Indian J Physiol Pharmacol 54 (5) 2010 : 65–74

Uterine Receptivity to Embryo Implantation

Allen C. Enders

Department of Cell Biology and Human Anatomy, University of California, Davis, School of Medicine, Davis, California, USA

Introduction

It is both flattering and humbling to be asked to address this topic, since quite a few people at this meeting could address it equally well or better. In fact, Koji wrote a review with almost exactly the same title 20 years ago (1). However, each of us would address the area somewhat differently.

Over the years I have had the privilege of examining blastocysts and implantation sites of a large number of diverse species. It is consequently from the point of view of a comparative anatomist that I view uterine receptivity to embryo implantation. In considering uterine receptivity, we can divide the area into three sequential series of events: the initial preparation of the blastocyst for implantation, the receptivity to blastocyst adhesion and penetration of the uterine luminal epithelium, and accommodation and limitations to expansion of the implantation site.

Preparation of the blastocyst for implantation

During the time when the blastocyst is unattached to the uterine luminal epithelium, there must be sufficient allowance for nourishment of the blastocyst to permit its differentiation. That the uterus has a prominent controlling role is most obvious in those species that undergo a delay of implantation such as the diprotodont marsupials, laboratory rat and mouse, armadillo, roe deer, a few bats, and a number of pinniped and mustelid carnivores. During delay the uterine environment results in relative quiescence of the blastocyst (2). In the rat and mouse there is a slight change in shape and increase in size. In the spotted skunk the effect of the uterine environment on the blastocyst is extreme: delayed blastocysts are small with cells loaded with lipid and little protein synthetic apparatus (3); as implantation approaches, the blastocysts are activated, develop an extensive protein synthetic apparatus, loose lipid, and expand dramatically.

Loss of the zona pellucida prior to implantation is quite variable. In the mouse a zona-lytic agent is produced by the uterus prior to implantation (4). Zona loss is delayed about a day in the rat and mouse during delayed implantation. In the armadillo and roe deer the blastocyst is free of the zona during delay, whereas in carnivores the zona is retained both throughout delay and normally. In some species an extra component is added, such as the capsule in the horse (5) and the gloiolemma in the rabbit (6). There may also be addition to the zona in animals such as the fur seal. Interestingly the zona is lost before implantation from outside the capsule and beneath the gloiolemma in the horse and rabbit respectively. It has been shown that the capsule of the horse is modified in composition by both proteolysis and absorption well before implantation (7). In the rabbit the gloiolemma itself is lost only under

Address for correspondence : A. C. Enders, Department of Cell Biology and Human Anatomy, University of California, Davis, California, 95616, USA. E-mail:acenders@ucdavis.edu

the abembryonic trophoblast as the blastocyst implants.

The syncytial trophoblastic plaques of the carnivore penetrate the zona while it remains for a short time between the epiblast of the blastocyst and the uterine epithelium (8). In the guinea pig, processes from syncytial trophoblast in the abembryonic portion of the blastocyst penetrate the zona pellucida and intrude between uterine epithelial cells at the initiation of implantation (9).

The shape of the uterus, muscle contraction and tone, fluid removal from the uterine lumen, and endometrial edema can all contribute to positioning of the blastocyst within the uterus before implantation. The role of the myometrium is often especially significant. In some species the position of the blastocyst is related to its transport within the oviduct, where it may be situated at the entry into the uterus in some bats (10), or be situated in an adjacent fold of the endometrium as in the armadillo (11). In most species, however, the blastocysts are distributed within the uterus and positioned by muscular activity. In the rabbit, it has been shown that the expanded blastocyst triggers local contraction waves resulting in even spacing of the blastocysts within the uterus (12). In the horse the blastocyst wanders from side to side until day 16, when increased muscle tone positions the blastocyst in one or the other of the potential implantation chambers situated in each horn adjacent to the uterine body (13).

