We here review the evolution of invasive placentation in primates towards the deep penetration of the endometrium and its arteries in hominoids. The strepsirrhine primates (lemurs and lorises) have non-invasive, epitheliochorial placentation, although this is thought to be derived from a more invasive type. In haplorrhine primates, there is differentiation of trophoblast at the blastocyst stage into syncytial and cellular trophoblast. Implantation involves syncytiotrophoblast that first removes the uterine epithelium then consolidates at the basal lamina before continuing into the stroma. In later stages of pregnancy, especially in Old World monkeys and apes, cytotrophoblast plays a greater role in the invasive process. Columns of trophoblast cells advance to the base of the implantation site where they spread out to form a cytotrophoblastic shell. In addition, cytotrophoblasts advance into the lumen of the spiral arteries. They are responsible for remodelling these vessels to form wide, low-resistance conduits. In human and great apes, there is additional invasion of the endometrium and its vessels by trophoblasts originating from the base of the anchoring villi. Deep trophoblast invasion that extends remodelling of the spiral arteries to segments in the inner myometrium evolved in the common ancestor of gorilla, chimp and human.

1. Introduction

Trophoblast invasion of the uterus is a necessary step at implantation of the human blastocyst. It leads to envelopment of the blastocyst by the endometrium, i.e. implantation is interstitial. During subsequent development of the placenta, trophoblast invades the decidualized endometrium and migrates into the spiral arteries. The result is extensive remodelling of the arterial wall and widening of the lumen to accommodate a high rate of blood flow [1]. In a healthy pregnancy, trophoblast invasion and arterial remodelling extend through the depth of the decidua and the inner myometrium. Shallow trophoblast invasion is associated with pregnancy pathologies especially preeclampsia and fetal growth restriction.

Apes resemble the human in having interstitial implantation, but in other primates implantation is superficial [2]. Chimpanzee and gorilla resemble the human condition in the routes and extent of trophoblast invasion during placenta- tion. This is not the case in other primates such as gibbons and Old World monkeys [3]. These differences have implications for the choice of animal models of human placentation [4].

Here, we review current knowledge about trophoblast invasion in primates and focus on two phases: penetration of the uterine epithelium and stroma by syncytiotrophoblast at implantation and the subsequent migration of cytotrophoblasts into the tissues and spiral arteries of the placental bed. The availability of dated pregnancies from primate breeding colonies and the advent of electron microscopy have deepened our understanding of the initial trophoblast invasion in marmosets, baboons and macaques. In human pregnancy, trophoblast invasion of the uterine spiral arteries leads to extensive remodelling of the vessel wall. Because shallow implantation has been linked to several obstetrical
syndromes [5], there has lately been a focus on arterial remodelling in baboons and macaques; early workers [6] had paid scant attention to the placental bed. Recently, these studies have been extended to the great apes. Uncertainties remain, however, about the extent of trophoblast invasion in Neotropical primates and little attention has been paid to tarsiers or to the lemurs and lorises.

2. Lemurs and lorises

Suborder Strepsirrhini comprises the Malagasy lemurs (seven families), the bush babies of Africa and the lorises of Africa, South and Southeast Asia and Indonesia. Strepsirrhines differ from other primates in having diffuse, epitheliochorial placentation. Histiotrophic nutrition is by means of chorionic vesicles situated above the mouths of uterine glands. Convergent evolution of epitheliochorial placentation in non-primates, including horses, whales and even-toed ungulates, similarly involved structures suited to histiotrophic nutrition [7].

(a) Implantation and early development

Hill [6] carefully examined early stages in his own collection and that of Hubrecht. He found an outer layer of trophoblast in intimate contact with the uterine epithelium with tapering processes that penetrated between the epithelial cells. The uterine epithelium remained intact.

