What Can Comparative Studies of Placental Structure Tell Us?—
A Review

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Paper accepted 2 January 2004

The diversity of placental structures in Eutherian mammals is such that drawing generalizations from the definitive forms is problematic. There are always areas of reduced interhaemal distance whether the placenta is epitheliochorial, synepitheliochorial, endotheliochorial or haemochorial. However, the thinning may be achieved by different means. The presence of a haemophagous area as an iron transport facilitator is generally associated with endotheliochorial placentae but is also found in sheep and goats (synepitheliochorial) and in tenrecs and hyaenas (haemochorial). Although similar chorioallantoic placentae are found within families, structure begins to diverge at the ordinal level and there is little correlation at the supraordinal level of phylogeny. Differences in formation and function of the yolk sac provide additional variation. There would appear to be considerable adaptive pressure for development or retention of the haemochorial type of chorioallantoic placenta. This type of placenta has several possible drawbacks including more ready passage of fetal cells to the maternal organism and, should the haemochorial condition be achieved early, oxidative stress. At any rate no animal larger than the human and gorilla has this type of placenta. The endotheliochorial condition is found in animals as large as the bears, manatee and elephants. In addition to the ungulates, the epitheliochorial condition is present in the largest animals with the longest gestation periods, the whales. Considering the length of time since the early stages of mammalian evolution, it is probable that few unmodified structural features are present in any currently surviving mammal. Nevertheless, more complete studies of divergent types of mammalian placenta should help our understanding of mammalian interrelationships as well as placental function.

INTRODUCTION

One of the more surprising and interesting results of recent research is the conservation throughout the animal kingdom of genes. Thus numerous distinct Wnt oncogenes occur in Drosophila, zebrafish, Xenopus, chick and mouse, and Wnt2 appears to participate in normal placental development in the mouse [1]. Consequently the large numbers of genes currently being discovered and analysed in mouse development [2,3] can be expected to be present in development in other mammals. Of course small variations in DNA of individual genes between species, factors controlling the time of expression and even microRNA repression of gene expression can be expected to add to diversity [4]. Although genes such as Indian hedgehog Ihh [5] may participate in both Drosophila and mouse development, the latter animals neither fly nor lay eggs. In contrast we are faced with a nearly overwhelming diversity of methods of implantation of the blastocyst and structure of the placenta. Can we in fact deduce any generalizations from observation of placental structure?

INTERHAEMAL DISTANCES

First, some of the more obvious conclusions. It is now well established that the number and nature of the layers between fetal and maternal blood bear no relationship to the placenta’s ability to provide oxygen to the fetus. Wooding and Flint [6], in their chapter in Marshall’s Physiology of Reproduction, tabulate the way in which all of the chorioallantoic placental types—epitheliochorial, synepitheliochorial, endotheliochorial and haemochorial—have areas of comparable proximity of the two blood streams reducing the diffusion distance. The way in which the interhaemal area is reduced varies in part with definitive placental type (Figure 1). In epitheliochorial and synepitheliochorial placentae the indenting of both trophoblast and uterine epithelium by capillaries decreases the interhaemal distance. In endotheliochorial placentae the indentation of trophoblast by fetal vessels within the labyrinth is the primary method of reducing interhaemal distance [7]. In haemochorial placentae thinning is achieved by a number of ways of reducing the thickness of the trophoblast; these include wide spacing of nuclei (elephant shrew), confining some of the trophoblast in contact with maternal blood to a spongy zone or interstitial area as in myomorph and histrionicognath rodents [8], alternating...
Figure 1. Micrographs of the definitive interhaemal areas in different types of placenta. (A) Diffuse epitheliochorial placenta of the bush baby (Galago). The taller light-staining trophoblast cells are closely apposed to the dark maternal epithelium. Note that fetal capillaries (arrows) indent the trophoblast, thinning the distance between the maternal vessel (mv) and the fetal vessels. (B) Synepitheliochorial placenta of the cow. Binucleate cells (arrows) are seen in the trophoblast. A trinucleate cell formed by fusion of a binucleate cell and uterine epithelial cell is also seen (asterisk) near maternal capillaries (arrowheads). (C) Endotheliochorial placenta of the African elephant (Loxodonta). Fetal vessels (arrows) indent the trophoblast adjacent to the maternal vessels (mv). (D) Endotheliochorial placenta of the mink. Note the hypertrophied endothelial cells in the maternal vessel (mv) and the indentation of the trophoblast by fetal vessels (arrows). (E) Haemomonochorial placenta of the woodchuck (Marmota). Note the segregation of many of the trophoblast nuclei into clusters or knots (arrows), resulting in thinner syncytial trophoblast lining the maternal blood spaces (mbs). (F) Cellular haemomonochorial placenta of the jumping mouse (Zapus). The interhaemal area between fetal capillary (fc) and maternal blood spaces (mbs) has a single layer of giant trophoblast cells with abutting thin processes between perinuclear regions. × 400.
thick and thin regions (rabbit), and accumulating nuclei in syncytial knots (many primates, marmot, hyaena) [9].

