MENSTRUATION: A NONADAPTIVE CONSEQUENCE OF UTERINE EVOLUTION

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ABSTRACT

Although adaptive explanations for menstruation go back at least twenty-five hundred years, in the last decade two new hypotheses have been advanced. The first suggests that menstruation evolved to cleanse the uterus of pathogens introduced by sperm, and the second argues that the function of endometrial regression (with the associated menstruation in humans) is to save energy by getting rid of tissue, rather than maintaining it in the absence of an available blastocyst. Both these suggestions may be questioned on the grounds that they do not take into account the physiology of the reproductive processes involved.

Menstruation is not an independent physiological process and is unlikely to have been selected for independently of the evolutionary events that led to it. Furthermore, most primitive menstruating animals would have menstruated infrequently, and many may have reproduced or died without ever menstruating. In order to provide a context for understanding how menstruation may have come about, the evolution of the female vertebrate reproductive tract is briefly reviewed.

In later stages, the coevolution of the embryo and uterus resulted in an intimate association between the trophoblast and the uterine blood vessels. As the embryo became more invasive, the uterus responded with increased cellular growth and differentiation of the endometrium to accommodate it. This reached its peak in mammals (such as rodents and humans), where the embryo passes through the epithelium into the endometrial stroma, which responds with differentiation of cells and blood vessels.

Progesterone, secreted after ovulation, plays a crucial role in preparation for pregnancy. In addition to its well-known effects on the uterus, progesterone may be important in suppressing the inflammatory reaction that would be expected in response to the presence of a foreign body, such as an embryo. It is also suggested that vascular and cellular differentiation of the endometrial stroma has evolved by adaptation of the inflammatory (granulation tissue) reaction. When progesterone levels fall at the end of the cycle, there is tissue breakdown and bleeding. The uterus then reforms for the next ovulatory cycle.

It is shown that the female reproductive tract has multiple functions that must occur in sequence. The coevolution of the embryo and maternal tract thus led to the close contact of two genetically different tissues, and problems such as the inflammatory reaction had to be overcome. Menstruation is a necessary consequence of these evolutionary changes, and needed no adaptive value in order to evolve.

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INTRODUCTION

TWO RECENT PAPERS in *The Quarterly Review of Biology* proposed a function for menstruation. In the first, Profet (1993) suggested that the purpose of menstruation is to assist the uterus in removing pathogens introduced with the sperm at coitus. This was discussed by Finn (1994a) and shown on several grounds to be unlikely. In the second paper, Strassmann (1996) disputes the pathogen theory and puts forth the alternative hypothesis that endometrial regression (and menstruation, when it occurs) conserves energy. Strassmann suggests that if regression did not occur at the end of the infertile cycle, energy would have to be expended to maintain the endometrium in a differentiated state when it is not needed. The problem with this explanation is that the indefinite maintenance of the uterus in a highly differentiated condition, ready for implantation of a blastocyst, is not a physiologically viable option since it would prevent the establishment of the conditions necessary for a future pregnancy. In order to become pregnant after an infertile cycle, a female has to both ovulate and be inseminated; the sperm have to be transported through the uterus and be capacitated (by contact with uterine fluid) in order for fertilization to take place.

After the arrival of the blastocyst in the lumen of the uterus, the uterine glands secrete histotroph for a short period, and then the endometrium differentiates in preparation for implantation. Thus there is a cycle of changes in the uterus as it prepares for pregnancy. These can be seen clearly in histological sections of uteri taken from animals during estrus and just before implantation. At the time of copulation (estrus in most mammals) and fertilization, the uterine lumen is filled with fluid, providing a suitable environment for sperm transport and sperm capacitation. By contrast the uterine lumen at the time of implantation is completely closed (Nilsson 1966), with very little fluid, providing the conditions necessary for attachment of the blastocyst.

