Comparative placentation in laboratory animals A review

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Introduction

Laboratory animals are utilized as systems for studying various biological parameters. The working hypothesis is that they mimic physiological processes in domestic animals and man. Any species can be used as an *ad hoc* experimental animal. However, certain categories are preferred, such as rodents and lagomorphs (rabbits). They are conveniently small and fairly inexpensive, have short gestation periods, and produce large litters. The animals can also be inbred for genetic conformity. However, rodent placentas are not as closely related to those of domestic species as would often be desired to reduce the risk of incorrect interpretation of experiments. For this reason larger and therefore more expensive and troublesome animals may be chosen.

The choice of model is especially important when the placenta is involved, inasmuch as its structural and functional diversity between species surpasses that of any other mammalian organ of comparable importance.

Species represented

The presentation comprises 3 main groups of animals:

1. Rodents and lagomorphs (Guinea pig, rat, mouse, rabbit).
2. Carnivores (cat, dog).
3. Ungulates (small ruminants, swine including minipig).

In addition the Rhesus monkey (Macaca mulatta) with a placenta closely related to the human organ has been included.

Definition

The mammalian placenta is an apposition or fusion of fetal membranes and endometrium for the purpose of physiological exchange (*Mossman* 1937).

Structure

Fetal membranes

The embryo develops four membranes: chorion, amnion, yolk sac and allantois (Fig. 1). The chorion develops first as a simple layer of epithelium (trophoblast), which is avascular. The amnion consists of ectoderm lining an avascular membrane of connective tissue. It forms a fluid-filled sac around the fetus. The yolk sac and allantois are entodermal

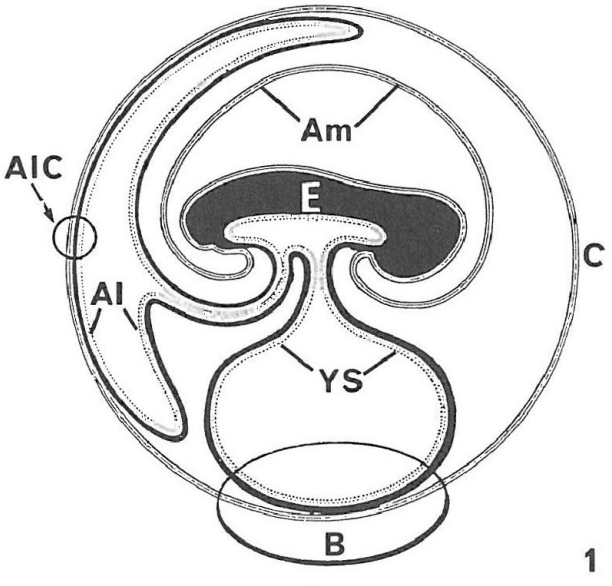

Fig. 1. Schematic drawing showing the fetal membranes of chorion (C), amnion (Am), allantois (Al) from the hindgut, yolk sac (YS) from the midgut of the embryo (E) and the combined allantochorion (AlC). The distal part of the yolk sac and the chorion might disappear as indicated by (B) to form an inverted yolk sac placenta (After Turner).

diverticles from the gut and are vascularized by vitelline and umbilical blood vessels, respectively.

The latter two membranes give rise to two fundamentally different placental types: yolk sac placenta and allantoic placenta. The yolk sac may or may not combine with the chorion. The allantois fuses with the chorion and provides the fetal vascularization of the chorioallantoic placenta. Among laboratory animals the arrangement and relative size of the fetal membranes are different in rodents and lagomorphs on one hand and carnivores and ungulates on the other. (*Steven & Morriss* 1975, *Ramsey* 1982, *Mossman* 1987).

The former group has a well developed yolk sac, which everts its entoderm towards the endometrium (inverted yolk sac placenta) early in gestation (Figs. 1, 2). Thus an epithelio-entodermal contact is established (*Björkman* 1958, 1968). This placenta is eventually surpassed by a chorioallantoic placenta (*Amoroso* 1952), where the trophoblast is in direct contact with maternal blood (hemochorial placenta), the allantoic sac is small or vestigial. The gestation period is short, except in primates (Table I).

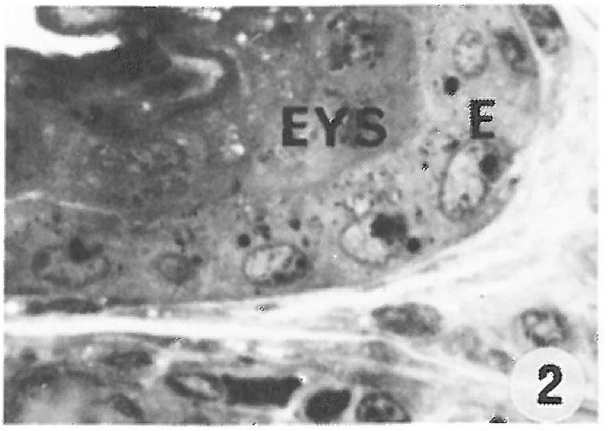

Fig. 2. Light micrograph of inverted yolk sac placenta of mouse. Entoderm of the yolk sac (EYS) closely related to the maternal epithelium (E). Mag. 1200 ×.

In the other group, carnivores and ungulates, the yolk sac, although initially large, undergoes rapid involution. On the other hand the allantois forms a voluminous sac in communication with the urinary bladder. It participates in the formation of a chorioallantoic placenta, where the trophoblast

Table I. Reproductive data related to placental structure and fetal development.

	Gestation time	No of offspring	Internal placental structure	Placental interhemal barrier	Blood flow interrelationship	Yolk sac development	Allantoic sac development	Development of new born
uman	270	1	villous	hemo-monochorial	multivillous	+	–	+
acaca	168	1	villous	hemo-monochorial	multivillous	+	–	+
uinea pig	67–68	3–4	labyrinth	hemo-monochorial	countercurrent	+++	+	+++
inchilla	105–115	1–4	labyrinth	hemo-monochorial	countercurrent	+++	+	+++
bbit	30–32	8 ±	labyrinth	hemo-dichorial	countercurrent	+++	+	+(+)
ouse	19	4–8 (1–12)	labyrinth	hemo-trichorial		+++	+	+
at	22	6–9 (4–11)	labyrinth	hemo-trichorial		+++	+	+
amster	20–22	5–10	labyrinth	hemo-trichorial		+++	+	+
olden hamster	15–16	1–12	labyrinth	hemo-trichorial		+++	+	+
og	60–63	4–6	folded/ lamellar	endothelio-chorial		+	+++	++
at	60–63	3–5	folded/ lamellar	endothelio-chorial	one way crosscurrent	+	+++	++
eep/goat	150	1–3	villous	epithelio-chorial	multivillous to countercurrent	(+)	+++	+++
ine	114	8–16	folded	epithelio-chorial	crosscurrent to countercurrent	(+)	+++	++(+)

a obtained from *Altman & Dittmer* (1962), *Ramsey* (1982), *Leiser & Kohler* (1984), *Mossman* (1987) and *Dantzer et* 1988).

Table II. Cell layers separating maternal and fetal blood.