**MORPHOLOGICAL EVIDENCE OF IRON TRANSFER**

Considerable information is available on different ways in which iron can be transferred to the developing fetus. In epitheliochorial placentae such as those of the pig [10], horse [11] and possibly galago [12], uterine secretions in the form of uteroferrin provide a major source of iron to the trophoblast. Yet the goat and sheep have haemophagous areas that apparently facilitate iron transport [13]. Mammals with endothermochorial placentae such as the carnivores (except the hyaena), shrews, elephants and some bats, have specifically but divergently situated haemophagous areas [14]. Nevertheless there are some species such as *Dipodomys* that have an endothermochorial placenta but no haemophagous area [15]; the pathway of iron transfer in this species is unknown. There are species with haemochorial placentae that also have large haemophagous areas such as several of the tenrecs [16]. On the other hand many species with haemochorial placenta use maternal and fetal transferrins and an elaborated receptor endocytosis and release mechanism as a major transfer system [17]. Some rodent species also use yolk sac transfer, especially early in gestation [18]. It would be interesting to know what pathways of iron transfer are present in a primitive mammal such as the armadillo with its villous haemochorial placenta and inverted yolk sac.

**PHYLOGENETIC RELATIONSHIPS**

It is abundantly clear that closely related species have similar definitive placental structure. For example, all 285 genera of the rodent family Muridae may be expected to have haemotrichorial chorioallantoic placentae, although only about a dozen species have been examined to date [19]. The general rule that all genera within a family have similar placenta might be thought to have an exception in the mole family Talpidae. The American mole *Scalopus* is considered to have an epitheliochorial placenta [20], whereas the European mole *Talpa* is definitely endotrichorial [21]. However, only a single midgestation specimen of *Scalopus* was available for examination by electron microscopy, and the looping arrangement of the maternal vessels is more similar to that seen in endothermochorial placentae than that in typical epitheliochorial placentae. Within many but by no means all orders of mammals different families have similar placentae. Carnivores, with the hyaena as the exception, all have endothermochorial placentae but the position of the haemophagous area and the presence or absence of decidual cells vary. Artiodactyls have either epitheliochorial or synepitheliochorial placentae; perissodactyls have diffuse epitheliochorial placentae but not all have endometrial cups [6]. The bats (Chiroptera) have either endotheliochorial or haemochorial placentae, primates either epitheliochorial or haemochorial placentae. Nearly all members of the most abundant order, Rodentia, have haemochorial placentae. The sciuriforms and hystricomorphs have similar but distinct types of syncytial haemomonochorial placentae. The vast majority of myomorph rodents have haemotrichorial placentae; however, both cellular haemomonochorial and endotheliochorial placentae are present in this group [9,14].

Using placental structure to aid in analysing relationships between orders is more problematic. The recent use of mitochondrial and nuclear DNAs to analyse interordinal relationships has elicited renewed interest in phylogeny and increased the search for morphological similarities [22]. These studies place several groups in the Afrotheria, linking such seemingly diverse species as the tenrecs with the elephants [23]. If we accept the premise that there are four superorders (Afrotheria, Laurasiatheria, Eutheria, Xenarthra) based on mitochondrial DNA and geographic regions of evolution, it can be seen that the definitive interhaemal structures bear little relationship to the superorders (Table 1). Luckett [24] suggested a cladistic approach using multiple developmental aspects (formation of the amniotic cavity, size of allantois, yolk sac development, etc.) and assigning these features to primitive (i.e. similar to reptiles) or derived (advanced) categories as a means of assessing relationships. This approach, taking into account the way in which extra-embryonic membranes are formed, provides appreciably more information than just considering definitive placental form. Unfortunately the information on early development of such membranes is even more spotty than that on the definitive form of the chorioallantoic placenta.