From the point of view of evolution, indefinite maintenance of the uterus in preparation for implantation would be counterproductive and would not have been selected for. The uterus is not an organ with a single function; unlike the heart or kidney, it does not continue to perform the same function from birth to death. For the kidney, this is the production of urine, and differentiated nephrons must be maintained throughout life. In contrast, the female reproductive tract has evolved by gradual adaptation over millions of years, and performs several different functions that must occur in an orderly sequence correlated with other events necessary to effect pregnancy. For pregnancy to happen, the various tissues of the endometrium undergo cycles of cell proliferation, cell differentiation and cell death (see Finn 1994b).

The suggestions made by Profet and Strassmann are among the more recent ideas about the purpose of menstruation, which extend back some two thousand five hundred years. Aristotle, the father of biology, in the 4th century BC suggested that menstrual fluid provided the inanimate matter from which embryos are molded by the action of semen (see Needham 1959). Galen (quoted in Grant 1974), a medical pioneer, thought that menstruation was a way of getting rid of superfluous blood that collected in women, and even provided guidance (quoted by Trotula in the 11th century) on how blood should be removed from women suffering from amenorrhea (Mason-Hohl 1940). The great 19th century zoologists Heape (1900) and Marshall (1910) thought that menstruation was analogous to proestrous bleeding in dogs, but did not assign any function to it. Medical scientists at the time, however, showed that menstrual bleeding occurred at the end of the ovulatory cycle, not at the time of ovulation (Grosser 1910), and consequently could not be analogous to proestrous bleeding.

The desire to find a reason for menstruation, however, persisted. Among the possibilities that have been suggested is the idea that menstruation is necessary if a woman is to ovulate again, thus allowing another opportunity for pregnancy (Fox 1985). Although it is true that the endometrial tissue in the uterus must be removed periodically to make way for insemination and pregnancy, as discussed above, this requirement would also apply to nonmenstruating animals. In fact, the restoration of the ovulatory cycle is no faster in humans than in most other mammals. One of the most imagi-

native suggestions is that menstruation provides women with vicarious sexual satisfaction, thus preserving their virginity (Ruddock 1930). The author was clearly not sure of this explanation, for he added that the modern view was that the function of menstruation is to get rid of unimplanted embryos, a theme taken up recently by Clarke (1994). This consequence of menstruation may, in fact, be a useful accompaniment to the tissue destruction and bleeding. However, the problem of dead embryos is not specific to menstruating animals. Menstruation is a very late arrival in the evolution of viviparity, and it is difficult to see how a process would evolve to solve a problem which had been around for millions of years, and still is for the majority of mammals.

Another intriguing theory (in a paper to the American Anthropological Society) suggested that the observation of menstrual fluid is used to confirm a woman's sexual potency (Worthman et al. 1992). This would be a surprising evolutionary development; many primates, including menstruating species, already have an effective method of signaling their sexual desirability, and it would be contrary to the well-established pattern in vertebrates (and some invertebrates) of signaling sexual preparedness at the time of ovulation, not at the end of the cycle. The problems associated with this idea are discussed in detail by Strassmann (1996).

One problem with all these suggestions is the difficulty of understanding how these processes, as proposed, could have evolved by natural selection. Evolution is thought to rely on chance genetic changes that are maintained or lost according to whether they benefit or harm the individual carrying them. If a genetic change is to be selected for its beneficial effect, then that effect must be exerted in the individual before or during the reproductive phase of the life history. A physiological process resulting from a genetic change would only be effective if it were operative before or during reproduction. This is true, of course, for the majority of biological structures and physiological processes. For example, a genetic change that makes the kidney more efficient in filtering blood would operate from birth, and might improve the survival of the animal and its chances of transmitting that change. Menstruation is unusual in that it does not occur until after puberty and even then only when reproduction is not taking place. Of course, present-day humans usually menstruate several times before reproduction begins. However, animals in the wild commence breeding as soon as they are able, and it is likely that the wild menstruating apes, from which humans evolved, would have produced offspring with little interruption by menstruation. Most animals that menstruate will thus have passed on their genes before any selective effect of menstruation is realized. It is difficult therefore, in the case of menstruation, to justify teleological explanations as a shorthand for natural selection.