Designation	Maternal layer(s) Endothelium	Epithelium	Fetal layers Trophoblast	Endothelium	Typical examples
Hemo-chorial					
„ mono „	–	–	+	+	Guinea pig, chinchilla, macaca, man
„ di „	–	–	++	+	Rabbit
„ tri „	–	–	+++	+	Rat, mouse, hamster
Endothelio-chorial	+	–	+	+	Dog Cat
Epithelio-chorial	+	+	+	+	Swine incl. minipigs Sheep and goat

Modified from *Grosser* (1909) and *Enders* (1965).

is shielded from maternal blood (Table II). The gestation period is moderately long (Table I).

Trophoblast

The trophoblast, originally a simple epithelium from the wall of the blastocyst, a cytotrophoblast at that stage, can differentiate in various directions. If the cell boundaries (plasma membranes) disintegrate, the cells coalesce and form a syncytial trophoblast. On the other hand, mitosis without division of the cytoplasm leads to the formation of bi- or multinucleated trophoblastic giant cells, or plasmodia.

The trophoblast appears to play a role in a complex system which protects the normal fetus and placenta – a physiological allograft – from the maternal immune system. This is a critical element in the development of the placenta. The major histocompatibility complex, of which the paternal one is the most interesting in this context, disappears on the trophoblast from mouse and human placenta during implantation. The major histocompatibility complex may therefore play a central role in placentation as the subtype of Class II antigens have not been reported on mouse or human trophoblast in later placental stages (*Beer & Sio* 1982, *Lala et al.* 1984, *Rodger & Drake* 1987).

So from the most recent literature the immune response to the paternal component of the fetal unit is directed against broadly shared class I antigens and not against the classical class I transplantation antigens responsible for tissue rejection. This may thus be the basic mechanism by which the placenta avoids rejection (*Gill* 1989).

Trophoblast cells are most versatile. They may be provided with a complete set of organelles for synthetic activity. They can also be extremely thin to facilitate diffusion.

Structural materno-fetal relationship

The allantoic placenta may contain a smooth membrane, the chorion laeve, apposed to the uterine tissue. A more intimate attachment is established by the chorion frondosum, which forms a vastly increased contact area between trophoblast and endometrial tissue. Among the species described in the present article, the chorion frondosum appears in three different forms: folded (swine, Fig. 3, carnivores), villous (ruminants, Fig. 4, rhesus monkey) and labyrinthine (rodents, Fig. 5, rabbit) placentas. In addition trophoblastic and, when present, uterine epithelial cells may be provided with microvilli to increase the surface area further (Figs. 7, 8 & 12).

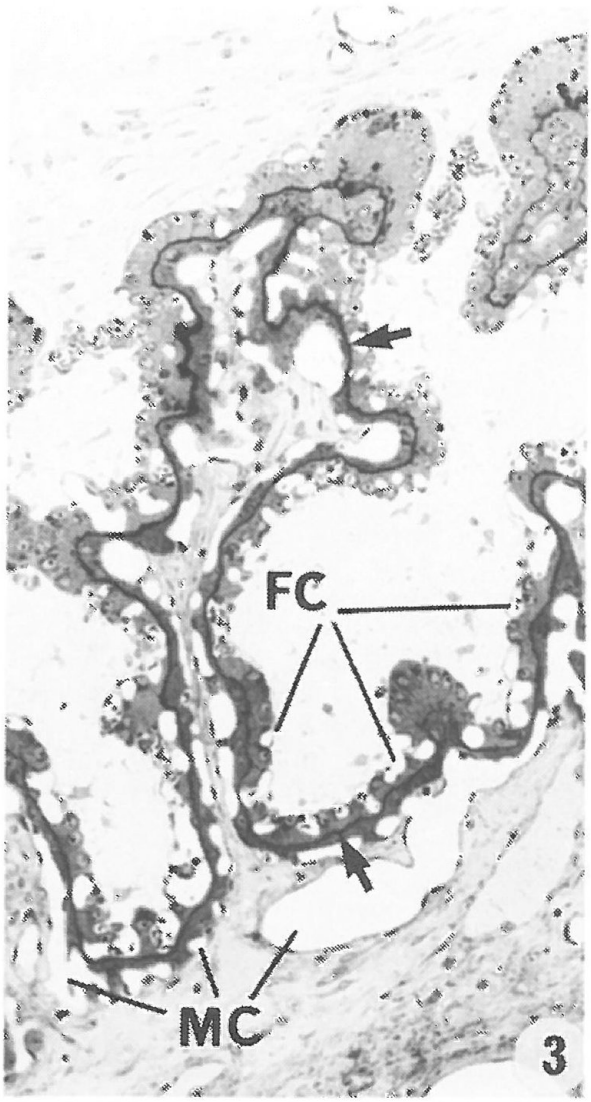

Fig. 3. Light micrograph of the folded epitheliochorial placenta of pig. Maternal capillaries (MC) are dilated due to perfusion-fixation. Fetal capillaries (FC). The dark line (→) represents interdigitating microvilli of maternal epithelium and trophoblast. Mag. 170 ×.

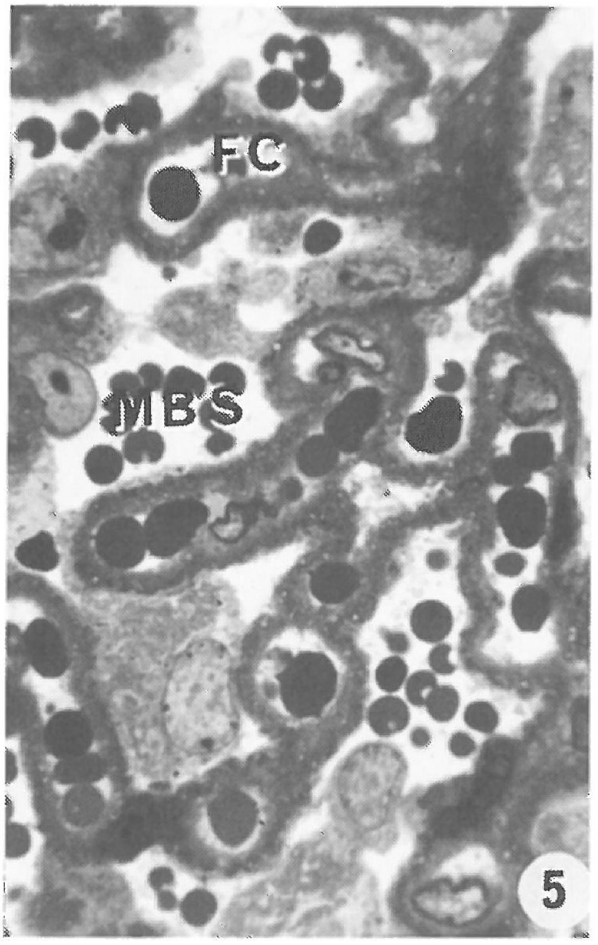

Fig. 5. Light micrograph of the labyrinthine hemotrichorial placenta of the mouse. Fetal capillaries (FC) and maternal blood space (MBS). Mag. 1200 ×.