The situation in other species is more subtle. In the rat and mouse, although we speak of the implantation as being antimesometrial, the position of the blastocyst is actually largely central with regard to distance from the myometrium (Fig. 1). The orientation of the rat

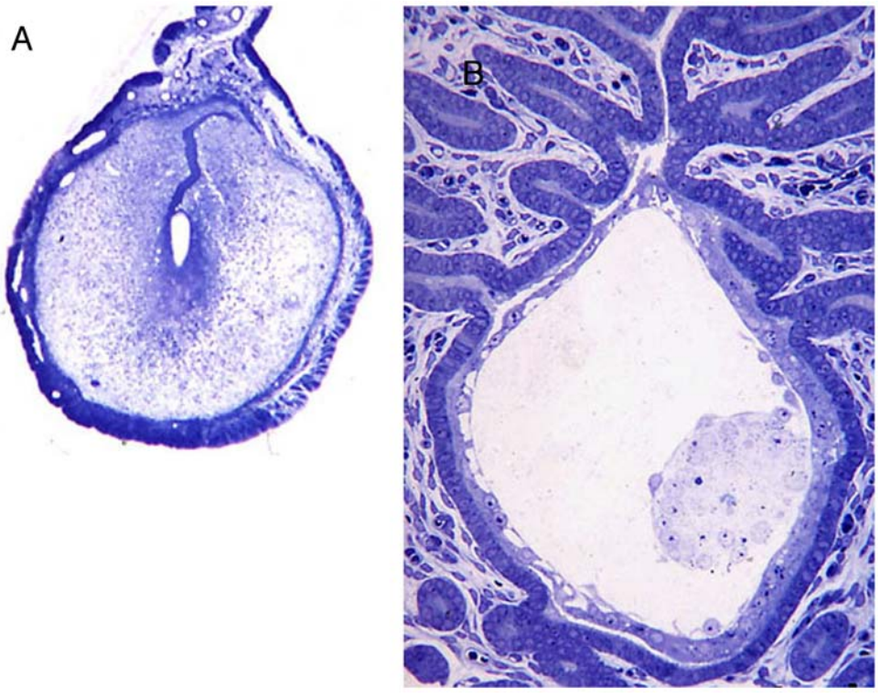

Fig. 1 : Clasped blastocysts. A. The mouse blastocyst on day 5 is situated in the middle of the uterus, equidistant from the myometrium, although it is considered to be antimesometrial. B. The blastocyst of the funnel-eared bat Natalus is fixed in position by swelling of the blastocyst and a glandular endometrium with a closed lumen.

blastocyst is an interaction of the blastocyst shape and luminal closure that results from endocytosis of fluid from the lumen and local endometrial edema (14). The position of the human and macaque blastocyst at implantation is also in the area most remote from contracting uterine muscle (15), with orientation of the blastocyst due to formation of syncytial trophoblast near the inner cell mass. The larger number of blastocysts implanting dorsally rather than ventrally in the human uterus is not readily explained.

Receptivity to adhesion and penetration, or not

In order to have the term implantation apply to all eutherian mammals, we can define it as the time when the blastocyst is both fixed in position and begins to undergo a more intimate relationship with the endometrium. This intimate relationship with the endometrium begins with apposition of trophoblast to the endometrial luminal epithelium, usually followed by interdigitation of microvilli, development of areas of adhesion between the two epithelia, and eventually epithelial penetration in those species that develop endotheliochorial or hemochorial placentas.

The molecules involved in adhesion of trophoblast and endometrial epithelium have been the subject of very considerable study. These molecules have been reviewed by Kimber (16) and by Aplin (17), as well as presentations in this symposium. Aplin and Singh (18) listed 18 soluble mediators associated with implantation in the mouse or human, and 10 paracellular adhesion molecules with a "predicted role implantation" while Kimber listed 32 "molecules potentially involved in the trophoblast adhesion cascade." Clearly, although many of the molecules appear in several species, one can expect differences in their importance in different species as well as redundancy in the involvement of several in any one animal. It is also probable that different molecules are involved with initial adhesion and later stage of adhesion, just as different adhesion partners are involved in rolling as opposed to adhesion to endothelial cells by leukocytes (16). Aplin (17) has recently pointed out what several of us have observed in vivo and in vitro, that there must be some specific adhesion at the lateral folds of the luminal epithelial cells. Whether there is leakage of junctional complex molecules onto these lateral folds or not, the fact that trophoblast penetrates between cells suggests involvement of some of the numerous potential mediators of junctional adhesion at these lateral areas, as well as changes in gap junctional constituents induced both hormonally and locally by the blastocyst or decidua (19).

Many years ago we noted that the ways in which initial penetration of the uterine epithelium by trophoblast occurred could be grouped into three or four types (20). At that time, the types of trophoblast penetration were classified as intrusive, facilitated, or fusing, with direct penetration into epithelial cells as illustrated in the horse added later (21).