Finn (1987) asked the question, "Why do women menstruate?" and argued that menstruation was not a separate physiological process for which it was sensible to assign a function, but rather a consequence of changes in the endometrium in preparation for pregnancy. Strassmann (1996) similarly concluded that menstrual bleeding is a side effect of endometrial regression but argued that the latter serves a useful function in saving energy. Such a view has been implicit, in fact, in most written opinion of the medical profession, at least since the time of Corner (1923). After a certain stage of differentiation in preparation for the arrival of the blastocyst, the uterus reaches a point at which it has to go forward to pregnancy (if a blastocyst is present), or revert to an undifferentiated form so that the endometrial tissues can be reorganized and sperm received from the male.

Finn (1987) suggested that a difference between humans and nonmenstruating viviparous mammals is that in humans the uterus, in anticipation of pregnancy, goes through more complex changes that involve the cells, matrix and blood vessels of the endometrial stroma, and not primarily the endometrial epithelial cells, as in most mammals. When, in the absence of implantation, regression occurs in the endometrial stroma, it is accompanied by tissue breakdown and bleeding, whereas when regression is confined largely to the epithelium, as in most viviparous vertebrates, the cells are removed by programmed cell death without major tissue breakdown. Profet (1993) and Strassmann (1996) both dismiss this explanation for the origin of menstruation on

the basis that "[t]he uteri of many overtly menstruating species, such as rhesus monkeys and baboons, do not undergo predecidualization at the preimplantation stage" (Profet 1993:336).

Unfortunately, the histological changes in the endometrium during the stages of the menstrual cycle have not been studied in many menstruating species. The baboon endometrium has been studied by MacLennan and Wynn (1971), who state that in the late secretory phase of the cycle, "[p]redecidual changes are maximal" (p 356). In a more recent study, Garde and Sheth (1992) state that "[m]orphological changes in baboon endometrium during menstrual cycle and during steroid treatment of ovariectomized animals was very similar to that observed in the human" (p 1007). Brenner et al. (1983) studied the endometrium of cynomolgus macaques and found that during the late luteal phase of the cycle, "there is considerable enlargement of the stromal cells in the immediate vicinity of these arteries" (p 1295). Whether these are predecidual cells is impossible to determine with the techniques used and, in fact, Bartelmez (1951) could not identify predecidual cells in the endometrium of the cycling rhesus monkey. However, he did find other changes, such as edema of the stroma and migration of granulated cells, typical of an early decidual reaction. In later papers, Finn (1994a, 1996) has stressed that it is the advanced preparation of the endometrial stroma that is critical, regardless of whether this leads to full differentiation of the stromal cells into decidual cells. From the limited evidence available, it appears that advanced differentiation of the endometrial stroma in the later stages of the ovarian cycle is a feature of menstruating species.

Evolution of the Female Reproductive Tract

During the evolution of vertebrates, how has it happened that the changes in the uterus make menstruation a necessary consequence of preparation for pregnancy in humans, but not in the majority of mammals? A brief review of the female reproductive tract in vertebrates will be instructive (Finn 1996). Information on the evolution of soft structures, such as those of the reproductive tract, is difficult to obtain. In order to establish a probable evolutionary sequence of adaptations in humans, it is important to examine structures of extant animals that are evolutionary predecessors of man. Of course, these animals will also have evolved since the time when new taxa arose from earlier ones. Some useful information can also be obtained from the study of embryonic development.

In mammalian embryos the uterus develops from bilateral ducts, which first appear as invaginations of the coelomic epithelium on the surface of the mesonephros. These eventually form tubes—the paramesonephric or Müllerian ducts—alongside the mesonephros. These simple tubes differentiate and fuse to form the uterine tubes, uterus, cervix and part of the vagina.