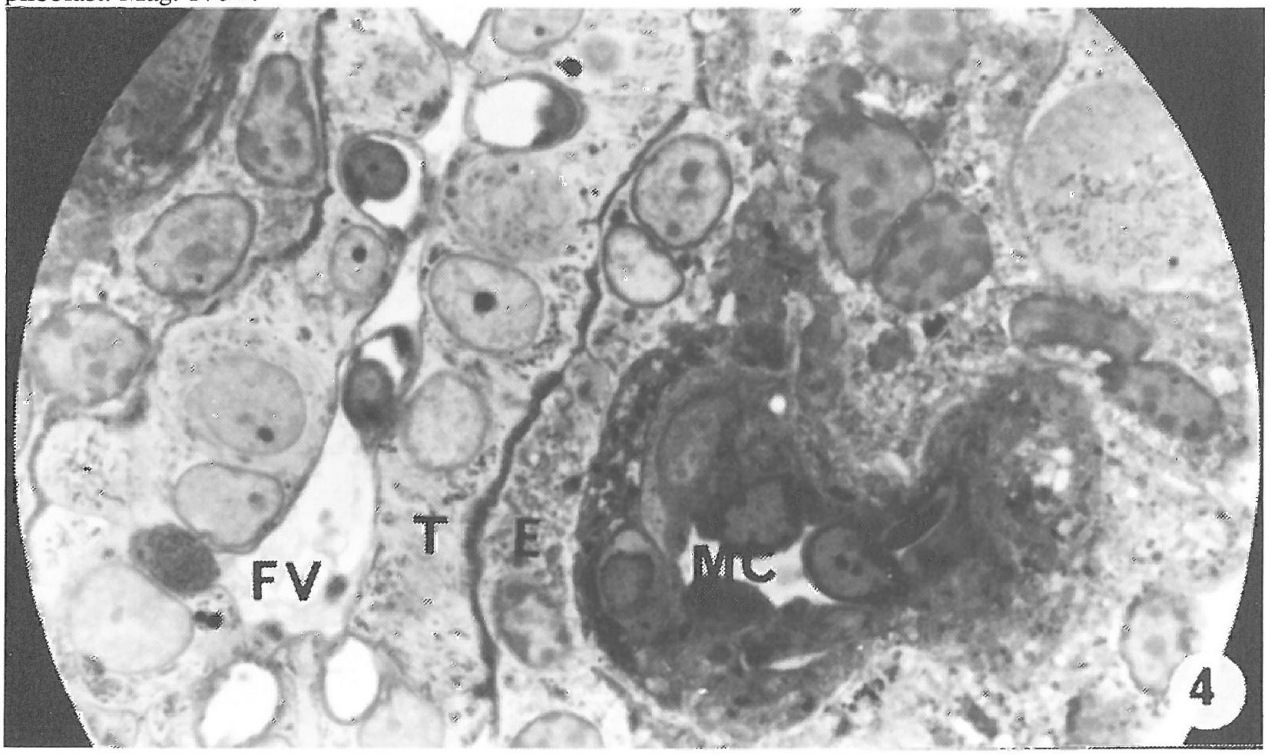

Fig. 4. Light micrograph of the villous epitheliochorial placenta of sheep. Fetal villi are seen in longitudinal section (FV). Trophoblast (T) and maternal epithelium (E). Maternal capillary (MC). Mag. 1100 ×.

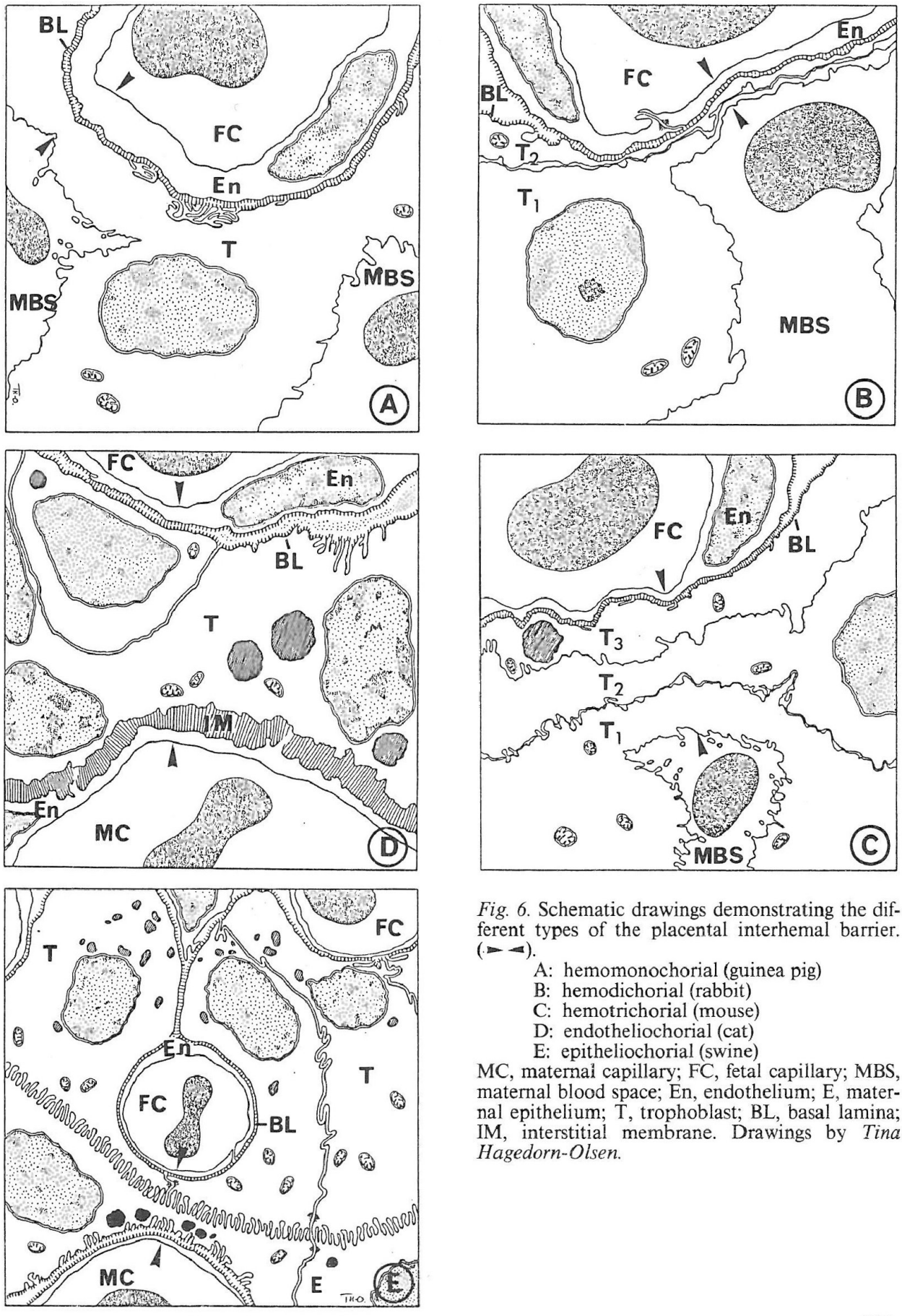

Fig. 6. Schematic drawings demonstrating the different types of the placental interhemal barrier. (►◄).