Penetration by intrusion is particularly common and is especially fascinating, since it involves both penetration of trophoblast between polarized uterine luminal epithelial cells and yet sharing of portions of the adhesion regions with these same cells. This method of penetration largely retains the integrity of the uterine epithelium, increases the adherence of the developing blastocyst to the epithelium, and directs the intruding trophoblast to the underlying basal lamina of the uterine luminal epithelium. This is the common method in many primates and carnivores, and so far is the most common method of penetrating the uterine luminal epithelium in mammals (Fig. 2A). Sharing of adhesion junctions is also seen in margins of the rat implantation site and during penetration of syncytial trophoblast into capillaries in many species (22).

Facilitated implantation, as seen in the rat

and mouse, is complex (Fig. 2B). There are changes in basal lamina constituents that apparently reduce the adhesion of the uterine epithelium to the basal lamina (23) as well as alterations in junctional complexes. Some uterine epithelial cells undergo apoptosis and are phagocytized by trophoblast (24). Toward the mesometrial end of the implantation site, trophoblast adheres to the lateral surfaces of the epithelial cells and intrudes beneath them. In normal implantation in the rat and mouse, the residual uterine luminal basal lamina is penetrated by processes from decidual cells (25, 26), but processes from trophoblast may penetrate this basal lamina when delay mouse blastocysts are implanting.

Fusion of trophoblast with uterine epithelial cells can be considered a primary, secondary or tertiary event. In the primary case such as the rabbit (Fig. 2C), there is direct fusion between the apical ends of uterine epithelial cells and the syncytial trophoblast of trophoblastic knobs, resulting in a heterokaryon (27). In artiodactyls only certain trophoblast cells, the binucleate cells, fuse with luminal epithelial cells, bringing gonadotropin-secreting cells closer