Inferring from modern species what may have occurred in the past, the first ducts for the transport of ova from the ovary to the outside probably evolved in vertebrates more than 400 million years ago. In primitive chordates (such as amphioxus) and the earliest vertebrates (cyclostomes), the gonads form in the body cavity, and the gametes are passed directly into the cavity. There is no duct to carry the gametes out of the body; the ova and sperm pass through a pore in the body wall into the surrounding water, where fertilization takes place. A duct first appears in jawed fishes, and from extant fishes one can infer that its evolution appears to have followed two different pathways. In teleosts, the ovary is surrounded by a fold of peritoneum that then becomes a tube through which the ova pass outside the body. In the remaining jawed fishes and other vertebrates, the oviduct is associated with the mesonephros. In elasmobranch fishes and urodeles, an archinephric duct splits longitudinally: one half initially appears to transport both urine and sperm (although many modern fish and amphibia have accessory ducts for carrying sperm and urine separately); the other half becomes the oviduct, which has an open, often expanded, end to collect the ova (which are released into the abdominal cavity) and at the distal end is joined with the urogenital sinus.

In amniote vertebrates, the mesonephros ceases to act as a kidney, and the mesonephric duct is used to transport sperm from the testis to the outside. The oviduct arises by an infolding of the coelomic epithelium, or by the

development of a cord of tissue, in close proximity to the mesonephric duct (paramesonephric or Müllerian duct). What is not clear is whether the oviduct has evolved from the split archinephric duct or has evolved independently. The formation of a duct provided a conduit for gametes, which gave fish greater control over gamete release. Thus it appears that, more than 400 million years ago, a conduit was formed for the passage of gametes into the surrounding water. This was an early stage in the gradual evolution of the uterus and of menstruation.

COEVOLUTION OF THE FEMALE TRACT AND THE EMBRYO

After millions of years, and further adaptations in the male and female reproductive tracts, the evolution of internal fertilization became possible. The selective advantage of internal fertilization may have been an increased efficiency of fertilization in those vertebrates in which it occurred. However, of much greater significance for terrestrial vertebrates, was the fact that it was a first step in allowing reproduction on land. It also had other far-reaching consequences. Once internal fertilization became established, the evolution of the embryo and the female reproductive tract would have to proceed in close association. One cannot consider the evolution of the female reproductive tract without following evolutionary changes occurring at the same time in the embryo and later fetus.

With the advent of internal fertilization, mothers would have the problem of tolerating first spermatozoa and then zygotes, both foreign tissues, inside their bodies. Mechanisms for resisting invasion by foreign tissue had already arisen much earlier in evolution with the development of inflammatory and immune responses (Rowley 1996). This aspect will be discussed below.

It is not possible to know exactly when internal fertilization first occurred in vertebrates. A minority of extant fish and amphibia have adopted it, although it is likely that the early amphibia from which reptiles evolved had internal fertilization and laid their zygotes in water, where young larval forms then developed. Many amphibia, although able to live on land, must return to the water to reproduce. Reptiles, which live and reproduce on land, have further adaptations to ensure that their embryos are able to survive on land; they are protected against damage and desiccation, and are able to take in oxygen and get rid of waste products, especially carbon dioxide and nitrogenous breakdown substances. An important innovation was the evolution of the cleidoic (closed) egg—a result of adaptations in the embryo (such as the yolk sac, amnion and allantois) and in the maternal tract (for the laying down of the albumen layer, shell membrane and shell).

It is clear, therefore, that at the time mammals evolved from reptiles, the reproductive tract had evolved from a simple gamete-conducting tube, as found in primitive fishes, to a fertilization chamber, seen in some later fishes and amphibia, and then to a secretory organ actively participating in the production of the cleidoic egg. These functional adaptations are mirrored in the structural changes in the oviduct, from a simple coiled tube seen in fish and amphibia, to a more complicated duct with structurally and functionally different regions, as found in reptiles, birds and mammals.

THE EVOLUTION OF VIVIPARITY

It is likely that mammals and birds evolved from egg-laying reptiles, and that mammals evolved the ability to produce living young independently of other viviparous vertebrates. The most primitive extant mammals, the monotremes, lay cleidoic eggs, whereas some modern reptiles and amphibia are viviparous. Viviparity is estimated to have evolved on at least 132 independent occasions among vertebrates (Blackburn 1993).