Shortly after, Gérard [8] described areas denuded of uterine epithelium during early development in Prince Demidoff’s bush baby, Galago demidoff. This was confirmed by Butler [9,10] for Galago senegalensis (Senegal bush baby). During initial attachment of the blastocyst, he found denudation of the uterine epithelium by large, columnar trophoblast cells, although with subsequent re-epithelialization of the uterine stroma. A similar sequence was observed in the grey mouse lemur, Microcebus murinus, where there was focal disintegration of the epithelium beneath a nidation plaque of tall columnar trophoblast cells [11]. These processes are dissimilar from those observed in all higher primates.

(b) Placenta and placental bed

In the species he examined, Hill [6] found only an epitheliochorial relationship. This was confirmed at the ultrastructural level by King [12] for the brown greater galago, Otogrammys crassicaudatus. The trophoblast formed an epithelium of cells joined by tight junctions and desmosomes. The apical membranes of these cells formed microvilli that interdigitated with similar structures on the surface of the uterine epithelial cells (electronic supplementary material, figure S1). Njogu et al. [13] published similar observations on the placenta of G. senegalensis in mid to late gestation.

The situation was different, however, in the mouse lemur M. murinus (family Cheirogaleidae). In the early stages of placentation, Reng [14] described differentiation of an outer layer of syncytiotrophoblast that eroded the uterine epithelium. In response to this, there was a decidual reaction of the endometrial stroma. The central part of the definitive placenta, which formed a disc with a labyrinth, was endotheiochorial. There was in addition an extensive paraplacental region that retained the diffuse, epitheliochorial structure found in other prosimians.

3. Tarsiers

All the remaining primates are classified in suborder Haplorhini, but tarsiers occupy their own infraorder (Tarsiiformes). They are small, nocturnal and carnivorous primates restricted to Indonesia and the Philippines. Their placenta is discoid, trabecular and haemochorial. The precocious appearance of the extraembryonic mesoderm and replacement of the allantoic sac by a connecting stalk are important criteria for including tarsiers with higher primates in the Haplorhini.

(a) Implantation and early development

Hubrecht’s large collection of uteri [15] was studied by Hill [6] and others, and it remains our principal source of information. The specimens are of the spectral tarsier (Tarsius spectrum), since split into several species. There are no studies at the ultrastructural level. Initial attachment of the blastocyst is by sprout-like outgrowths of trophoblast, consisting of narrow elongated cells, which pass through gaps in the uterine epithelium. Subsequently, the uterine epithelium undergoes degeneration. A rounded mass of cells found at the site of implantation has been interpreted both as modified stroma [15] and as trophoblast [6]. Luckett [16] suggested that it was derived from the gland neck epithelium although observing it to be invaded by trophoblast giant cells that were the forerunner of the placental disc.

(b) Placenta and placental bed

As the placental mass expands, it comes to consist largely of syncytiotrophoblast enclosing maternal blood spaces. With penetration by the chorionic mesoderm, bringing fetal capillaries, this is transformed into a trabecular arrangement in which the narrow maternal blood channels are lined by syncytiotrophoblast. According to Hill [6, p. 88], the trophoblast, ‘shows no tendency to proliferate and to invade the surrounding decidual tissue as does the syncytiotrophoblast of the higher primates’. The placental disc is separated from the decidua by a thin zone of disintegrated syncytiotrophoblast. The maternal blood channels are supplied from a central sinus fed by a central artery that enters through the zone of disintegrated syncytiotrophoblast. Lack of interest in the placental bed may explain why Hill [6] did not inspect the vessel wall more closely. Gruenwald [17], examining specimens in the Carnegie Collection, observed that the central artery lost its wall at the point of entry into the placenta and thereafter was lined by fibrin.

4. New World monkeys

New World monkeys (parvorder Platyrrhini) comprise three families. They are thought to be descended from a single founder that reached South America in the Miocene epoch [18,19]. Their placenta are discoid or double discoid and haemochorial. For most of gestation, the fetal villi are connected by bridges of trophoblast and present a trabecular structure, but free villi can occur closer to term. The intraembryonic space is supplied from maternal capillaries that penetrate deep into the decidua. Haematopoietic foci are a striking feature of the placenta in Cebidae and Atelidae.