A: hemomonochorial (guinea pig)
B: hemodichorial (rabbit)
C: hemotrichorial (mouse)
D: endotheliochorial (cat)
E: epitheliochorial (swine)

MC, maternal capillary; FC, fetal capillary; MBS, maternal blood space; En, endothelium; E, maternal epithelium; T, trophoblast; BL, basal lamina; IM, interstitial membrane. Drawings by *Tina Hagedorn-Olsen.*

The interhemal membrane

This structure belongs to the chorioallantoic form of placentation. The uterine and umbilical blood of the interchange areas is separated by layers of cells and amorphous structures, the interhemal membrane or barrier (*Steven* 1975, *King* 1982).

Among the non-cellular structures, basal laminae are always present, their number generally depending on the number of cell layers between the two circulations (Fig. 6). In domestic carnivores, an amorphous interstitial membrane is also present (Fig. 11).

The cells of the interhemal membrane form 2–4 continuous layers. They are partly sealed by tight junctions. The most important part of the chorioallantoic placenta is the trophoblast, which is always present together with the fetal endothelium. This constitutes a 2-layered cellular membrane,

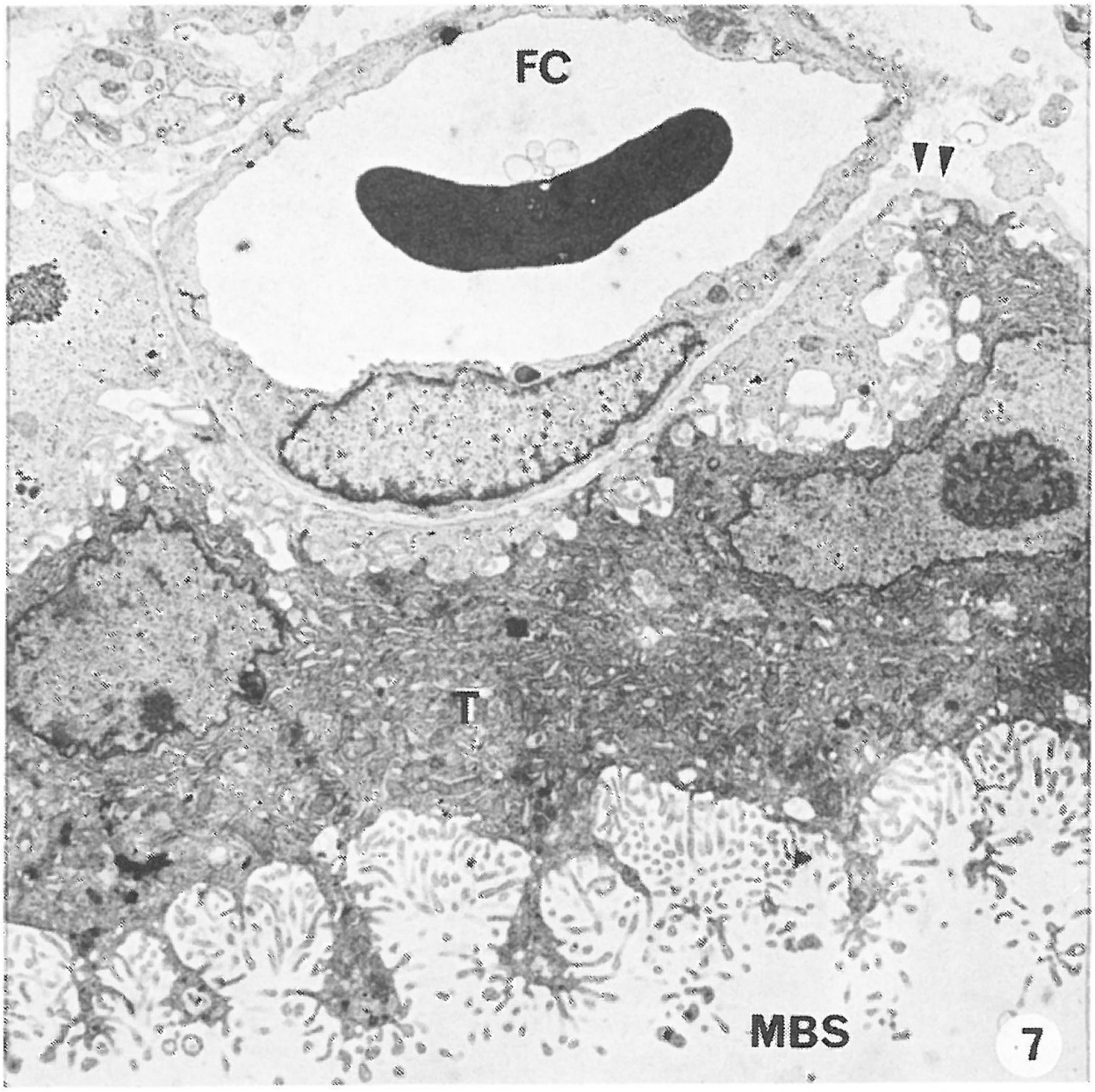

Fig. 7. Macaca mulatta. Electron micropraph of the interhemal barrier of the hemomonochorial primate placenta. Maternal blood space (MBS), trophoblast with microvilli (T), basal lamina (→) and fetal capillary lumen (FC). Mag. 6700 × (by courtesy of *P. W. Luckett,* Anat. Rec. 1970, *167,* 141–164).

where fetal blood flows in capillaries. When the trophoblast is exposed to maternal blood the placenta is termed hemochorial. There can also be 2 or 3 layers of trophoblast. Thus there are 3 types termed hemomonochorial (Figs. 6, 7, 8), hemodichorial (Figs. 6, 9) and hemotrichorial (Figs. 6, 10) (*Enders* 1965).

Maternal cell layers can also enter into the membrane, namely uterine endothelium (endotheliochorial placenta) (Figs. 6, 11) as well as uterine endothelium and epithelium (epitheliochorial placenta) (Figs. 6, 12). In these cases the trophoblast only forms one continuous layer (Table II). The physical distance between maternal and fetal bloodstreams in all placental types apparently decreases in the late stages of gestation to about 2 μm in the thinnest parts.

The blood flow interrelationship

The materno-fetal vascular arrangement in the placental exchange area is an important criterion for placental effectiveness. The study of vascular casts combined with serial sections for light microscopy has revealed combinations of 3 different principles, namely multivillous, crosscurrent and counter-