Monotremes show an interesting variation in the physiology of the female reproductive tract. While reptile embryos get most of their nutrition from the yolk, which is made in the liver and processed in the ovary, monotremes get only part of their nutrition from ovarian yolk. Their nutrition is augmented by secretions from glands in the lower part of the reproductive tract, where the egg spends a significant amount of time and where early embryonic development is completed (Hughes and Carrick 1978). Thus the lower part of the female tract in monotremes has a role in the

nutrition of the embryo and can be viewed as the forerunner of the mammalian uterus. In reptiles and birds, the region where the shell is added is sometimes called the uterus, but it is probably best to reserve that term for structures in which the embryo is retained for a lengthy period and receives nutrients. The transition from shell gland to uterus is crucial to the evolution of viviparity, and the first sign of this transition is seen in extant monotremes. Whether this adaptation started in reptiles is not known.

There is some question about whether viviparous mammals evolved from egg-laying mammals (like the monotremes) or independently, from egg-laying reptiles. One species of lizard (*Sphenomorphus fragilis*) has incipient viviparity. As in monotremes, the egg is retained in the lower part of the reproductive tract for an extended period, and nutrients are added to the yolk (Guillette 1992). It is possible, therefore, that this intermediate stage, as seen in monotremes, may already have been present in the reptiles from which mammals evolved.

The next major development in the evolution of the mammalian uterus probably occurred in marsupials, or animals similar to them (see Tyndale-Biscoe and Renfree 1987). In such animals the production of yolk is reduced to insignificant amounts, and the major, or only, source of nutrition for the early development of the embryo comes from secretions of the uterine glands. The later stages of fetal development occur in the pouch, with the joey attached to the nipple. Whether this marsupial mode was part of the evolutionary lineage from egg laying to eutherian viviparity is not certain and, in the present context, not important. Nevertheless, it is very probable that histotrophic nutrition occurred in the female tract of early mammals, regardless of whether this was followed by a period in a pouch.

As mentioned earlier, viviparity has evolved in all classes of vertebrates except cyclostomes and birds. In fish, amphibia and reptiles, however, viviparity exists in only a few modern species; the majority are still egg-laying. In contrast, mammals have adopted viviparity almost exclusively.

A major difference between reptiles and mammals is that the latter are homeothermic. In most mammals the embryo is maintained at a constant temperature during embryogenesis, but in others such as monotremes there must be mechanisms for controlling the temperature of the embryo. Of the two monotreme species, the echidna keeps the egg warm by placing it in a skin pouch, whereas the platypus digs a burrow, in which the egg is laid, and remains with the egg while the embryo is developing. Both solutions are hazardous, especially to animals living on land, which may explain why they survive in only a few places. The question of why birds, which are also homeothermic, are not viviparous is outside the scope of this review, but see Blackburn and Evans (1986) and Williams (1992) for more on this topic.

VIVIPARITY IN MAMMALS

In most marsupials, nutrition for the embryo comes from endometrial glandular secretions which are taken up by the yolk sac (Tyndale-Biscoe and Renfree 1987). Many eutherian mammals also go through such a stage of histotrophic nutrition at the start of pregnancy. The yolk sac is initially active but is replaced later in pregnancy (in fact, for almost all of pregnancy in women) by hemotrophic nutrition (Amoroso 1952). In this nutrition, the allantois becomes vascularized and fuses with the trophoblast to become the chorion, and nutrients and respiratory gases pass directly between the maternal and embryonic bloods. For this to occur, both the chorion of the conceptus and the lining epithelium of the uterine lumen are modified to facilitate the passage of substances between the circulatory systems of the mother and embryo. This process usually involves considerable growth of both the uterine lumen and the trophoblast. At the same time, the surfaces of both tissues are differentiated to allow them to adhere over the largest possible area; this attachment is greatly enhanced by the development of microvilli and the secretion of attachment molecules on their surfaces (Anderson 1989).