(a) Implantation and early development

Early differentiation of syncytiotrophoblast and proliferation of the endometrial and glandular epithelia are distinctive
features of the implantation site described by Hill [6]. More recently, they have been studied at the ultrastructural level in timed gestations of the common marmoset, Callithrix jacchus [20,21].

Implantation of the blastocyst occurs 11–12 days after ovulation [22]. At the implantation site, syncytiotrophoblast penetrates between the uterine epithelial cells to the level of the basal lamina. Between days 13 and 15, there is rapid expansion of syncytiotrophoblast beyond the initial implantation site, but only little penetration of the basal lamina (figure 1a,b). Comparison of peripheral, intermediate and central areas suggests the following sequence of events. First the syncytiotrophoblast intrudes between the epithelial cells to the basal lamina. The epithelial cells are then detached and appear as islands within the trophoblast. Finally, in the central areas the syncytiotrophoblast forms a uniform layer and extends elaborately towards the basal lamina (figure 1b). Syncytiotrophoblast also extends into the glands, and the glandular epithelium is transformed from columnar to rounded cells. They have compared to the plaque cells seen in catarrhine primates [16], but it is by no means clear that they undergo the specific series of changes seen in macaques. The subepithelial capillaries become highly dilated and are traversed by strands of connective tissue covered by a thin endothelium. They are

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Figure 1. Invasive trophoblast in platyrrhine primates. (a) Overview of the implantation site in the common marmoset (Callithrix jacchus) on day 13 of pregnancy. The amniotic cavity is well formed. At the extreme right is the edge of the implantation site, where mtr (mtr) overlies uterine epithelium. In the rest of the implantation site, the syncytial trophoblast has largely eliminated the uterine epithelium. Note the dilution of the superficial maternal vessels (mv). Scale bar, 74 μm. (b) Syncytial trophoblast from the central region of the implantation site of C. jacchus. Numerous lamellipodia abut the residual basal lamina (bl) of the uterine luminal epithelium. Scale bar, 2.4 μm. (c) Breach of the basal lamina in C. jacchus. A process from the syncytial trophoblast (long arrow) has penetrated the residual basal lamina (bl) of the uterine luminal epithelium. Note that the projection has reached but not penetrated the basal lamina underlying the endothelium of the maternal vessel. Scale bar, 2.2 μm. Adapted with permission from Enders & Lopata [20] Copyright © 1999 Wiley-Liss, Inc. (d) Transition between a uterine artery and an intraplacental capillary in C. jacchus at 60 days of pregnancy. The thick basal lamina (bl) beneath the capillary endothelium is clearly visible. No basal lamina is seen beneath the artery, which appears devoid of endothelium and is lined by a thick layer of cells that we suggest is trophoblast. Boyd Collection, Centre for Trophoblast Research. Cambridge. Scale bar, 105 μm. (e) Transition between a uterine artery and an intraplacental capillary in the white-fronted capuchin (Cebus gracilis). The arterial lumen appears to be lined by fibrin and beneath it is a thick pad of cells. Hill Collection, Museum für Naturkunde, Berlin. Scale bar, 100 μm. (Online version in colour.)
not penetrated by the trophoblast (figure 1c) but already at this stage have a multilayered basal lamina.

The implantation site continues to expand between days 13 and 31 [21,22]. At this time, columns of cytotrophoblast are formed and extend between the endometrial capillaries. Opening of maternal vessels to supply lacunae occurs much later and typical trabeculae are not present before day 50 [23].

(b) Placentation and placental bed
Unlike in catarrhine primates, there is no cytotrophoblastic shell. Instead the fetal–maternal interface is formed by a thick pad of sincytiotrophoblast resting directly on the undecidualized endometrium. The conventional wisdom is that trophoblast does not invade the placental bed and its vessels, although multinucleate giant cells are found in the endometrium.

