos Genetics* 6.
- Garratt, M., J.-M. Gaillard, R. C. Brooks, and J.-F. Lemaître. 2013. Diversification of the eutherian placenta is associated with changes in the pace of life. *Proceedings of the National Academy of Sciences* 110: 7760–7765.
- Gootwine, E. 2004. Placental hormones and fetal-placental development. *Animal Reproduction Science* 82–83:551–566.
- Goswami, A., P. D. Polly, O. B. Mock, and M. R. Sánchez-Villagra. 2012. Shape, variance and integration during craniogenesis: contrasting marsupial and placental mammals. *Journal of Evolutionary Biology* 25:862–872.
- Goswami, A., V. Weisbecker, and M. R. Sánchez-Villagra. 2009. Developmental modularity and the marsupial-placental dichotomy. *Journal of Experimental Zoology Part B—Molecular and Developmental Evolution* 312B:186–195.

- Guillette, L. J., and N. Hotton. 1986. The evolution of mammalian reproductive characteristics in therapsid reptiles. Pp. 239–262 in N. Hotton, P. D. MacLean, J. J. Roth, and E. C. Roth, eds., *The Ecology and Biology of Mammal-Like Reptiles*. Washington, DC: Smithsonian Institution Press.
- Haig, D. 1993. Genetic conflicts in human pregnancy. *Quarterly Review of Biology* 68:495–532.
- Haig, D. 1996. Placental hormones, genomic imprinting, and maternal-fetal communication. *Journal of Evolutionary Biology* 9:357–380.
- Haig, D. 1998. Genomic imprinting. *American Journal of Human Biology* 10:679–680.
- Haig, D. 2000. The kinship theory of genomic imprinting. *Annual Review of Ecology and Systematics* 31:9–32.
- Haig, D. 2004. Genomic imprinting and kinship: how good is the evidence? *Annual Review of Genetics* 38:553–585.
- Haig, D. 2008. Placental growth hormone-related proteins and prolactin-related proteins. *Placenta* 29:S36–S41.
- Haig, D. 2012. Retroviruses and the placenta. *Current Biology* 22:R609–R613.
- Harris, J. R. 1998. Placental endogenous retrovirus (ERV): structural, functional, and evolutionary significance. *Bioessays* 20:307–316.
- Hayssen, V., R. C. Lacy, and P. J. Parker. 1985. Metatherian reproduction: transitional or transcending? *American Naturalist* 126:617–632.
- Heidmann, O., C. Vernochet, A. Dupressoir, and T. Heidmann. 2009. Identification of an endogenous retroviral envelope gene with fusogenic activity and placenta-specific expression in the rabbit: a new “syncytin” in a third order of mammals. *Retrovirology* 6.
- Hemberger, M. 2007. Epigenetic landscape required for placental development. *Cellular and Molecular Life Sciences* 64:2422–2436.
- Hill, J. P. 1900. On the foetal membranes, placentation and parturition of the native cat (*Dasyurus viverrinus*). *Anatomischer Anzeiger* 18:364–373.
- Hopson, J. A. 1973. Endothermy, small size and the origin of mammalian reproduction. *American Naturalist* 107:446–451.
- Hughes, R. L. 1974. Morphological studies on implantation in marsupials. *Journal of Reproduction and Fertility* 39:173–186.
- Hughes, R. L., and L. S. Hall. 1988. Structural adaptations of the newborn marsupial. In H. Tyndale-Biscoe and P. A. Janssens, eds., *The Developing Marsupial*. New York: Springer-Verlag.
- Jenkins, F. A. 1984. A survey of mammalian origins. Pp. 32–47 in P. D. Gingerich and C. E. Badgley, eds., *Mammals: Notes for a Short Course*. Knoxville: University of Tennessee.
- Jirtle, R. L., and J. R. Weidman. 2007. Imprinted and more equal. *American Scientist* 95:143–149.
- Johnson, M. H. 1996. Origins of pluriblast and trophoblast in the eutherian conceptus. *Reproduction, Fertility and Development* 8:699–709.
- Johnson, M. H., and L. Selwood. 1996. Nomenclature of early development in mammals. *Reproduction, Fertility and Development* 8:759–764.
- Kavanagh, J. R., A. Burk-Herrick, M. Westerman, and M. S. Springer. 2004. Relationships among families of Diprotodontia (Marsupialia) and the phylogenetic position of the Autapomorphic honey possum (*Tarsipes rostratus*). *Journal of Mammalian Evolution* 11:207–222.