Presumably, being able to exchange nutrients, metabolites and respiratory gases directly between the maternal and fetal bloods is an advantage over nutrition that relies on glandular secretion. The evolutionary drive to improve the nutrition of the embryo did not end there, however. Substances in the mater-

nal blood still had six tissue layers through which to pass before reaching the fetal blood (Wooding and Flint 1994). Various processes have evolved that increase the ability of the embryo to access the blood supply of the mother. The main one, in the present context, is the invasion of the uterine wall by the embryo. In pigs and horses, for example, nutrients in the mother's blood vessels must pass through the endothelial lining, into the endometrial stroma, through the uterine luminal epithelium, and then through similar layers in the conceptus in order to reach the embryo. In some animals, the embryo passes into the wall of the uterus in order to reduce the number of barriers to nutrient transfer. Although this stage has not been seen in humans, it is assumed from studies in great apes (Heuser 1940), and from later stages in women (Hertig and Rock 1938), that the blastocyst actively pushes between the uterine luminal epithelial cells to enter the endometrial stroma and thus gain access to the maternal blood vessels.

The human blastocyst is unusual in that the cells of the trophoblast fuse together very early in implantation and form the syncytiochorion, which may assist in penetrating between the epithelial cells of the endometrium. The invasiveness of the early human embryo was recognized by Fothergill (1899), who described the fertilized ovum as attacking the maternal structures, thereby assuring its own nutrition. The greatly increased invasiveness of the human embryo is probably the reason that ectopic (usually oviductal) implantations occur in women but not in other animals.

Mouse and rat embryos also invade the uterine stroma, but they appear unable to pass through the luminal epithelium (the trophoblast remains cellular) by their own activity. However, the presence of a blastocyst on the luminal surface causes the adjacent uterine epithelial cells to die, by a process of programmed cell death, thus allowing access to the endometrial stroma (Finn and Lawn 1968). The nature of the stimulus from the trophoblast is not known but, since it can be mimicked by a drop of oil, it is presumably physical (Finn and Keen 1962).

Once inside the stroma and released from the restriction of the luminal epithelium, the rodent trophoblast is very invasive. This was shown by transplanting blastocysts from the uterus to the kidney or testis, which resulted in massive invasion and destruction of tissue (Kirby 1969). It is likely that increased aggressiveness of the embryonic trophoblast and the uterine response to it evolved slowly in mammals. Initially, intrusion of the blastocyst into the uterine stroma was restricted by the intact luminal epithelium. Later, owing to programmed cell death, controlled entry of the blastocyst into the stroma was brought about over a small area of the luminal epithelium. Eventually, the trophoblast became very aggressive, and the blastocyst was able to pass between the uterine epithelial cells by its own activity.

FOREIGN GENES AND INFLAMMATION

The entry of an invasive blastocyst into the wall of the uterus presented further problems that had to be overcome if both the mother and embryo were to survive. Parasites that destroy their hosts are not usually successful. The problem of having a foreign tissue inside an animal, first evident with the evolution of internal fertilization, was mentioned earlier. The inflammation reaction to a foreign body precedes internal fertilization by millions of years (Rowley 1996). Vertebrates would therefore have mechanisms already in place to deal with the sperm, as well as the zygote resulting from internal fertilization. The inflammation reaction is a nonspecific first line of defense to a foreign body (Ryan and Majno 1977) and is frequently, but not always, followed by an immune response. It is characterized by increased vascular permeability and invasion by polymorphonuclear leukocytes. The latter does occur in the uterus in response to sperm, and most of the sperm are phagocytosed by the invading white blood cells. However, a sperm that is involved in fertilization passes through the membranes of the ovum. This maternally derived encasement hides the foreign nature of the sperm, thus protecting it from the inflammation reaction. Furthermore, the resulting zygote, which is also genetically foreign, is encased as well. In nonviviparous (egg-laying) mammals the maternal coverings are augmented as the ovum passes down the female tract, thus presumably helping to prevent a foreign body (inflammation) reaction. In viviparous animals, however, the membranes cov-

ering the zygote are removed early in pregnancy, thus exposing the foreign nature of the zygote, and this raises the question of how the inflammation reaction is suppressed.