In the squirrel monkey, Saimiri sciureus, Gruenwald [17] found that the maternal vessels remained intact during the initial invasion of the endometrium by trophoblast. Subsequently, however, the wall of arteries entering the placenta was replaced by a layer of fibrin. There were fewer uteroplacental arteries than in catarrhines, and their number did not increase once trophoblast invasion had been completed [24]. He did not explain how the vessels adapted to accommodate an adequate blood supply to the growing fetus.

A distinctive feature of the platyrrhine placenta is the presence within it of large maternal capillaries with multiple openings into the intertrabecular space. Merker et al. [23,25] considered them to be derived from subepithelial capillaries, since at no stage did they have muscular walls. There was no consideration in their papers of the arteries supplying the capillaries.

The endothelium of these capillaries rests on a thick basal lamina [23,25]. We have looked at the transition between a uterine artery and an intraplacental capillary in two species, the common marmoset (C. jacchus) and the white-fronted capuchin (Cebus gracilis). In contrast to the capillary, the artery lacked both the endothelium and its basal lamina and was lined by a thick pad of cells that we propose is trophoblast (figure 1d,e). These observations suggest to us transformation of the arterial wall consistent with widening of the lumen to reduce resistance to blood flow. Fresh material would be needed to establish whether or not this occurs under the influence of invasive trophoblast. The position adopted by previous authors is that trophoblast invasion does not occur further to the initial events of implantation. Absent contrary evidence, this stance is no longer tenable.

5. Old World monkeys
Old World monkeys (parvorder Catarrhini, superfamily Cercopithecoidae, family Cercopithecidae) have a wide distribution in Africa and Asia. Together with apes, they comprise the catarrhine primates. These have in common a discoid, villous and haemochorial placenta supplied by highly modified uterine spiral arteries. Many Old World monkeys have a secondary attachment site and thus a double discoid placenta.

Our knowledge of their implantation and early development is based on macaques and baboons from the subfamily Cercopithecinae. Seminal studies chronicling early development in the rhesus macaque (Macaca mulatta) were performed at the Carnegie Institution [26]. More recent studies have used, in addition, the crab-eating macaque (M. fascicularis). Placentation has also been investigated in the yellow baboon (Papio cynocephalus) and olive baboon (P. anubis); colonies may include both and perhaps hybrids of the two. A limited amount of information is available for the second subfamily, Colobinae, represented by the dusky leaf monkey (Trachypithecus obscurus) [6,27].

(a) Implantation and early development
In the macaque and baboon, implantation occurs approximately 9 days after ovulation [28]. Syncytiotrophoblast forms shortly after apposition of the blastocyst to the uterine wall. It penetrates the uterine epithelium, initially as far as the basal lamina (figure 2a), sharing junctional complexes with intact epithelial cells [28]. The trophoblast tends to spread along the basal lamina so that uterine epithelial cells at the centre of the implantation site become isolated and disappear. By contrast, there is extensive proliferation and hypertrophy of the epithelium at the periphery and lateral to the implantation site, as well as of the superficial glandular epithelium, resulting in formation of epithelial plaques. At a slightly later stage, the syncytiotrophoblast penetrates into the stroma and breaches the endothelium of maternal vessels (figure 2b). Within a day of implantation, there begins to be a change in the nature of some of the syncytiotrophoblast, which becomes polarized and forms clefts lined by microvilli [29]. Blood entering these clefts initiates the lacunar stage (1–3 days after initial implantation), which marks a rapid expansion of the implantation site. In this stage, there is segregation of syncytiotrophoblast and cytotrophoblast. Clusters of invasive trophoblast cells from the cell columns begin to pass beyond the syncytiotrophoblast. They have a preferred pathway into the endometrium, tending to bypass the plaque cell clusters and penetrating into the stroma and expanded venous capillaries [30] (figure 2c). Whereas in the lacunar stage there was a thin syncytiolayer at the maternal–fetal junction, it is soon replaced by a thick cytotrophoblastic shell that starts with invasion of many cells (figure 2d) and thickens further as they secrete extracellular matrix (figure 3a).