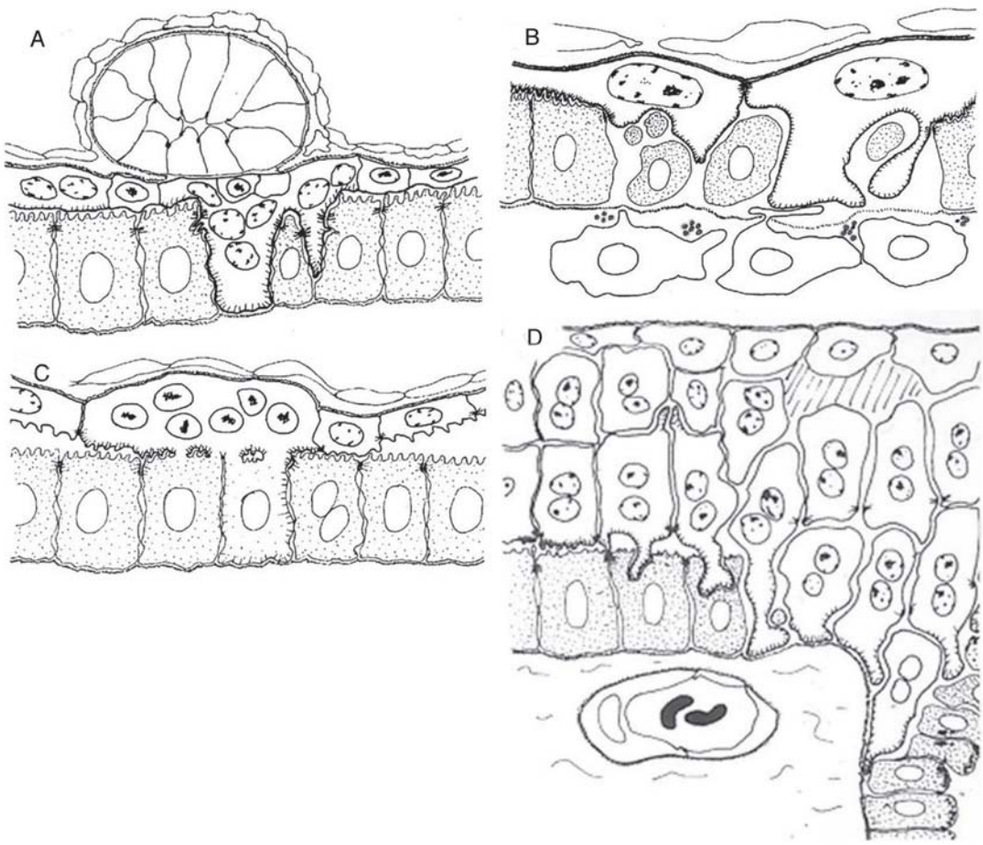

Fig. 2 : Cartoon of different methods of epithelial penetration during implantation. A. Intrusion of trophoblast between uterine epithelial cells, with sharing of adhesion junctions. B. Facilitated penetration involving cell sloughing, apoptosis, and decidual cell penetration of the uterine epithelial basal lamina. C. Fusion of syncytial trophoblast with individual uterine epithelial cells. D. Direct penetration of processes from binucleate trophoblast cells from the equine chorionic girdle into the apical ends of the uterine epithelial cells. Drawings modified from illustrations in Carson et al. (22).

to the endometrium after the initiation of implantation (28). In other mammals such as the marmoset it appears that individual uterine epithelial cells fuse with syncytial trophoblast after they have become largely surrounded by trophoblast (29). This third situation may be fairly widespread in primates, but needs to be verified by such methods as using Y-chromosome markers.

The direct penetration of trophoblast into epithelial cells (Fig. 2D) has been seen only in the mare, where the binucleate trophoblast girdle cells of the blastocyst send processes intruding into the apical ends of the uterine luminal epithelial cells (30, 31). Interestingly these binucleate cells also show basal processes toward underlying girdle cells, are originally slow to penetrate the uterine basal lamina, but eventually penetrate into the endometrial stroma, including lymphatic vessels but not blood vessels (32).

In species in which the entire placenta is epitheliochorial such as the pig, the uterine epithelium resists penetration. It has been suggested that this lack of invasion is an adaptation (33), since Samuel and Perry (34) showed that when inserted interstitially into the uterus, pig trophoblast, instead of being a unilaminar cellular layer, formed syncytial masses.

Blastocyst transfers both to ectopic sites and asynchronously into the uterine lumen have lead to the concept that the uterine luminal epithelium is unique in allowing only a limited time when blastocysts may initiate epithelial penetration and thus establishment of an implantation site. Several investigators (35, 36) illustrated this window of implantation to be quite narrow in laboratory rodents, using blastocyst transfer methods. In the human Wilcox et al. (37) compared the time of first appearance of chorionic gonadotropin in maternal urine with ovulation, and determined that 8 to 10 days separation was optimal and that with a separation of 11 days there was 82% failure of the implantation site. This indicates that the window of implantation in the human is wider than that in laboratory rodents.

Many experiments illustrate that non-uterine sites and non-uterine epithelia are not necessarily as restrictive to trophoblast penetration as the uterine luminal epithelium. Ectopic implantation of the human blastocyst in the oviduct is also considered an indication that uterine luminal epithelium is not essential for blastocyst penetration; however, a recent observation of Fukuda (38) indicates that blastocysts may be able to induce trophinin production in oviductal epithelia, similar to the situation in the uterus. One of the earlier experiments with ectopic placement was the introduction of mouse blastocysts into the anterior chamber of the eye (39). Here the blastocysts successfully penetrated into the stroma and produced hyperemia as well as rapidly increasing the amount of trophoblast. More recently we showed that when rhesus monkey blastocysts are cultured in vitro, the trophoblast underlying the inner cell mass can readily penetrate a number of epithelia, including those derived from liver and from MDCK cells (40). This illustrates further that that the unique aspect of uterine epithelium is not that it is receptive to blastocyst attachment and penetration but that it can be either receptive or resistant.

Accommodation and limitations to expanding the implantation site

One of the general responses of the endometrium to implantation is hyperemia (Fig. 3). However, there is considerable variation in the timing and extent of modification of the endometrial vessels at implantation. The rapid enlargement of the superficial vessels in the baboon facilitates the formation and expansion of the lacunar stage (41). In the macaque, there is an extraordinary modification of the endothelial cells, which become tall cuboidal to columnar, sometimes show apically situated