A characteristic of viviparity is the formation of the corpus luteum from the granulosa cells of the ovulated follicle (see Porter et al. 1982). Many nonviviparous vertebrates form corpora lutea from atretic follicles, but not from the ovulated follicle (Browning 1973). Thus, nonviviparous vertebrates secrete progesterone before ovulation, but viviparous vertebrates secrete large quantities after ovulation, during the time when the embryo is in the uterus. It has been suggested (Finn 1996) that progesterone from the corpus luteum plays an important role in suppressing the inflammation reaction. Progesterone is structurally very similar to the main anti-inflammatory steroids (adrenal glucocorticoids) and has been shown to have anti-inflammatory properties in other situations. Certainly, if progesterone is removed from an animal early in pregnancy, an inflammation reaction occurs, with rapid passage of leukocytes into the uterine stroma (Deanesly 1972; Staples et al. 1983; Finn and Pope 1986).

Of course, progesterone is responsible for other major parameters of viviparity, such as maintaining the passivity of the myometrium and preventing ovulation (Callard et al. 1992). However, it should be stressed that progesterone was being secreted by the ovary long before the adoption of viviparity. It appears to play some role in the control of ovulation in nonviviparous animals. Possibly, with the transition to viviparity and the reduced need for yolk, the granulosa cells of the ovarian follicle, formerly involved in processing the yolk, began to secrete more progesterone, which then took on the special functions of viviparity, including acting as an anti-inflammatory steroid.

It is very interesting to note that in some mammals the placenta exerts control in maintaining the corpus luteum, or secretes progesterone itself, thus providing another example of the coevolution of the embryo and mother in order to maintain pregnancy. This adaptation reaches its peak in humans, where the embryo controls the maintenance of the corpus luteum in early pregnancy through its secretion of human chorionic gonadotropin (HCG); see Haig 1993, 1996 for a discussion of the evolutionary implications. For most of pregnancy the embryo secretes progesterone itself, superseding the function of the corpus luteum. However, while the anti-inflammatory effects of progesterone appear to allow the uterine lumen to retain the embryo safely, further problems arise when the blastocyst implants in the endometrium. The increased invasiveness of the trophoblast now poses a hazard to the mother, who must respond by constraining the activity of the blastocyst and preventing destruction of the uterus.

Finn (1986) has speculated that the response adopted by the mother makes use of the one already in place in vertebrates as a response to a foreign body—the offending body is encased in granulation tissue. He suggested that the decidual cell reaction, as seen in animals where the blastocyst passes into the uterine stroma, is an evolutionary adaptation of the granulation tissue reaction. The similarity of decidual cells to granulation tissue cells was noted much earlier (Turner 1883), and the similarity of the implantation reaction to the inflammation reaction has also been long known (see Finn 1986 for discussion of earlier ideas).

The first observable change at the site of an implanting blastocyst is increased permeability of the blood vessels that supply the endometrium (Psychoyos 1961), which can be shown by the passage of a dye such as Pontamine Sky Blue from the blood vessels into the tissues. This change leads to edema in the stroma; such a reaction is typical in cases of inflammation. Several hours later there is passage of polymorphonuclear leukocytes into the tissues (Finn and Pope 1991). The reaction is moderate and short-lived unless, as discussed earlier, the source of progesterone is removed.

The next change occurs when the fibroblasts differentiate into decidual cells (Loeb 1908). These are large cells joined by tight junctions (Finn and Lawn 1967); they probably control and limit the invasion of the embryo. The suggestion that decidual cells have this function was actually put forward nearly a hundred years ago by Fothergill (1899). He suggested that the decidual cell evolved as a protection, its function being to prevent injurious invasion of the uterine wall by the fetal

part of the placenta. At the same time, there are other changes in the blood vessels and connective tissue matrix of the endometrium.