- Kelly, E. M., and K. E. Sears. 2011. Limb specialization in living marsupial and eutherian mammals: constraints on mammalian limb evolution. *Journal of Mammalogy* 92:1038–1049.
- Kemp, T. S. 2006. The origin of mammalian endothermy: a paradigm for the evolution of complex biological structure. *Zoological Journal of the Linnean Society* 147:473–488.
- Kemp, T. S. 2007. The origin of higher taxa: macroevolutionary processes, and the case of the mammals. *Acta Zoologica* 88:3–22.
- Keyte, A. L., and K. K. Smith. 2010. Developmental origins of precocial forelimbs in marsupial neonates. *Development* 137:4283–4294.
- Keyte, A. L., and K. K. Smith. 2012. Heterochrony in somitogenesis rate in a model marsupial, *Monodelphis domestica*. *Evolution & Development* 14:93–103.
- Keverne, E. B. 2013. Importance of the matriline for genomic imprinting, brain development and behaviour. *Philosophical Transactions of the Royal Society B* 368:1–10.
- Killian, J. E., J. C. Byrd, V. Jirtle, B. L. Munday, M. K. Stoskopf, and R. L. Jirtle. 2000. M6P/IGF2R imprinting evolution in mammals. *Molecular Cell* 5:707–716.
- Kirsch, J. A. W. 1977a. Biological aspects of the marsupial-placental dichotomy: a reply to Lillegraven. *Evolution* 31:898–900.
- Kirsch, J. A. W. 1977b. The six-percent solution: second thoughts on the adaptedness of the Marsupialia. *American Scientist* 65:276–288.
- Klisch, K., and A. Mess. 2007. Evolutionary differentiation of cetartiodactyl placentae in the light of the viviparity-driven conflict hypothesis. *Placenta* 28:353–360.
- Koteja, P. 2012. Energy assimilation, parental care and the evolution of endothermy. *Proceedings of the Royal Society of London B* 267:479–484.
- Kumpel, B. M., and M. S. Manoussaka. 2012. Placental immunology and maternal alloimmune responses. *Vox Sanguinis* 102:2–12.
- Lee, A. K., and A. Cockburn. 1985. *Evolutionary Ecology of Marsupials*. Cambridge: Cambridge University Press.
- Lefèvre, C. M., J. A. Sharp, and K. R. Nicholas. 2010. Evolution of lactation: ancient origin and extreme adaptations of the lactation system. *Annual Review of Genomics and Human Genetics* 11:219–238.
- Lewitus, E., and C. Soligo. 2011. Life-history correlates of placental structure in eutherian evolution. *Evolutionary Biology* 38:287–305.
- Lillegraven, J. A. 1969. Latest Cretaceous mammals of the upper part of the Edmonton formation of Alberta, Canada, and a review of the Marsupial-placental dichotomy in mammalian evolution. *University of Kansas Paleontological Contributions* 50:1–1222.
- Lillegraven, J. A. 1975. Biological considerations of the marsupial-placental dichotomy. *Evolution* 29:707–722.
- Lillegraven, J. A. 1984. Why was there a “marsupial-placental dichotomy”? Pp. 72–86 in P. D. Gingerich and C. E. Badgley, eds., *Mammals: Notes for a Short Course*. Knoxville: University of Tennessee.
- Lillegraven, J. A. 2004. Polarities in mammalian evolution seen through the homologs of the inner cell mass. *Journal of Mammalian Evolution* 10:277–330.

- Lillegraven, J. A., S. D. Thompson, B. K. McNab, and J. L. Patton. 1987. The origin of eutherian mammals. *Biological Journal of the Linnean Society* 32:281–336.
- Low, B. S. 1978. Environmental uncertainty and the parental strategies of marsupials and placentals. *American Naturalist* 112:197–213.
- Luckett, W. P. 1977. Ontogeny of amniote fetal membranes and their application to phylogeny. Pp. 439–516 in M. K. Hecht, P. C. Goody, and B. M. Hecht, eds., *Major Patterns in Vertebrate Evolution*. New York: Plenum Press.
- Luckett, W. P. 1993. Uses and limitations of mammalian fetal membranes and placenta for phylogenetic reconstruction. *Journal of Experimental Zoology* 266:514–527.
- Luo, Zhe-Xi. 2007. Transformation and diversification in early mammal evolution. *Nature* 450:1011–1019.