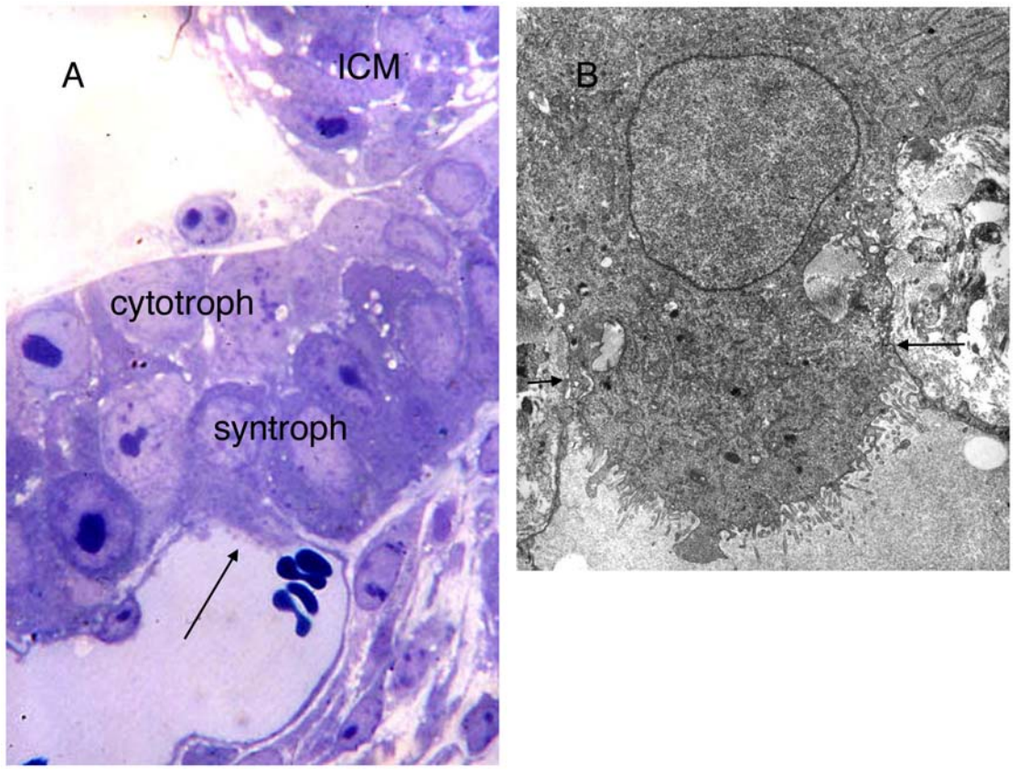

Fig. 3 : Penetration of trophoblast into dilated endometrial capillaries during implantation in the baboon. A. Syncytial trophoblast penetrates into the capillary lumen (arrow). B. Electron micrograph showing microvillous trophoblast penetrating into an underlying capillary (between arrows).

nuclei, and are the only endothelial cells to become TGFa positive (42). This transition is a non-specific response that can be induced by trauma or by relaxin (43, 44). The forming endometrial cups of the mare are unusual in that the invasion of trophoblast cells elicits little or no increase in localized vasculature; indeed the regions with cups appear pale in comparison to the rest of the endometrium (32, 45). It is possible that in some of the bats with delayed development, in which implantation occurs but both placenta and fetus are initially slowed in development, there may be restricted vascularity. A remarkable example of vascular accommodation is that of the nine-banded armadillo (46). In this species the uterus is essentially pre-receptive in that the blastocyst is held in the fundic end where it is closest to the endometrial blood sinuses. Placental villi penetrate into these sinuses, then expand into the body of the uterus resulting in an intervillous region bounded by maternal endothelial cells and with a pre-established directional blood flow.

Epithelial plaque formation consists of hypertrophy of luminal epithelial cells and cells in the necks of uterine glands, which occurs in a number of primates but not anthropoid primates (47, 48). In the macaque these cells store glycogen, but by about day 16 begin to degenerate. The presence of such clusters of cells tends to limit the areas of invasion of cytotrophoblast following the lacunar stage in the macaque (49). Later as plaque cells

degenerate they appear to contribute nutritive materials and to form part of a necrotic layer that separates much of the trophoblastic shell from the endometrium for a few days. In this fashion they may be one of the factors limiting the extent of endometrial invasion by cytotrophoblast during placenta formation in this species.