Although the initial breach of the epithelium and of the superficial maternal capillaries is achieved by syncytiotrophoblast, in subsequent stages invasive cytotrophoblast plays a more prominent role. As early as 4 days after implantation, cytotrophoblasts have entered the lumen of the spiral arteries and by 6 days those directly at the implantation site have been plugged by trophoblast [32] (figure 3b.i). In later stages, the trophoblast migrates into the walls of the vessels as well as penetrating into deeper coils [33]. The presence of endovascular trophoblast is paralleled by loss of the vascular endothelium and disruption of vascular smooth muscle cells [33]. Despite the extensive changes rendered upon the endothelium and its vasculature, decidualization of endometrial fibroblasts is slow in the macaque, although well developed by two months.

In the olive baboon, formation of plaque cells is less extensive and the decidual reaction, although slow, is earlier than in the macaque [32]. The signalling pathways controlling plaque formation and decidualization in baboons have been the object of close scrutiny [34]. Decidual cells occur also in the vervet monkey (Chlorocebus aethiops) [35]. The dusky leaf monkey is more distantly related to the macaque, but...
resembles it more closely in having extensive plaque formation and no early decidual reaction [27].

(b) Placentation and placental bed
The rapidly increasing cytotrophoblast forms continuous columns (the primary villi) within the syncytial septae between lacunae. These primary villi then develop a mesodermal core, and the intercommunicating lacunae expand to form the intervillous space.

The mature placenta of cercopithecids is bounded on the fetal side by the chorionic plate and on the maternal side by the trophoblastic shell. There are many villous trees extending from the chorionic plate and attached to the basal plate by slender anchoring villi. The arterial supply and venous drainage of the intervillous space are through vessels that traverse the trophoblastic shell. Numerous species have a double discoid placenta [36], but the basic design is similar in both discs. There is a sharp border between the cytotrophoblastic shell and the underlying endometrium. Few cells migrate from the shell in macaques [37] or baboons [38] in contrast to the extensive migration that occurs by the interstitial route in apes and human. Multinuclear giant cells are not found [37,38].

The most striking feature of the placental bed is the progressive dilatation of the spiral arteries, which is closely

Figure 2. Invasive trophoblast at the implantation site in Old World monkeys. (a) Implantation site of a baboon (Papio sp.) at 10 days of pregnancy. Dark cytotrophoblast cells differentiating to syncytial trophoblast are seen towards the endometrium and pale cytotrophoblast cells are adjacent to the blastocyst cavity. The trophoblast has removed the uterine epithelium. ICM: inner cell mass. Scale bar, 50 μm. (b) Detail of the same implantation site showing syncytial trophoblast entering a superficial maternal capillary. Scale bar, 6.4 μm. (c) Implantation site of a rhesus macaque (Macaca mulatta) at 15 days of pregnancy. Columns of cytotrophoblast cells (cc) are advancing into the uterine stroma, bypassing the epithelial plaques (pl). Scale bar, 56 μm. (d) By 24 days of pregnancy in the macaque, the cells have spread out to form a cytotrophoblastic shell. Scale bar, 80 μm. (Online version in colour.)
linked to trophoblast invasion [39,40]. Endovascular trophoblast invades to the full depth of the endometrium in the baboon and can reach as far as myometrial segments of the spiral arteries in the macaque [37]. Initially, the spiral arterioles are obstructed by trophoblast plugs, although with channels that may allow for passage of some blood [37]. The vessel lumina become patent by the end of the second month at which time blood flow through the intervillous space can be registered by Doppler ultrasonography [41,42].

The portion of the vessel closest the shell is invaded first; as deeper segments are involved, there remains a leading edge where the endothelium is intact and the vessels are not dilated (figure 3b) [43]. The full sequence of events has been closely explored in macaques [44]. The endovascular trophoblast cells send processes between the endothelial cells, dislodging them and reaching the basal lamina. This is shortly breached by trophoblastic processes. The trophoblasts then migrate into the tunica media. Here they immediately begin to secrete a large amount of extracellular matrix that contains type IV collagen and laminin. There is disruption and loss of the smooth muscle. However, the vessel transformation often involves only one side of the vessel with scattered smooth muscle cells remaining on the other. As gestation progresses, there is continued widening of the vessel lumen and an increase in thickness of the highly modified wall.