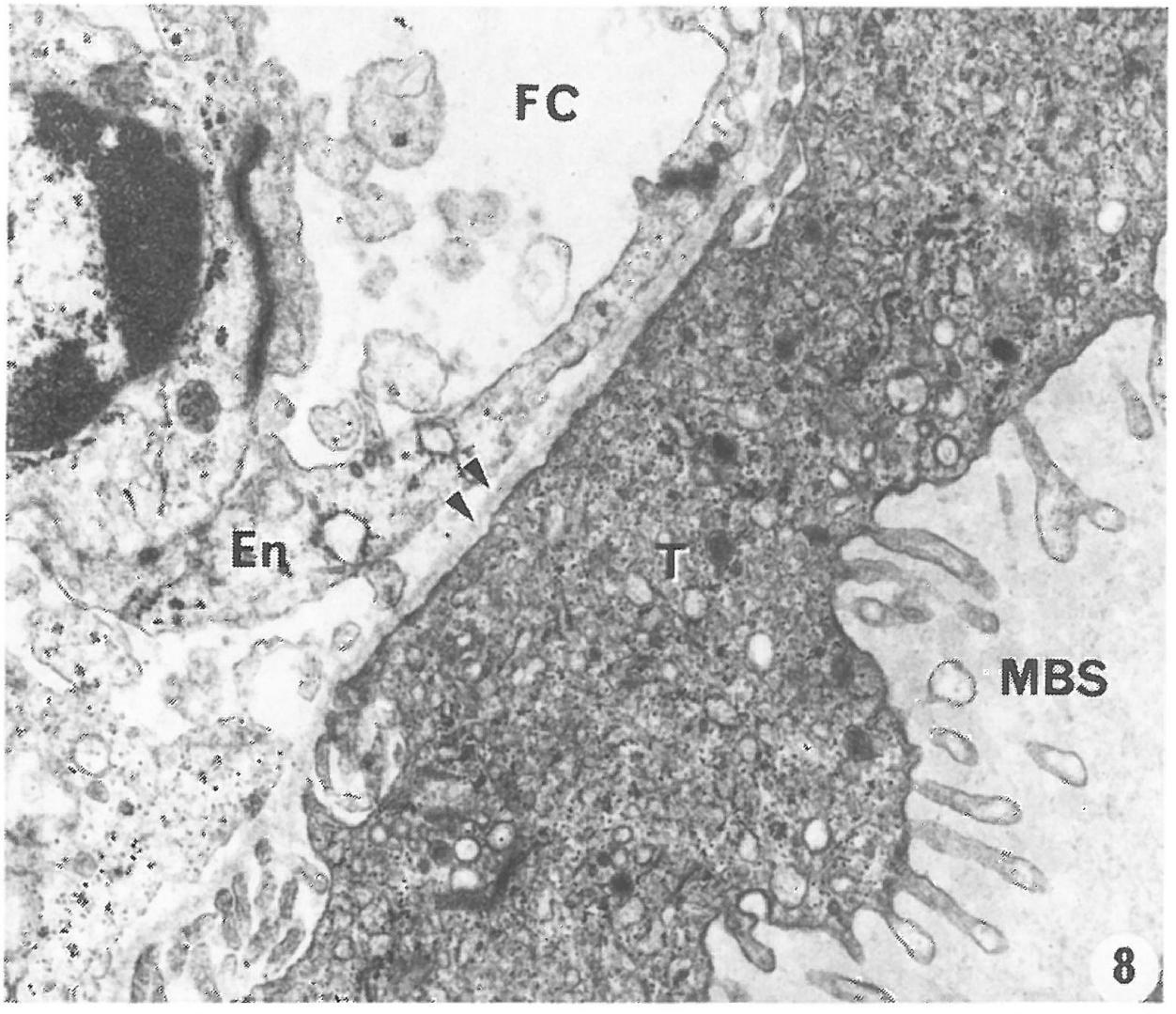

Fig. 8. Guinea pig. Electron micrograph of the interhemal barrier of the hemomonochorial guinea pig placenta. Maternal blood space (MBS), one layer of trophoblast (T), basal lamina (→) and fetal capillary endothelium (En), fetal capillary lumen (FC). Mag. 22000 ×.

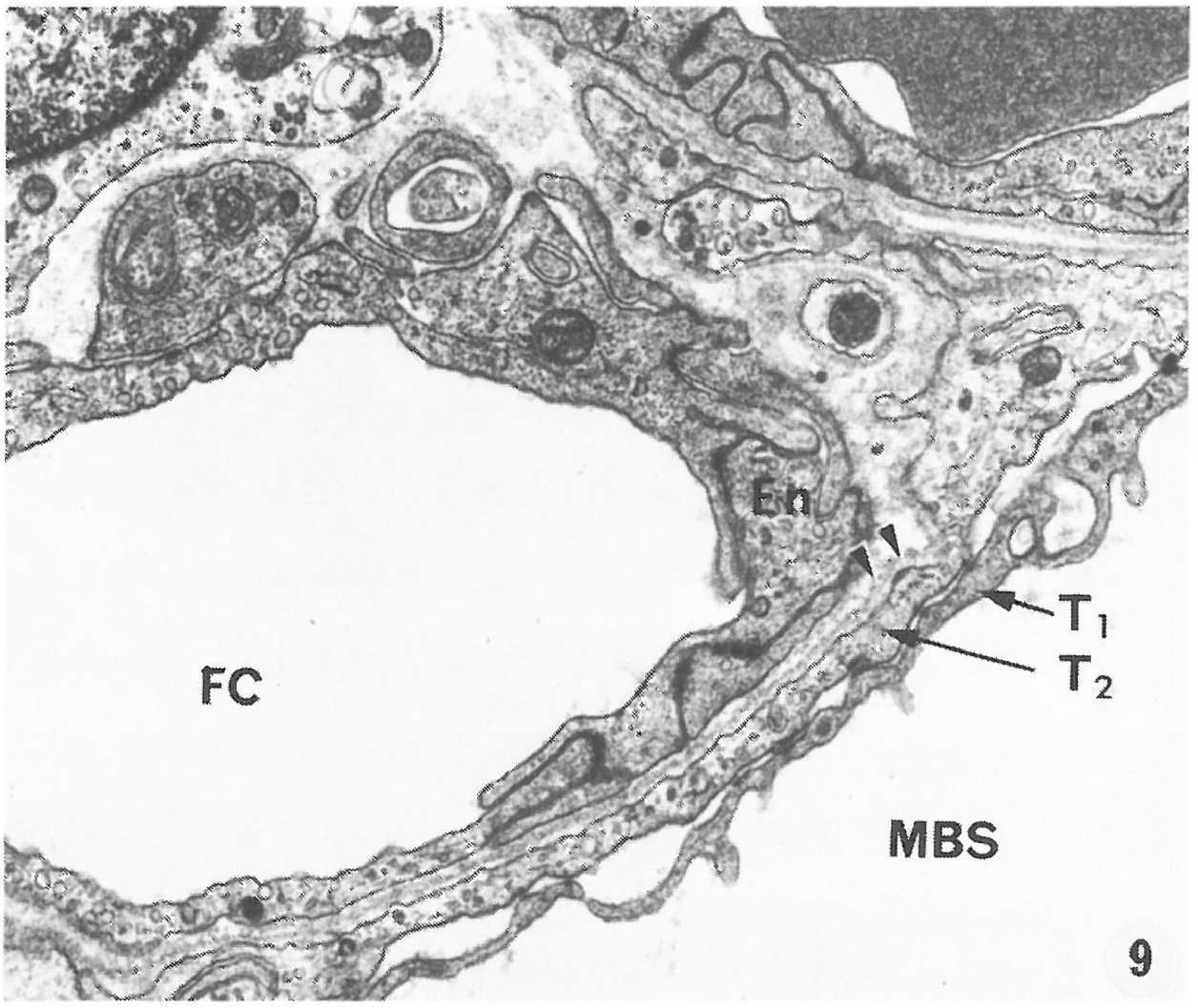

Fig. 9. Rabbit. Electron micrograph of the interhemal barrier of the hemodichorial rabbit placenta. Maternal blood space (MBS), two layers of trophoblast (T_1, T_2), basal lamina (→) fetal capillary lumen (FC), fetal capillary endothelium (En). Mag. 22000 ×.

current (cf. *Dantzer et al.* 1988). The assumed effectiveness increases from multivillous to crosscurrent and to countercurrent as the most efficient exchange system. This efficiency is also partly reflected in gestation time, neonatal weight and development (Table I). The vascular arrangement is to some extend dependent on internal placental structure and components of the interhemal membrane, as the human hemomonochorial and the goat epitheliochorial placenta both have a multivillous type of blood flow and a villous type of fetomaternal interdigitation. In the guinea pig hemomonochorial and in the rabbit hemodichorial placenta with a labyrinthine type of interrelations, the blood flow is countercurrent. This is also the case for the folded, epitheliochorial pig placenta where the blood flow interrelation is predominantly of the countercurrent type with some crosscurrent arrangement as well (*Leiser & Dantzer* 1988). The one-way crosscurrent placenta of the cat represents a middle efficiency (*Leiser & Kohler* 1984).