- Lynch, V. J., A. Tanzer, Y. J. Wang, F. C. Leung, B. Gellersen, D. Emera, and G. P. Wagner. 2008. Adaptive changes in the transcription factor HoxA-11 are essential for the evolution of pregnancy in mammals. *Proceedings of the National Academy of Sciences USA* 105:14928–14933.
- Martin, R. D. 1996. Scaling of the mammalian brain: the maternal energy hypothesis. *News in Physiological Sciences* 11:149–156.
- Martin, R. D. 2008. Evolution of placentation in primates: implications of mammalian phylogeny. *Evolutionary Biology* 35:125–145.
- McGowen, M. R. 2013. Gene expression in the term placenta of the opossum *Monodelphis domestica* and the evolution of the therian placenta. *Placenta* 34:A24–25.
- McNab, B. K. 1978. Evolution of endothermy in phylogeny of mammals. *American Naturalist* 112:1–21.
- Mess, A., and A. M. Carter. 2006. Evolutionary transformations of fetal membrane characters in Eutheria with special reference to Afrotheria. *Journal of Experimental Zoology Part B—Molecular and Developmental Evolution* 306B:140–163.
- Mess, A., and A. M. Carter. 2007. Evolution of the placenta during the early radiation of placental mammals. *Comparative Biochemistry and Physiology A—Molecular & Integrative Physiology* 148:769–779.
- Mi, S., X. Lee, X. P. Li, G. M. Veldman, H. Finnerty, L. Racie, E. LaVallie, X. Y. Tang, P. Edouard, S. Howes, J. C. Keith, and J. M. McCoy. 2000. Syncytin is a captive retroviral envelope protein involved in human placental morphogenesis. *Nature* 403:785–789.
- Moffett, A., and C. Loke. 2006. Immunology of placentation in eutherian mammals. *Nature Reviews Immunology* 6:584–594.
- Moffett, A., C. Loke, and A. McLaren. 2006. *Biology and Pathology of Trophoblast*. Cambridge: Cambridge University Press.
- Moffett, A., and Y. W. Loke. 2004. The immunological paradox of pregnancy: a reappraisal. *Placenta* 25:1–8.
- Moore, T. 2012. Review: parent-offspring conflict and the control of placental function. *Placenta* 33:S33–S36.
- Mor, G., and I. Cardenas. 2010. The immune system in pregnancy: a unique complexity. *American Journal of Reproductive Immunology* 63:425–433.
- Morton, S. R., H. F. Recher, S. D. Thompson, and R. W. Braithwaite. 1982. Comments on the relative advantages of marsupial and eutherian reproduction. *American Naturalist* 120:128–134.
- Mossman, H. W. 1937. Comparative morphogenesis of the fetal membranes and accessory uterine structures. *Carnegie Institute Contributions to Embryology* 26:129–246.
- Nancy, P., E. Tagliani, C.-S. Tay, P. Asp, D. Levy, and A. Erlebacher. 2012. Chemokine gene silencing in decidual stromal cells limits T cell access to the maternal-fetal interface. *Science* 336:1317–1321.
- Nilsson, M. A., G. Churakov, M. Sommer, N. Van Tran, A. Zemann, J. Brosius, and J. Schmitz. 2010. Tracking marsupial evolution using archaic genomic retroposon insertions. *Plos Biology* 8.
- O’Leary, M. A., J. I. Bloch, J. J. Flynn, T. J. Gaudin, A. Giallombardo, N. P. Giannini, S. L. Goldberg, B. P. Kraatz, Z. Luo, J. Meng, et al. 2013. The placental mammal ancestor and the post K-Pg radiation of placentals. *Science* 339:662–667.
- Padykula, H. A., and J. M. Taylor. 1976. Ultrastructural evidence for loss of the trophoblastic layer in the chorioallantoic placenta of Australian bandicoots (Marsupialia: Peramelidae). *Anatomical Record* 186:357–386.
- Padykula, H. A., and J. M. Taylor. 1982. Marsupial placentation and its evolutionary significance. *Journal Reproduction and Fertility (Suppl.)* 31:95–104.
- Parker, P. J. 1977. An ecological comparison of marsupial and placental patterns of reproduction. Pp. 273–286 in B. Stonehouse and E. Gilmore, eds., *The Biology of Marsupials*. Baltimore: University Park Press.