Not surprisingly the Eutherian yolk sac, freed of its relationship to yolk uptake, takes a variety of forms. It retains the primitive function of blood cell formation and some synthetic and uptake function but also specializes in a variety of fashions [25]. The yolk sac can invert to make uptake from uterine secretion more direct as in rats, guinea pigs, rabbits, armadillos and others. Some of its original cells can be used to form the earliest extraembryonic mesoderm as in higher primates [26,27]. The function of the mesothelium and endoderm can be modified as in some species of bats in which the mesothelium becomes an endocytic epithelium and the glandular aspect of the endoderm is emphasized [25,28]. It should be noted that a ‘free’ yolk sac (not attached to the trophoblast) can still participate in uptake functions. Even the secondary yolk sac of haplorhine primates appears to have absorptive functions [29].

Mossman [14] attempted to group Eutherian taxa by their definitive yolk sac structure; he divided the types of yolk sacs into three major groups with nine subgroups. Using this system of classification, bat families were found in all three major groups, and one of the nine minor groups consisted of vespertilionid bats, tree shrews, and golden moles. This lack of conformity with other means of classification further indicates both the variation that can occur in yolk sac structure and its derived nature.
ADVANTAGES AND DISADVANTAGES OF PLACENTAL ARRANGEMENT

Haemochorial placentae

The evolutionary pressure favouring some type of haemochorial placenta has obviously been extreme. Haemochorial placentae are found in insectivores, primates, tenrecs, rodents, bats, hyraxes, elephant shrews, anteaters, armadillos, flying lemurs and even hyaenas. The large variation in the definitive form of the placenta, the divergent way in which the haemochorial condition is achieved, and the variety of unrelated orders in which it is found suggest considerable convergent evolution.

Many of the advantages of the haemochorial relationship are quite obvious. Not only does the haemochorial placentate type provide direct access to maternal blood for oxygen–CO₂ exchanges between it and trophoblast, but more importantly it places the surface of the trophoblast with its receptors for glucose [30] and amino acids [31,32] in contact with maternal blood facilitating maternal-fetal transport. Water and inorganic ions that participate in cotransport or are necessary for skeletal development are also directly available [33]. Trophoblast in this position also participates in active receptor-mediated transfer of IgG, possibly by molecular binding of the IgG that has been internalized by endocytosis [34,35]. It also provides direct access to the maternal organism for hormones derived from the fetus and trophoblast. In the human placenta hCG is preferentially secreted from the microvillous surface of syncytiotrophoblast [36]. It has been argued that LH as an efficient pregnancy-establishing signal to the corpus luteum evolved in primates with the haemochorial condition [37]. In murid rodents the trophoblast giant cells which are essentially situated in maternal blood are the source of prolactins [38].

Despite the obvious advantages of the haemochorial arrangement, it has several disadvantages. There is the possibility of extensive bleeding at parturition. There is a greater chance of passage of cells between organisms, especially from the fetus to the maternal organism resulting in such phenomena as microchimerism or more acute situations such as erythroblastosis fetalis [39–41]. The villous haemochorial condition appears morphologically particularly vulnerable to such exchanges. This tendency somewhat counteracts the advantage immunologically of having maternal cells in their inactivated circulating form and the absence of more direct access to maternal connective tissue with its repertoire of immunoactivators [42]. Nevertheless the human and great apes appear to be at the upper limits of size and length of gestation for haemochorial placenta.

In species that rapidly tap maternal vessels, another potential disadvantage is the possibility of too much oxygen for good embryonic development. Oxidative stress may be alleviated by physiological means such as elevated thioredoxin levels [43,44] and other molecules with antioxidant properties [45]. This disadvantage is also limited in a number of other ways. Relatively slow development of the chorioallantoic placenta and especially its circulation is common. For example in rats