Functions

The materno-fetal attachment forms an an-

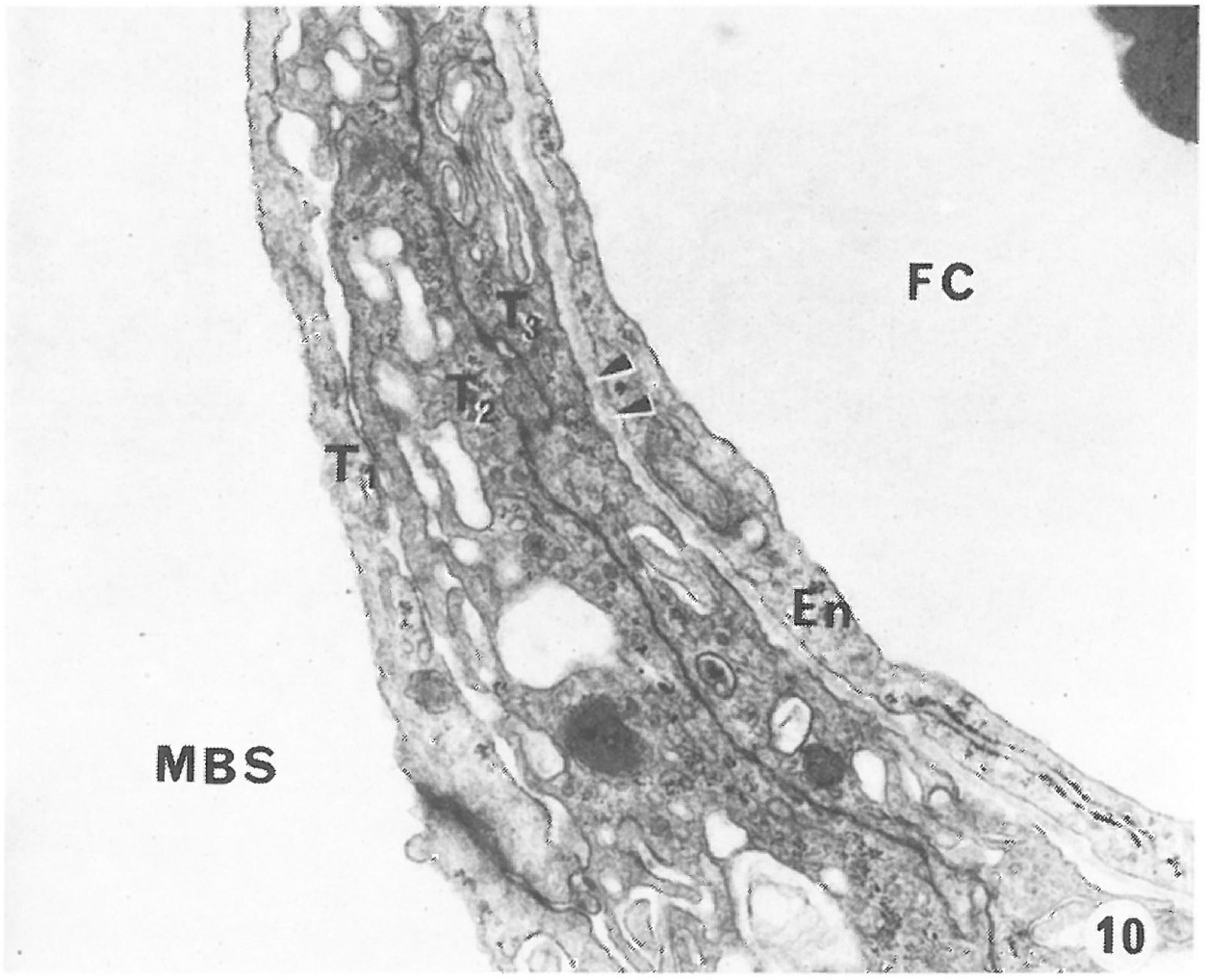

Fig. 10. Mouse. Electron micrograph of the interhemal barrier of hemotrichorial mouse placenta. Maternal blood space (MBS), three layers of trophoblast (T_1, T_2, T_3), basal lamina (→), fetal endothelium (En) and fetal capillary lumen (FC). Mag. 22000 ×.

choring device for the fetus. The surrounding amniotic sac provides buoyancy and freedom of growth and movement in an aquatic environment. The amniotic fluid offers constant thermal, osmotic and chemical conditions (*Björkman* 1970, 1973). The allantois, when forming a sac, collects fetal urine and participates in ionic and aquatic regulation and provides an extrafetal "circulation" (*Skydsgaard* 1965a, b). The placenta, mainly the trophoblast, also carries out metabolic functions such as synthesis, e.g. of hormones, storage and breakdown of compounds. The inverted yolk sac absorps immunoglobulins in rodents and lagomorphs (*Brambell & Halliday* 1956, *Brambell* 1958).

The main function, however, is physiological exchange over the interhemal membrane. This structure prevents mixing of maternal and fetal blood, but otherwise it constitutes a highly selective combined barrier and transport avenue with uni- or bi-directional traffic. Particles and high-molecular-weight compounds are hindered by basal laminae or the interstitial membrane, which act as filters. Other elements pass through by simple or controlled diffusion (cf. *Faber & Thornburg* 1983).