In baboons, too, fully modified spiral arterioles have walls with multiple layers of cytotrophoblast embedded in a periodic acid-Schiff-positive extracellular matrix. Although the endothelium is removed initially, re-endothelialization later occurs [38].

6. Apes
Apes (parvorder Catarrhini, superfamily Hominoidea) are divided into Hylobatidae, comprising the gibbons, and Hominidae, which includes orangutans, gorillas, chimpanzees,
bonobo and human. The two families differ in their placentation but share the unique feature of primary interstitial implantation. There have been no systematic studies of trophoblast invasion in species other than human, but recent observations of the placental bed in chimpanzees and gorillas cast some light on the evolution of the human state.

(a) Implantation and early development

Primary interstitial implantation, where the entire conceptus is drawn into the endometrium, probably occurs in all apes, including gibbons [6]. A single chimpanzee embryo at the late lacunar stage (10.5 days post coitum) has served to establish the close similarity in initial implantation between this species (Pan troglodytes) and the human [45,46]. As discussed in recent reviews [47,48], pre-implantation development of the human blastocyst has been closely studied in recent years, but for implantation we must rely on earlier work that used conventional histology [49,50]. A single human embryo at the late lacunar stage (11 days post coitum) has been examined by electron microscopy [51].

Human embryos are classified in stages based on the developmental horizons defined by Streeter [52]. None has been observed at the time of implantation (stage 4). The earliest embryos are at the trophoblastic plate stage (stage 5a), by which time syncytiotrophoblast has penetrated the uterine epithelium and invaded the endometrial stroma and glands (electronic supplementary material, figure S2a). At the early lacunar stage (stage 5b), the lacunae are lined by syncytiotrophoblast with microvilli and superficial capillaries have been tapped, allowing blood to enter the lacunae (electronic supplementary material, figure S2b). In the late lacunar stage (stage 5c), cytotrophoblast is largely confined to an area close to the fetal mesenchyme (electronic supplementary material, figure S2c), but later (stages 6–7) there is build-up of cytotrophoblast leading to formation of the primary villi (electronic supplementary material, figure S2d). Already at this time, extravillous trophoblast cells extending from the cytotrophoblast cell columns migrate interstitially into the endometrium.

In a stage 5c embryo, electron microscopy revealed desmosomes shared between glandular epithelial cells and syncytiotrophoblast [51]. This is reminiscent of the interaction between uterine epithelium and syncytiotrophoblast in the macaque and might suggest that initial penetration of the epithelium occurs in similar fashion in the human.

An interesting difference between human and Old World monkeys is that decidualization occurs in the luteal phase of the ovarian cycle and is not dependent on conception or implantation. During implantation, however, transformation to decidual cells is not observed until the early lacunar stage and in the chimpanzee slightly later [46].

(b) Placentation and placental bed

In human placenta, the villous trees attach to the basal plate by anchoring villi. Some trophoblast cells from the anchoring villi are sessile and become surrounded by extracellular matrix, thus forming a discontinuous cytotrophoblastic shell. Meanwhile, trophoblasts emanating from cell columns at the base of other anchoring villi undergo a change in phenotype and invade the endometrium by the so-called interstitial route. This extravillous trophoblast penetrates to the full depth of the endometrium and the inner myometrium. Invasion apparently stops when clumps of cytotrophoblast cells fuse to form multinucleate giant cells [53,54]. Concomitantly, cytotrophoblasts migrate into the spiral arteries—the endovascular route—reaching segments in the inner myometrium [55]. These events are spatially and temporally associated with transformation of the spiral arteries. In the process, trophoblast cells become resident in the vessel walls, where they secrete extracellular matrix and form stellate protrusions. There is still controversy about whether intramural trophoblast is solely endovascular in origin or derived in part from the interstitial trophoblast [1].