Decidualization, the modification of stromal cells of the endometrium from fusiform to rounded polyhedral shape, is widespread but not universal in species with hemochorial placentation. These changes are brought about by activation of transcription (50) and involve changes at both the transcriptome and proteome level (51). In the rat and mouse the role of these cells in shaping the implantation chamber, encouraging its expansion by degeneration in the antimesometrial portion of the chamber, its role in eliminating the uterine epithelium mesometrial to the initial implantation site, and its eventual disintegration antimesometrially to permit inversion of the yolk sac are all well documented. Although decidualization probably helps in determining the arrangement of the vessels in the mesometrial area of the implantation site, stimulation of angiogenesis probably comes from uterine dendritic cells (52). Originally the nature and function of decidualization in primates has been less revealing. It is encouraging to see recent studies by several of the scientists at this symposium indicating the ways in which decidual cells may act to limit the expansion of the implantation site beyond normal parameters (53-55). Because endometrial responses can be studied in vivo in non-human primates, they can serve to compare with the in vitro approaches commonly used with the human. The macaque has already been useful in showing that, although the three major responses to blastocyst implantation- venule expansion, plaque formation, and decidual cell formation- can be induced by trauma, it does not mean that all changes will be the same as in pregnancy, since IGFbp-1 expression in endometrial glands is different (56).

Local endometrial conditions clearly control leukocyte trafficking and changing cell populations (57). The dramatic changes in some NK cells and their possible roles in relationship to different aspects of implantation remain areas of current research (58, 59). From a morphological point of view, one of the intriguing unsolved relationships is the way in which decidual cells may surround individual NK cells of the LGL type in some primates (60).

While this kaleidoscopic view has emphasized the endometrium and other conference members have appropriately focused on signalling between trophoblast and uterus, some changes during implantation appear to be intrinsically controlled. The syncytial trophoblast that initially penetrates the endometrium in primates and other species tends to be multinucleate with non-mitotically active nuclei, and survives for only a short period of time (42). It is this syncytial trophoblast that also is the first to breach maternal vessels in the macaque, baboon and human. Is the limited duration of this type of trophoblast intrinsically controlled or are we simply unaware of factors from the endometrium that might contribute to limiting its life span?

The later and more extensive invasion by cytotrophoblast that occurs during placental expansion has and is being extensively studied. But why do these cell columns occur only from the late lacunar stage on? Why do these primates that we study bother with a lacunar stage rather than invading initially with cytotrophoblast? The non-human primates can be useful in studying these questions from stages that are unavailable in the human, and are quite different in non-primates.

References

1. Yoshinaga K. Uterine receptivity for blastocyst implantation. *Ann NY Acad Sci* 1988; 541: 424–431.
2. Lopes FL, Desmarais JA, Murphy BD. Embryonic diapause and its regulation. *Reprod* 2004; 128: 669–678.

3. Enders AC, Schlafke S, Hubbard NE, Mead RA. Morphologic changes in the blastocyst of the western spotted skunk during activation from delayed implantation. *Biol Reprod* 1986; 34: 423–437.

4. Pinsker MC, Sacco AC, Mintz B. Implantation-associated proteinase in mouse uterine fluid. *Devel Biol* 1974; 38: 285–290.

5. Flood PF, Betteridge KJ, Diocee MS. Transmission electron microscopy of horse embryos 3-16 days after ovulation. *J Reprod Fertil* 1982; Suppl 32: 319–327.

6. Denker HW, Gerdes HJ. The dynamic structure of rabbit blastocyst coverings. I. Transformation during regular preimplantation development. *Anat Embryol* 1979; 157: 15–34.

7. Quinn BA, Hayes MA, Waelchli RO, Kennedy MW, Betteridge KJ. Changes in major proteins in the embryonic capsule during immobilization (fixation) of the conceptus in the third week of pregnancy in the mare. *Reprod* 2007; 134: 161–170.

8. Enders AC, Schlafke S. Implantation in the ferret: epithelial penetration. *Am J Anat* 1972; 133: 291–326.

9. Enders AC, Schlafke S. Cytological aspects of trophoblast-uterine interaction in early implantation. *Am J Anat* 1969; 125: 1–30.

10. Rasweiler JJ IV. Early embryonic development and implantation in bats. *J Reprod Fertil* 1979; 56: 403–416.

11. Enders AC. Implantation in the nine-banded armadillo: how does a single blastocyst form four embryos? *Placenta* 2002; 23: 71–85.

12. Boving BG. Rabbit blastocyst distribution. *Am J Anat* 1956; 98: 403–434.

13. Enders AC, Liu IKM. Lodgement of the equine blastocyst in the uterus from fixation through endometrial cup formation. *J Reprod Fertil* 1991; Suppl 44: 427–438.

14. Enders AC. The implantation chamber, blastocyst and blastocyst imprint of the rat: a scanning electron microscopy study. *Anat Rec* 1975; 182: 137–150.