In the case of simple diffusion, the transfer

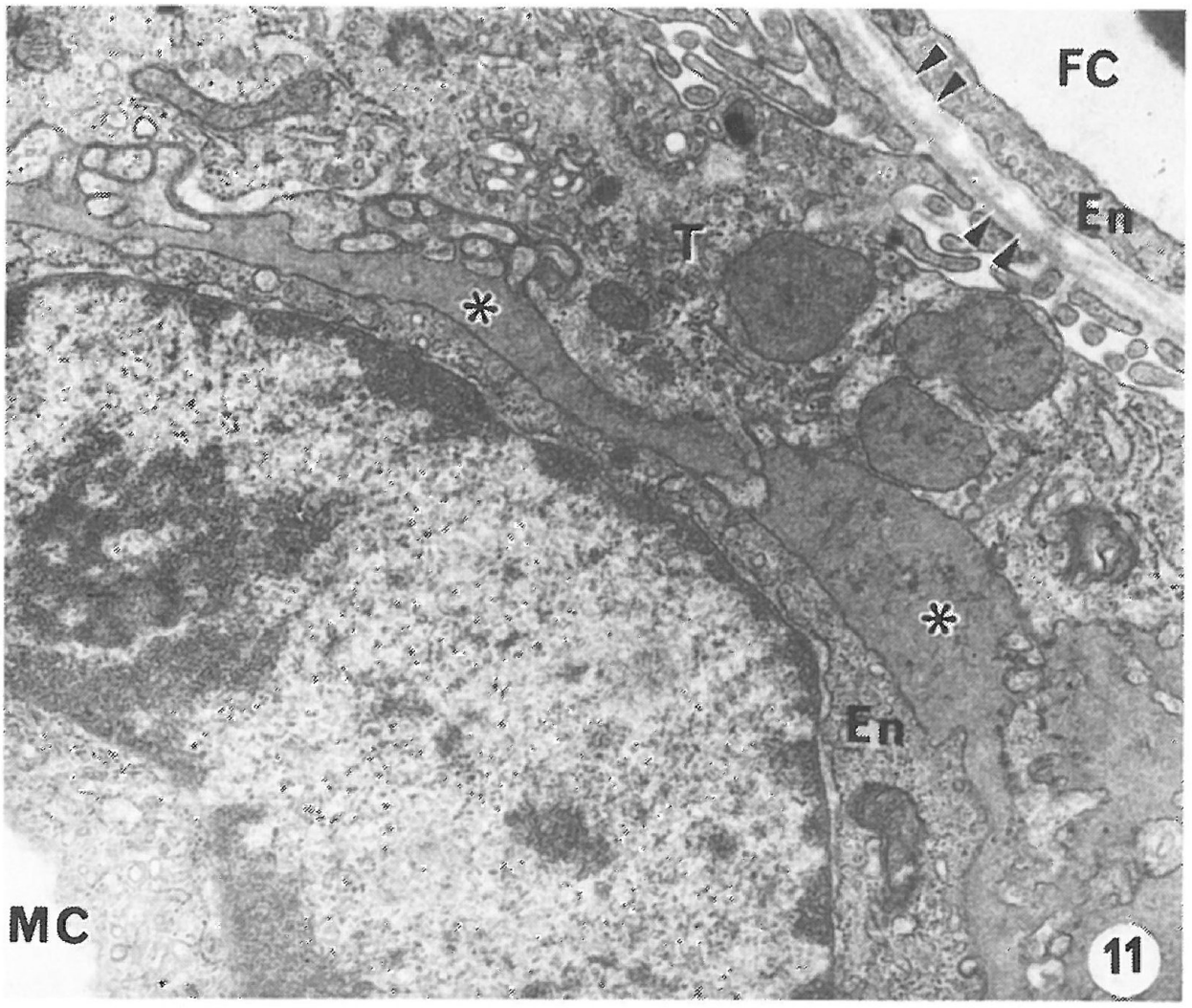

Fig. 11. Cat. Electron micrograph from the interhemal barrier of the endotheliochorial cat placenta. Maternal capillary lumen (MC), endothelium (En), interstitial membrane (*), part of syncytial trophoblast with basal infoldings (T), basal lamina (→), endothelium (En), fetal capillary lumen (FC). Mag. 22000 ×.

rate is directly proportional to the area of exchange and inversely proportional to the thickness of the membrane (Fick's law). Facilitated diffusion is mediated by carrier molecules in the plasma membrane, and is intensified by the presence of microvilli (Figs. 7 & 12) and basal infoldings (Figs. 8 & 11).

Transfer mechanisms also include active transport against the concentration or potential gradient. This requires energy and manifests itself morphologically by the presence of numerous mitochondria in the cytoplasm. Another means of transport is micropinocytosis. Then vesicles traverse cells or undergo internalization and degradation by lysosomes (*Dantzer* 1984 a, 1986).

Transported elements and compounds

The most acute demand is for oxygen. A lung or rather gill function for the exchange of O_2 and CO_2 is therefore of the utmost importance. This transfer is mainly a passive diffusion process. In addition to concentration gradients partly reflected by the feto-maternal blood flow interrelationship (*Silver & Steven* 1975, cf. *Battaglia & Meschia* 1986), the flow velocity of the blood and the

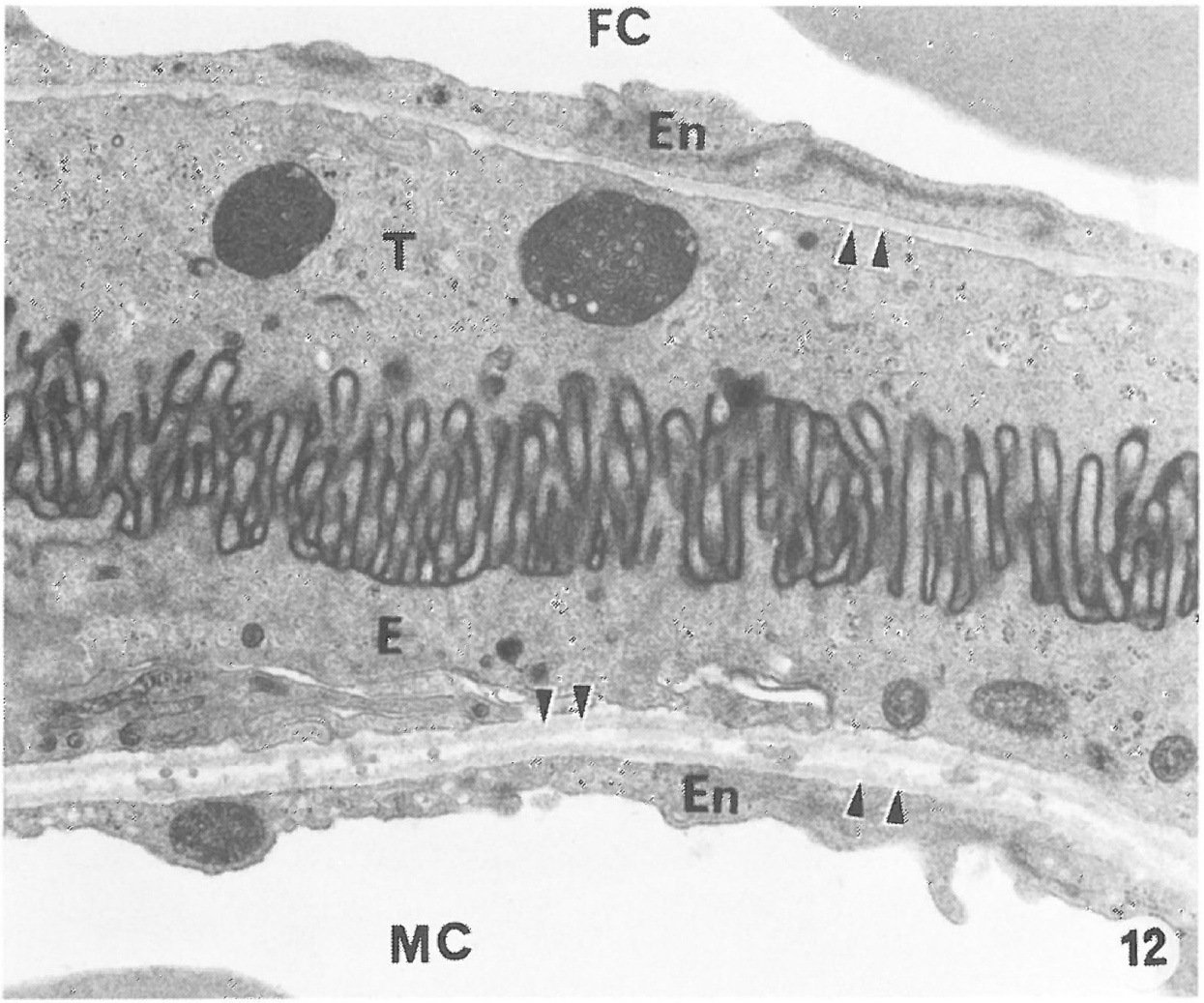

Fig. 12. Swine. Electron micrograph of the interhemal barrier of the epitheliochorial pig placenta. Maternal blood capillary lumen (MC), endothelium (En), basal lamina (→), maternal epithelium (E), trophoblast (T), basal lamina (→), endothelium (En) and fetal capillary lumen (FC). Mag. 22000 ×.