- Pijnenborg, R., and L. Vercruyssen. 2013. A. A. W. Hubrecht and the naming of the trophoblast. *Placenta* 34: 314–319.
- Pond, C. M. 1977. The significance of lactation in the evolution of mammals. *Evolution* 31:177–199.
- Reik, W., M. Constancia, A. L. Fowden, N. Anderson, W. Dean, A. C. Ferguson-Smith, B. Tycko, and C. Sibley. 2003. Regulation of supply and demand for maternal nutrients in mammals by imprinted genes. *Journal of Physiology* 547:35–44.
- Renfree, M. B. 1983. Marsupial reproduction: the choice between placentation and lactation. Pp. 1–29 in C. A. Finn, ed., *Oxford Reviews of Reproductive Biology*. Oxford: Oxford University Press.
- Renfree, M. B. 1993. Ontogeny, genetic control, and phylogeny of female reproduction in monotreme and therian mammals in F. S. Szalay, ed., *Mammal Phylogeny: Mesozoic Differentiation, Multituberculates, Monotremes, Early Therians, and Marsupials*. New York: Springer-Verlag.
- Renfree, M. B. 1995. Monotreme and marsupial reproduction. *Reproduction Fertility and Development* 7:1003–1020.
- Renfree, M. B. 2000. Maternal recognition of pregnancy in marsupials. *Reviews of Reproduction* 5:6–11.
- Renfree, M. B. 2010. Marsupials: placental mammals with a difference. *Placenta* 31:S21–S26.
- Renfree, M. B., E. I. Ager, G. Shaw, and A. J. Pask. 2008. Genomic imprinting in marsupial placentation. *Reproduction* 136:523–531.
- Renfree, M. B., T. A. Hore, G. Shaw, J. A. Graves, and A. J. Pask. 2009. Evolution of genomic imprinting: insights from marsupials and monotremes. *Annual Review Genomics and Human Genetics* 10:241–262.
- Renfree, M. B., E. M. Russell, and R. D. Wooller. 1984. Reproduction and life history of the honey possum, *Tarsipes rostratus*. Pp. 427–437 in A. P. Smith and I. D. Hume, eds., *Possums and Gliders*. Sydney: Australian Mammal Society.
- Renfree, M. B., S. Suzuki, and T. Kaneko-Ishino. 2012. The origin and evolution of genomic imprinting and viviparity in mammals. *Philosophical Transactions of the Royal Society B* 368:20120151
- Roberts, C. T., and W. G. Breed. 1994. Placentation in the dasyurid marsupial, *Sminthopsis crassicaudata*, the fat-tailed dunnart,

- and notes on placentation of the didelphid, *Monodelphis domestica*. *Journal of Reproduction and Fertility* 100:105–113.
- Rodger, J. C., T. P. Fletcher, and C. H. Tyndale-Biscoe. 1985. Active anti-paternal immunization does not affect the success of marsupial pregnancy. *Journal of Reproductive Immunology* 8:249–256.
- Rougier, G. W., J. R. Wible, and M. J. Novacek. 1998. Implications of *Deltatheridium* specimens for early marsupial history. *Nature* 396:459–463.
- Ruben, J. 1995. The evolution of endothermy in mammals and birds—from physiology to fossils. *Annual Review of Physiology* 57:69–95.
- Russell, E. M. 1982. Patterns of parental care and parental investment in marsupials. *Biological Reviews* 57:423–485.
- Sánchez-Villagra, M. R. 2013. Why are there fewer marsupials than placentals? on the relevance of geography and physiology to evolutionary patterns of mammalian diversity and disparity. *Journal of Mammalian Evolution* 20:279–290.
- Sánchez-Villagra, M. R., A. Goswami, V. Weisbecker, O. Mock, and S. Kuratani. 2008. Conserved relative timing of cranial ossification patterns in early mammalian evolution. *Evolution & Development* 10:519–530.
- Sánchez-Villagra, M. R., and W. Maier. 2003. Ontogenesis of the scapula in marsupial mammals, with special emphasis on perinatal stages of didelphids and remarks on the origin of the therian scapula. *Journal of Morphology* 258:115–129.
- Sears, K. E. 2004. Constraints on the morphological evolution of marsupial shoulder girdles. *Evolution* 58:2353–2370.
- Sears, K. E. 2009. Differences in the timing of prechondrogenic limb development in mammals: the marsupial-placental dichotomy resolved. *Evolution* 63:2193–2200.