15. Enders AC. Perspectives on implantation. *Infertil Reprod Med Clinics NA* 2001; 12: 251–269.

16. Kimber SJ, Spanswick C. Blastocyst implantation: the adhesion cascade. *Semin Cell Devel Biol* 2000; 11: 77–92.

17. Aplin JD. Embryo implantation: the molecular mechanism remains elusive. *Reprod Biomed Online* 2006; 13: 933–939.

18. Aplin JD, Singh H. Bioinformatics and transcriptomics studies of early implantation. *Ann NY Acad Sci* 2008; 1127: 116–120.

19. Grummer R, Hewitt SW, Traub O, Korach KS, Winterhager E. Different regulatory pathways of endometrial connexin expression: preimplantation hormonal-mediated pathway versus embryo implantation-initiated pathway. *Biol Reprod* 2004; 71: 273–281.

20. Schlafke S, Enders AC. Cellular basis of interaction between trophoblast and uterus at implantation. *Biol Reprod* 1975; 12: 41–65.

21. Enders AC, Liu IKM, Mead RA, Welsh AO. Active and passive morphological interactions of trophoblast and endometrium during early implantation. In: Dey SK, ed. Molecular and Cellular Aspects of Periimplantation Processes. New York, Springer Verlag 1995: 168–82.

22. Carson DD, Bagchi I, Dey SK, Enders AC, Fazleabas AT, Lessey BA, Yoshinaga K. Embryo implantation. *Devel Biol* 2000; 223: 217–237.

23. Blankenship TN, Given RL. Loss of laminin and type IV collagen in uterine luminal epithelial basement membranes during blastocyst implantation in the mouse. *Anat Rec* 1995; 243: 27–36.

24. Parr EL, Tung HN, Parr MB. Apoptosis as the mode of epithelial cell death during embryo implantation in mice and rats. *Biol Reprod* 1987; 36: 211–225.

25. Schlafke S, Welsh AO, Enders AC. Penetration of the basal lamina of the uterine luminal epithelium during implantation in the rat. *Anat Rec* 1985; 212: 47–56.

26. Blankenship TN, Given RL. Penetration of the uterine epithelial basement membrane during blastocyst implantation in the mouse. *Anat Rec* 1992; 233: 196–204.

27. Enders AC, Schlafke S. Penetration of the uterine epithelium during implantation in the rabbit. *Am J Anat* 1971; 132: 219–240.