Although previous authors had remarked upon the great similarity in architecture of the villous trees and intervillous space between human and great apes, none had looked in any detail at the placental bed. We endeavoured to amend this by examining archival material from the Hubrecht and Hill Collections at the Museum für Naturkunde in Berlin [3,56,57].

We found a significant difference in placentation between the two families of apes. In the Javan gibbon (Hylobates moloch), there was a cytrophoblastic shell with little or no invasion by the interstitial route (figure 4a). The same pattern, which resembles that of Old World monkeys, was seen in the agile gibbon (H. agilis). By contrast, the maternal–fetal interface of the chimpanzee (P. troglodytes) and lowland gorilla (Gorilla gorilla) bore a close resemblance to that of the human placenta.

In a young gorilla placenta, extravillous trophoblasts were found throughout the endometrium and the inner myometrium (figure 4b). In addition, trophoblasts embedded in extracellular matrix occupied the walls of the spiral arteries including segments from the inner myometrium. The extent and depth of trophoblast invasion resembled that of the human placental bed at 10–14 weeks gestation [56].

The Hill collection included two pregnant uteri of a chimpanzee, containing fetuses comparable in size to human fetuses of 12 and 18 weeks of pregnancy, although we obviously cannot be sure about an equivalence of fetal growth according to gestational age. There was extensive trophoblast invasion of the endometrium and inner myometrium. No spiral artery invasion was seen in the younger chimpanzee specimen (figure 4c), although endovascular invasion of the decidual spiral arteries is well underway in the human at that gestational age. In the later specimen, endovascular invasion and intramural embedding had occurred in both decidual and myometrial segments of the spiral arteries, extending as far as the deeper radial arteries (figure 4d)—at a depth not frequently encountered in normal human pregnancy [57]. These observations indicate a basically similar invasion process of the placental bed as in the human, but there are hints at possible shifts in the timing of the process.

7. Concluding remarks

In most primates, initial penetration of the uterine epithelium is achieved by syncytiotrophoblast that insinuates itself between the cells and pauses for a short time at the basal lamina before invading the underlying stroma and tapping the maternal blood vessels [2]. Syncytium formation requires cell fusion and appears to be dependent on the expression of syncytins. These are endogenous retroviral genes coding for envelope proteins whose original function was to promote fusion of the plasma membranes of a virus and its host cell; there is also an immunosuppressive domain [58]. Capture of retroviral envelope (env) genes and their expression in the placenta to promote cell fusion has occurred multiple times in mammals.
and different syncytins are found in different clades [59,60].
Syncytins 1 and 2, which promote syncytiotrophoblast formation in human placenta, are present in other platyrrhine and catarrhine primates, but could not be detected in the brown lemur (Eulemur fulvus). It is therefore likely that they were incorporated into the genome after divergence of the strepsirrhine and haplorhine lineages [61]. Further studies are needed to establish whether these or other env genes occur in tarsiers or in strepsirrhine primates where syncytium formation is known to occur (e.g. M. murinus).

Once implantation has been initiated, there is a change in the phenotype of the syncytiotrophoblast, which then forms the lining to the emerging lacunae and later the intertrabecular or intervillous space. Syncytiotrophoblast remains at the maternal–fetal interface in platyrrhines, but in catarrhines columns of trophoblast invade to form a cytotrophoblastic shell that is largely continuous in the Old World monkeys and gibbons and rapidly becomes discontinuous in gorilla, chimpanzee and human. In addition, cytotrophoblasts invading by the interstitial and/or endovascular routes enter the walls of the spiral arteries and are associated with transformation of these vessels into wide, low-resistance conduits. It is of interest to see how these processes have evolved.