- Selwood, L., and M. H. Johnson. 2006. Trophoblast and hypoblast in the monotreme, marsupial and eutherian mammal: evolution and origins. *BioEssays* 28:128–145.
- Shine, R. 1995. A new hypothesis for the evolution of viviparity in reptiles. *American Naturalist* 145:809–823.
- Smith, K. K. 1997. Comparative patterns of craniofacial development in eutherian and metatherian mammals. *Evolution* 51:1663–1678.
- Smith, K. K. 2001. The evolution of mammalian development. *Bulletin of the Museum of Comparative Zoology* 156:119–135.
- Smith, K. K. 2006. Craniofacial development in marsupial mammals: developmental origins of evolutionary change. *Developmental Dynamics* 235:1181–1193.
- Stewart, J. R., and M. B. Thompson. 2003. Evolutionary transformations of the fetal membranes of viviparous reptiles: a case study of two lineages. *Journal of Experimental Zoology Part A—Comparative Experimental Biology* 299A:13–32.
- Taylor, J. M., and H. A. Padykula. 1978. Marsupial trophoblast and mammalian evolution. *Nature* 271:588.
- Thompson, M. B., and B. K. Speake. 2006. A review of the evolution of viviparity in lizards: structure, function and physiology of the placenta. *Journal of Comparative Physiology B—Biochemical Systemic and Environmental Physiology* 176:179–189.
- Tyndale-Biscoe, H. 2005. *Life of Marsupials*. Collingwood, Australia: CSIRO Publishing.
- Tyndale-Biscoe, H., and M. Renfree. 1987. *Reproductive physiology of marsupials*. Cambridge: Cambridge University Press.
- Vaglia, J. L., and K. K. Smith. 2003. Early differentiation and migration of cranial neural crest in the opossum, *Monodelphis domestica*. *Evolution & Development* 5:121–135.
- van Nievelt, A. F. H., and K. K. Smith. 2005. To replace or not to replace: the significance of reduced functional tooth replacement in marsupial and placental mammals. *Paleobiology* 31:324–346.
- Vogel, P. 2005. The current molecular phylogeny of eutherian mammals challenges previous interpretations of placental evolution. *Placenta* 26:591–596.
- Wake, M. H. 1993. Evolution of oviductal gestation in amphibians. *Journal of Experimental Zoology* 266:394–413.
- Walker, K. Z., and C. H. Tyndale-Biscoe. 1978. Immunological aspects of gestation in the Tammar wallaby, *Macropus eugenii*. *Australian Journal of Biological Science* 31:173–182.
- Wang, X., D. C. Miller, R. Harman, D. F. Antczak, and A. G. Clark. 2013. Paternally expressed genes predominate in the placenta. *Proceedings of the National Academy of Sciences*. 110:10705–10710.
- Weisbecker, V. 2011. Monotreme ossification sequences and the riddle of mammalian skeletal development. *Evolution* 65:1323–1335.
- Weisbecker, V., and A. Goswami. 2010. Brain size, life history, and metabolism at the marsupial/placental dichotomy. *Proceedings of the National Academy of Sciences USA* 107:16216–16221.
- Weisbecker, V., A. Goswami, S. Wroe, and M. R. Sánchez-Villagra. 2008. Ossification heterochrony in the therian postcranial skeleton and the marsupial-placental dichotomy. *Evolution* 62:2027–2041.
- Weisbecker, V., and M. Sánchez-Villagra. 2007. Postcranial sequence heterochrony and the marsupial-placental dichotomy. *Journal of Vertebrate Paleontology* 27:164A..
- Wildman, D. E., C. Y. Chen, O. Erez, L. I. Grossman, M. Goodman, and R. Romero. 2006. Evolution of the mammalian placenta revealed by phylogenetic analysis. *Proceedings of the National Academy of Sciences USA* 103:3203–3208.
- Wooding, P., and G. Burton. 2008. *Comparative Placentation*. Berlin: Springer-Verlag.
- Yoshinaga, K. 2012. Two concepts on the immunological aspect of blastocyst implantation. *Journal of Reproduction and Development* 58:196–203.
- Zeller, U., and C. Freyer. 2001. Early ontogeny and placentation of the grey short-tailed opossum, *Monodelphis domestica* (Didelphidae : Marsupialia): contribution to the reconstruction of the marsupial morphotype. *Journal of Zoological Systematics and Evolutionary Research* 39:137–158.