Table 1. Placental types in superorders and orders

<table>
<thead>
<tr>
<th>Placenta type</th>
<th>Superorder</th>
<th>Order</th>
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<tr>
<td>Haemochorial</td>
<td>Laurasiatheria</td>
<td>Carnivora—hyaenas only</td>
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<td>Insectivora—many bat families</td>
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<td></td>
<td>Euarchontoglires</td>
<td>Rodentia—most families</td>
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<td>Primata—monkeys, gorillas, man, Tarsius</td>
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<td>Dermoptera—flying lemurs</td>
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<td>Xenarthra</td>
<td>Xenarthra—armadillos, anteaters</td>
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<td></td>
<td>Afrotetheria</td>
<td>Hyracoidae—hyraxes, conies</td>
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<td>Afrosoricida—tenrecs, golden moles</td>
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<td>Macroscelidea—elephant shrews</td>
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<td>Endotheliochorial</td>
<td>Laurasiatheria</td>
<td>Carnivora—all but hyaena</td>
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<td>Pinnipedia—seals, walruses</td>
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<td></td>
<td>Euarchontoglires</td>
<td>Rodentia—kangaroo rat</td>
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<td>Scandentia—tree shrews</td>
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<td>Xenarthra</td>
<td>Xenarthra—sloths</td>
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<td>Afrotetheria</td>
<td>Proboscidea—elephants</td>
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<td>Tubulidentata—ardvark</td>
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<td>Sirenia—manatee</td>
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<tr>
<td>Epitheliochorial</td>
<td>Laurasiatheria</td>
<td>Cetacea—whales, porpoises</td>
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<td>Artiodactyla—cows, pigs, deer</td>
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<td>Perissodactyla—horses, tapirs</td>
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<td>Pholidota—pangolin</td>
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<tr>
<td></td>
<td>Euarchontoglires</td>
<td>Primata—lemurs, lorises</td>
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and mice the chorioallantoic placenta does not develop until nearly half way through the gestation period. The initial association with maternal blood is in the yolk sac placenta and is formed by decidual cell modifications that lead to trophoblast spaces within the parietal trophoblast [46]. When the ectoplacental cone reaches the mesometrial chamber the remodeled chamber is filled with maternal blood from the surrounding sinusoidal venules [47]. In many species of bats the definitive haemochorial placenta is preceded by an endotheliochorial placenta. In species such as primates in which trophoblast taps maternal blood quickly the conceptus is initially poorly oxygenated [48,49], and the initial maternal blood flow in the forming placenta is probably both sluggish and at low pressure [50]. In the armadillo the maternal vessels that are invaded by the developing villi are endometrial venous sinuses [51].

Endotheliochorial placentae

The advantages of the endotheliochorial placenta are less obvious. The presence of a maternal endothelium presumably reduces the incidence of passage of fetal cells into the maternal organism. In many species with this type of placenta the maternal capillaries grow into the trophoblast without most of the cellular elements that are ordinarily found in endometrial connective tissue. The induction of elongated anastomotic sinusoidal capillary beds allows for an orderly pathway into the resulting placental labyrinth [52]. The labyrinth has large amounts of trophoblast in contact with an interstitial membrane and at places with the maternal endothelium. However, neither dendritic cells nor extravasated B and T lymphocytes are normally present in the labyrinth. The function of the highly modified endothelial cells is more problematic. Especially strange is the situation in some of the shrews in which the trophoblast layer becomes much reduced and highly fenestrated [53,54]. The endotheliochorial type of placenta is found in some very large animals such as the elephant with its large size and long gestation [55].

Epitheliochorial placentae

The epitheliochorial type of arrangement has as its advantage the safety factor of the isolation of fetal and maternal components. The presence of two complete epithelia should diminish both immunological problems as well as the deportation of fetal cells to the maternal organism. Indeed the largest mammals with long gestation periods, the whales, have this type of placenta. The disadvantage of the greater difficulty in passage of materials between organisms is partially overcome by a variety of mechanisms. In the horse, secreted eCG passes readily into the maternal vascular system because of the migration of trophoblastic girdle cells into the endometrium to form endometrial cups. The resultant proximity of these cells to maternal capillaries and invasion into maternal lymphatics facilitates CG passage to the mare [56–58]. In the cow as an example of a synepitheliochorial placenta, the fusion of binucleate trophoblast cells with maternal epithelial cells facilitates passage of prolactin to the maternal organism [59]. Passive immunity on the other hand is normally passed to the neonate via colostrum rather than prior to parturition.