buffer capacity of the plasma can be considered to be part of the placental transport system. It is also noteworthy that embryonic and fetal hemoglobins possess a higher affinity to oxygen than adult hemoglobin. This compensates for the low oxygen tension in the fetal circulation (cf. *Carlson* 1981).

The major metabolic fuel for the fetus is glucose, followed by lactate (cf. *Battaglia & Meschia* 1986). Its transport is active. Amino acids, especially important for protein synthesis in the fetus, are also actively transported against a substantial gradient (*Miller et al.* 1976). The control of transfer across the mature placenta is not fully understood at present. However in a recent review the mechanisms and control of placental transfer are considered, and substances as sodium, potassium, calcium, glucose and amino acids have been selected for a more detailed consideration about the physiological modulation of their transfer rates (*Sibley & Boyd* 1988).

Absorption of iron by the placenta is effected in different ways. In the hemochorial placenta, iron bound to transferrin is picked up by receptors on the surface of the tro-

phoblast and transported further (*Burton* 1982, *Poelmann & Meutick* 1982). In the endotheliochorial placenta of the cat (*Leiser & Enders* 1980, *Malassiné* 1982) and in the dog, maternal erythrocytes are extravasated into the marginal hematoma of the placental girdle, and broken down by lysosomal activity. The epitheliochorial placenta of sheep contains a hematophagous region in the center of the placentomes, where the erythrocytes are dissolved (*Myagkaya & Schellens* 1981). In the epitheliochorial porcine placenta, iron bound to a glycoprotein to form uteroferrin is secreted by uterine glands and delivered to areolae, where it is absorbed by the trophoblast (*Dantzer & Nielsen* 1984, *Raub et al.* 1985). The allantoic fluid of the pig is a reservoir for iron (*Buhi et al.* 1983).

Discussion and conclusions

There is a fundamental difference between the hemochorial and the non-hemochorial types of placentation. The small laboratory animals, rodents and lagomorphs (rabbit), differ mainly in their tooth structure and locomotive apparatus. However, the morphogenesis of their fetal membranes indicates a very close affinity (*Mossman* 1987).

In these hemochorial orders the placenta is a dual organ with a bimodal function. An inverted yolk sac placenta (*Everett* 1935) and an allantoic hemochorial placenta mediate physiological exchange. The yolk sac is dominant early in gestation and the allantochorion in the later stages.

The yolk sac of the rabbit and the guinea pig transmits passive immunity prenatally from the time of implantation, and in the rat and the mouse by the end of gestation (*Brambell* 1958). The route of transmission in man and rhesus monkey is transplacental (*Bangham et al.* 1958). Intermediate transmission of passive immunity from the mother both before and after birth is seen in the rat, the mouse, the dog and probably in the cat (*Brambell* 1958). No immunologically significant amounts of antibodies are transferred over the placental barrier in domestic and laboratory animals with epitheliochorial placenta (*Brambell* 1958).

The neonatal piglet and lamb are essentially devoid of immune antibodies before ingesting colostrum (*Lecce & Morgan* 1962). The absorption of antibodies by the jejunal epithelium, which, like the yolk sac epithelium, is of entodermal origin – is a dramatic process as seen in light and electron microscopy (*Sibalin & Björkman* 1966). With the pig as a model these phenomena have been utilized to study antibody production and absorption in digestive physiology (cf. *Pond & Haupt* 1978).

Common placental features among rodents and rabbit are a hemochorial membrane and the absence of a functional allantoic sac. However, there are also differences in that the interhemal membrane has one (guinea pig, chinchilla), two (rabbit) or three (rat, mouse, hamster) trophoblastic layers (Table II). Although the human placenta also has a hemochorial interhemal membrane, the placental complexes are entirely different in many other respects (yolk sac, internal structure, time of gestation etc., cf. *Ramsey* 1982). The placentas of apes and some monkeys, e.g. rhesus, are better suited as models for the human placenta.

As opposed to the above-discussed animals with hemochorial placenta, the laboratory animals with non-hemochorial placenta, which are domestic animals as well, are provided with a voluminous allantoic sac. The allantois has an important functional and pathological (hydroallantois) role (*Skydsgaard* 1965a, b). The yolk sac produces blood cells and gonia but regresses early in the latter group, and plays no important role in physiological exchange.

When the whole group of laboratory animals is considered, there are many variations in the placental properties. The layers of cells in the interhemal membrane varies between 2 and 4 (Table II), but the membrane in one species can have the same number as that of another unrelated species, e.g. rat vs. swine, 4 layers and rabbit vs. dog,

3 layers. However, some of these layers have different origin and may have different transfer functions. The permeability can therefore not be determined from the thickness or number of layers only.

There is also a considerable variation in length of pregnancy, litter size and development of the newborn young (Table I).

Swine have some anatomical and physiological features in common with humans and are therefore widely used as a model for studying human biology. However, the porcine placenta is entirely different from the primate placenta.

The adult conventional pig is inconviently heavy for many experiments. *Glodek & Oldings* (1981) have examined the use of genetically small pigs, miniature pigs, in biomedical research. For this reason we have included the minipig in our review. We have not noticed any major morphological differences between the placenta of minipigs and domestic pigs, in our own studies (*Dantzer* 1984).

As pointed out above there are many structural and functional differences between different placentas. This should be considered when species are selected for experiments involving the placenta.

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Summary

Many structural and functional differences between various placentas of laboratory animals are pointed out with emphasis on the two major groups, namely hemochorial and non-hemochorial types of placentation. This should be considered when species are selected for experiments involving placenta.

Sammendrag

Forskelle i placentas structur og funktion hos forskellige forsøgsdyr er beskrevet, især med henblik på de to hovedgrupper, nemlig hemochorial og non-hemochorial placentation. Disse forhold bør tages i betragtning ved valg af species til eksperimenter, hvor placentaforholdene vil spille en rolle.

Yhteenveto / K. Pelkonen

Artikkelissa käsitellään eri koe-eläinlajien istukoiden välisiä eroja, kiinnittäen erityistä huomiota kahteen päätyyppiin: hemokoriaaliseen ja non-hemokoriaaliseen tyypiin. Nämä erot tulee huomioida valittaessa koe-eläinlajia istukkaa koskeviin tutkimuksiin.

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