None of these changes take place in the infertile estrous cycle of rodents (or, of course, in animals where the blastocyst remains in the uterine lumen), or indeed during the pseudopregnant cycle of rodents, which is equivalent to the estrous cycle of most mammals. In these animals there is differentiation of the luminal and glandular epithelium during the luteal phase of the pseudopregnant cycle, but only cell proliferation in the stroma (see Finn 1994b). In humans, however, there is considerable differentiation of the uterine stroma at the end of the luteal phase of the cycle, and distinct layers can be seen in histological sections. Analysis of the changes shows that they resemble changes seen in rodents as a response to the presence of a blastocyst, with edema, vascular changes, leukocyte invasion and differentiation of stromal fibroblasts. Information on other menstruating primates is rather sparse, although (as discussed earlier) the endometria of the baboon and the rhesus and spider monkeys show clear differentiation of the stroma into layers, just before the expected time of menstruation. There is very little information on changes in the endometrial stroma during the luteal phase of the menstrual cycle in any of the great apes. Nevertheless, it appears, in humans and in those old world monkeys that have been studied in sufficient detail, that there is differentiation of the endometrial stroma which goes beyond that seen during the cycle of nonmenstruating animals. Finn (1996) has suggested that this is a further evolutionary adaptation of the granulation tissue reaction, occurring in anticipation of the arrival of the increasingly active embryo, rather than in response to it. The selective advantage of the increased invasiveness of the trophoblast, counterbalanced by the defensive modification of the endometrium, is apparent.

In the absence of implantation, the differentiated tissue of the endometrium breaks down rapidly and is lost with bleeding—the process of menstruation. The reason for the very abrupt breakdown of the endometrium is the rapid deterioration of the corpus luteum and the decline of the progesterone level. In most mammals, the corpus luteum is removed and progesterone secretion decreases soon after the time of possible implantation has passed, thus allowing a new ovulatory cycle to take place. Animals have evolved several mechanisms to ensure rapid destruction of the corpus luteum at the end of the cycle. It appears that, in humans, it is the rapid demise of the corpus luteum, combined with the anticipatory differentiation of the endometrial stroma, at the end of the cycle, which results in menstruation. This view has been supported by experiments in mice. Although they do not menstruate or differentiate the stroma during the cycle, if ovariectomized mice are treated with ovarian hormones on a schedule that mimics early pregnancy, they will undergo endometrial changes in preparation for implantation (Finn and Pope 1984). These changes involve differentiation of the luminal epithelial cells so that they are sensitive to the stimulus normally provided when the blastocyst attaches. If a blastocyst is placed in the uterus, the stroma will respond by undergoing the implantation reaction (vascular permeability, leukocyte invasion, edema, and transformation of stromal fibroblasts into decidual cells). The luminal epithelial cells will be destroyed by programmed cell death, and the blastocyst will lie in the stroma surrounded by decidual cells.

A similar "implantation" response is initiated if, instead of a blastocyst, a small drop of oil is placed in the uterine lumen (Finn and Keen 1962). This experiment produces a situation very similar to that found at the end of the luteal phase of the menstrual cycle in humans. If the source of progesterone is removed soon after the oil is instilled into the uterine lumen, there is massive degeneration of the endometrium with bleeding into the uterine lumen, a condition resembling menstruation. If oil is not instilled into the uterine lumen, removal of the source of progesterone does not produce overt degeneration of the endometrium. It is clear that massive degeneration and bleeding from the endometrial stroma occurs only if there has been differentiation of the stroma, thus supporting the suggestion that menstruation in women is due to the anticipatory differentiation of the endometrial stroma at the end of the luteal phase of the cycle.

This brief review of the evolution of the fe-

male reproductive tract and its relationship to the evolving embryo suggests that menstruation has come about as a byproduct of increased cellular changes in the endometrium in response to increased aggressiveness of the blastocyst. Menstruation is not an end in itself, any more than is defecation or micturition. This may well be the simplest explanation for the evolution of menstruation and, applying Ockham's razor, the easiest to accept.

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