COUNTERCURRENT BLOOD FLOW

There is a strong tendency for placentae to form counter current blood flow systems within the interhaemal areas. Since the maternal and fetal blood vessels normally enter interhaemal areas from different directions, there is a tendency for general counterflow. However, when we examine the microvasculature the problem increases in complexity. Dantzer et al. [60] elucidate some of the problems with classification of blood flow as crosscurrent or countercurrent at the level of the capillaries or blood spaces. The relationships can also vary with gestational age as in the change from a simple series of capillary loops in early gestation in the cow to a more elaborately branched exchange area but more of a crosscurrent in later gestation [61]. One might think that the endotheliochorial placenta would produce a countercurrent arrangement, but the multiple branching anastomotic network shown beautifully in the corrosion casts of the mink placenta for example results in a countercurrent at the microvessel level [62]. Physiological studies also tend to show varying degrees of crosscurrent exchanges [63]. With haemochorial placentae it might be thought that there would be less tendency for countercurrent situations. However, in a great many species the maternal blood enters the labyrinth in trophoblast-lined channels that direct the arterial flow to the fetal side of the labyrinth before the blood enters thin parallel channels which return maternal blood to veins in the basal plate. Whereas usually the path of the fetal blood is not as straight and therefore less rigorously countercurrent with branching occurring at various levels in the labyrinth, there is nevertheless a region near the chorionic plate where fine fetal capillaries are parallel to the maternal channels that are most richly oxygenated. Such an arrangement has been reported for the rabbit and caviomorph rodents, and on anatomical grounds the arrangement is similar in the tenrec and the elephant shrew.

The advantage of countercurrent over various crosscurrent flow patterns is greatest for highly diffusible molecules such as oxygen or carbon dioxide. Even then, the difference in transfer efficiency tends to disappear when the diffusing capacity of the placenta is low in relation to blood transport capacity [64]. In other words, when oxygen transfer is flow-limited, the vascular geometry assumes greater importance. Placental diffusing capacity is greater by several orders of magnitude in the haemochorial placentae of rodents and lagomorphs, which have a predominantly countercurrent arrangement, than in the epitheliochorial placenta of the sheep, which has a largely crosscurrent arrangement of blood vessels [65].
In addition to the interhaemal areas and other areas not associated with maternal-fetal exchanges, there is often a spongy zone formed by a meshwork of trophoblastic channels but free of the fetal vessels or connective tissue that are present in the labyrinth. This arrangement places trophoblast cells in contact with maternal blood without increasing the interhaemal distance and may also tend to reduce the possibility of cells of fetal origin and embolisms entering the blood stream. This type of arrangement is found in many species irrespective of the number of trophoblast layers, whether the trophoblast is cellular or syncytial, and in such diverse species as the hedgehog tenrec [16] and the capybara [66], as well as laboratory rodents.

CONCLUSIONS

Study of comparative placentation is a humbling experience. Even keeping track of the definitive type of placenta in the known examples of over 100 families of the 19 or 20 orders of Eutherian mammals is a difficult task. More significantly, the lack of substantial electron microscopic studies of the placenta of many families and the lack of studies of the way in which the definitive placentae form limit our attempts to generalize. The absence of fossil evidence of placental structure in species thought to be ancestral adds to the difficulty in determining what aspects of placentation are primitive or derived features. Although placentation is only indirectly related to the environment (for example animals that must be actively mobile at birth have a longer gestation), clearly the placenta is of extreme importance in survival of the species. Animals with less efficient placentae would be expected to be eliminated rapidly, especially in small mammals whose populations must bloom when food is available. It has recently been estimated that in a single fish genus (*Poeciliopsis*) it has taken 750 000 years or less to evolve a placenta [67]. *Eomaia*, one of the best preserved primitive Eutherian mammal fossils, is considered to be 125 million years old [68]. It is therefore probable that in all modern mammals many aspects of placental development are derivative and cannot really be considered primitive. However, more complete studies of divergent types of mammalian placentae would certainly help our understanding of mammalian interrelationships.

ACKNOWLEDGEMENTS

It is a pleasure to acknowledge Diana Mossman and Paula Holahan for making available material from the Mossman Collection at the University of Wisconsin Zoological Museum. We also wish to thank Graham Burton for access to and assistance with the Boyd Collection at Cambridge University, and Heinz Kunzle for continued provision of tenrec materials. The blocks of elephant placenta were graciously provided by Twink Allen and Peter Wooding.

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