(a) Placental evolution in primates
In an influential review, Hill proposed that evolution of placentation in primates occurred in sequential fashion through lemuroid, tarsioid, pithecoïd and anthropoid stages [6]. More recent analyses, based on current views of mammalian phylogeny, contradict this view and the implication that the epitheliochorial placenta of lemurs and lorises represents a primitive state from which haemochorial placentation is derived. On the contrary, epitheliochorial placentation is now seen as a derived state [62–64]. A more likely scenario is that the villous placenta of catarrhine primates is derived from a labyrinthine type such as that found in most rodents and lagomorphs. In labyrinthine placentas, fetal capillaries and maternal blood channels are closely aligned with blood flowing in opposite directions. This promotes countercurrent exchange and is highly efficient, especially for transfer of oxygen from maternal to fetal blood [65]. The narrow maternal blood channels are arranged in parallel so that the placenta as a whole is a low-resistance circuit. Nevertheless, there may be a limit to the volume flow that can be achieved in a labyrinthine placenta. Widening of the vessels would further lower the resistance and a first step might have been opening up of the labyrinth as occurs in colugos. It was suggested long ago by Wislocki [66] that this would be a logical intermediate step between a labyrinthine placenta and the trabecular arrangement found in platyrrhines. Trabeculae are bridges of trophoblast that connect the villi through most of gestation in platyrrhines although free villi may appear towards term. By contrast, the catarrhine placenta is villous from an early stage.

Achievement of a high rate of blood flow through the placenta requires more than a change in architecture. There must
be a reduction in the resistance to flow through the afferent vessels and this has been attained by transformation of the spiral arteries. While maternal factors undoubtedly play a role in this process, the chief player would seem to be the invading cytотrophoblast [1,67]. In Old World monkeys and gibbons, these cells invade by the endovascular route and achieve transformation of the endometrial segments of the arteries. In gorilla, chimpanzee and human, there is additional invasion of the uterus by the interstitial route and spiral artery transformation consistently extends through the inner third of the myometrium. This further reduces resistance, augments blood flow and increases oxygen delivery to the placenta. These developments have been linked to brain growth, culminating with the large brain of the human infant at term [68]. Deeper penetration of the uterine wall may require adaptation of the maternal immune response, including altered interaction between HLA Class I antigens on trophoblast and maternal immune cells, especially the uterine natural killer cells [69,70].

(b) Models of human placentation
The evolution of deep trophoblast invasion and modulation of the maternal immune response seems to have come at a price [5]. Firstly, there is a high incidence of postpartum haemorrhage in human pregnancy, with little evidence for excessive bleeding in other primates [71]. Secondly, shallow invasion and inadequate transformation of the spiral arteries can occur, and this has been linked to fetal growth restriction and preeclampsia; it may also be the cause of recurrent abortion [72–74]. In these pregnancies, the lower rate of blood flow restricts oxygen delivery and thus fetal growth. Because these reproductive disorders play a prominent role in obstetrics, there is interest in developing animal models.

Despite its current popularity, the mouse would seem to us to be an inappropriate model for human pregnancy. Its placenta is labyrinthine rather than villous, trophoblast invasion is shallow, and transformation of the uterine arteries is dependent mainly on maternal factors, foremost uterine natural killer cells [4,75]. Other rodents such as the rat show deeper trophoblast invasion, involving both endovascular and interstitial invasion [76,77], although it is principally the endovascular trophoblast that is closely involved in vascular remodelling. In the guinea pig, endovascular trophoblast invades deeply into the mesometrial arteries [78]; the origin of the invading trophoblast appears to be the subplacenta [79].

Only the great apes resemble human both in the routes and depth of trophoblast invasion. Given the embargo on invasive procedures in apes, the best models available are macaques and baboons. Neotropical primates deserve closer attention and elucidation of the routes and extent of trophoblast invasion in marmosets should be a priority. Meanwhile their utility as models of human placentation is difficult to assess. The differences between model species and the great apes including human must be kept in mind, especially with regard to the extensive interstitial migration of cytотrophoblast in the latter group. Pregnancy complications such as hypertension and postpartum haemorrhage seem to be rare in non-human primates, but do sometimes occur [80] and might be provoked by appropriate stress. A good example of what can be achieved is a model based on restriction of uteroplacental blood flow in the Hamadryas baboon (P. hamadryas) [81].

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