28. Wooding FBP. Role of binucleate cells in fetomaternal cell fusion at implantation in the sheep. *Am J Anat* 1984; 170: 233–250.
29. Enders AC, Lopata A. Implantation in the marmoset monkey: expansion of the early implantation site. *Anat Rec* 1999; 256: 279–299.
30. Enders AC, Liu IKM. Trophoblast-uterine interactions during equine chorionic girdle cell maturation, migration, and transformation. *Am J Anat* 1991; 192: 366–381.
31. Allen WR, Hamilton DW, Moor RM. The origin of equine endometrial cups. II. Invasion of the endometrium by trophoblast. *Anat Rec* 1973; 177: 485–502.
32. Enders AC, Lantz KC, Schlafke S, Liu IKM. New cells and old vessels: the remodeling of the endometrial vasculature during establishment of endometrial cups. *Biol Reprod 1995*; Mono 1: 181–90.
33. Bowen JA, Burghardt RC. Cellular mechanisms of implantation in domestic farm animals. *Semin Cell Devel Biol* 2000; 11: 93–104.
34. Samuel CH, Perry JS. The ultrastructure of pig trophoblast transplanted to an ectopic site in the uterine wall. *J Anat* 1972; 113: 139–149.
35. Noyes RW, Dickmann Z, Doyle, LL, Gates AH. Ovum transfers, synchronous and asynchronous, in the study of implantation. In: Enders AC, ed. Delayed Implantation. Chicago, Univ of Chicago Press 1963: 197–211.
36. Psychoyos A. Endocrine control of egg implantation. *Handb Physiol* 1973; Sect 7 Part 1 Vol. I: 187–215.
37. Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. *N Engl J Med* 1999; 340: 1796–1799.
38. Nakayama J, Aoki D, Suga T, et al. Implantation-dependent expression of trophinin by maternal fallopian tube epithelia during tubal pregnancies: possible role of human chorionic gonadotrophin on ectopic pregnancy. *Am J Pathol* 2003; 163: 2211–2219.
39. Fawcett DW, Wislocki GB, Waldo CM. The development of mouse ova in the anterior chamber of the eye and in the abdominal cavity. *Am J Anat* 1947; 81: 413–443.
40. Enders AC, Douglas GC, Meyers S, VandeVoort CA. Interactions of macaque blastocysts with epithelial cells *in vitro*. *Hum Reprod* 2005; 20: 3026–3032.
41. Enders AC. Overview of the morphology of implantation in primates. In: Wolf DP, Stouffer RL, Brenner RM, eds. In Vitro Fertilization and Embryo Transfer in Primates. New York, Springer-Verlag 1993: 145–57.
42. Enders AC. Implantation in the macaque: expansion of the implantation site during the first week of implantation. *Placenta* 2007; 28: 794–802.
43. Dallenbach-Hellweg G, Dawson AB, Hisaw FL. The effect of relaxin on the endometrium of monkeys. Histological and histochemical studies. *Am J Anat* 1966; 124: 307–340.
44. Denker H-W, Enders AC, Schlafke S. Bizarre hypertrophy of vascular endothelial cells in rhesus monkey endometrium: experimental induction and electron microscopical characteristics. *Verh Anat Gesel* 1985; 79: 545–548.
45. Enders AC, Jones CJ, Lantz KC, Schlafke S, Liu IKM. Simultaneous exocrine and endocrine secretion: trophoblast and glands of the endometrial cups. *J Reprod Fertil* 2000; Suppl 56: 615–625.
46. Enders AC. Placentation in armadillos, with emphasis on development of the placenta in polyembryonic species. In: Loughry WJ, Vizcaino SF, eds. Biology of the Xenarthra. Gainesville, Univ Press of Florida 2008: 172–180.
47. Enders AC. Structural responses of the primate endometrium to implantation. *Placenta* 1991; 12: 309–325.
48. Jones CJ, Fazleabas AT. Ultrastructure of epithelial plaque formation and stromal cell transformation by post-ovulatory chorionic gonadotrophin treatment in the baboon (*Papio anubis*). *Hum Reprod* 2001; 16: 2680–2690.
49. Enders AC. Transition from lacunar to villous stage of implantation in the macaque, including estabishment of the trophoblastic shell. *Acta Anat* 1995; 152: 151–169.
50. Nakamura H, Kimura T, Koyama S, et al. Mouse model of human infertility: transient and local

inhibition of endometrial STAT-3 activation results in implantation failure. *FEBS Lett* 2006; 580: 2717–2722.

51. Gellersen B, Brosens IA, Brosens JJ. Decidualization of the human endometrium: mechanisms, functions, and clinical perspectives. *Semin Reprod Med* 2007; 25: 445–453.
52. Pollard JW. Uterine DCs are essential for pregnancy. *J Clin Invest* 2008; 118: 3832–3835.
53. Cohen M, Bischof P. Factors regulating trophoblast invasion. *Gynecol Obstet Invest* 2007; 64: 126–130.
54. Fujiwara H. Membrane-bound peptidases regulate human extravillous trophoblast invasion. *Placenta* 2007; 28 suppl A: S70–S75.
55. Paiva P, Salamonsen LA, Manuelpillai U, Dimitriadis E. Interleukin 11 inhibits human trophoblast invasion indicating a likely role in the decidual restraint of trophoblast invasion during placentation. *Biol Reprod* 2008.
56. Ghosh D, Bell SC, Sengupta J. Immunohistological localization of insulin-like growth factor binding protein-1 in primary implantation sites and trauma-induced deciduomal tissues of the rhesus monkey. *Placenta* 2004; 25: 197–207.
57. Slukvin II, Breburda EE, Golos TG. Dynamic changes in primate endometrial leukocyte populations: differential distribution of macrophages and natural killer cells at the rhesus monkey implantation site and in early pregnancy. *Placenta* 2004; 25: 297–307.
58. Nakashima A, Shiozaki A, Myojo S, et al. Granulysin produced by uterine natural killer cells induces apoptosis of extravillous trophoblasts in spontaneous abortion. *Am J Pathol* 2008; 173: 653–664.
59. Trowsdale J, Moffett A. NK receptor interactions with MHC class I molecules in pregnancy. *Semin Immunol* 2008; 20: 317–320.
60. Jones CJ, Aplin JD, Fazleabas AT. Decidual stromal cell-lymphocyte interactions in pregnancy. *Placenta* 2001; 22: 380–382.