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MENSTRUATION AS A DEFENSE AGAINST PATHOGENS TRANSPORTED BY SPERM

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ABSTRACT

Sperm are vectors of disease. During mammalian insemination bacteria from the male and female genitalia regularly cling to sperm tails and are transported to the uterus. I propose that menstruation functions to protect the uterus and oviducts from colonization by pathogens. Menstrual blood exerts mechanical pressure on uterine tissue, forcing it to shed, and delivers large numbers of immune cells throughout the uterine cavity, directly combating pathogens. The mechanisms of menstruation show evidence of adaptive design. Spiral arteries that open to the lining of the uterus trigger menstruation by abruptly constricting, which deprives the local tissue of blood, and then abruptly dilating, which causes blood to force loose the necrotic tissue. Menstrual blood flows easily, unlike blood at most wound sites, because it lacks the normal level of clotting factors.

Overt (externally visible) or covert (not externally visible) menstruation has been documented in many species of primate, including Old World monkeys and apes, New World monkeys, and prosimians, as well as in various species of bat and insectivore. The antipathogen hypothesis predicts that: (1) menstruation (overt or covert) is either universal or nearly so among mammalian species; (2) if the latter, then the existence of menstruation among species varies inversely with the probability of becoming pregnant per estrous cycle (menstruation would be especially adaptive in species with significantly less than 100% probability of becoming pregnant per estrous cycle); (3) among menstruating species, the average degree of menstrual bleeding for a given species is a function of the factors affecting menstruation's costs and benefits—in particular, the degree of bleeding is positively correlated with the average body size and sexually transmitted pathogen load of that species (profuse bleeding would be especially adaptive in large-bodied species with either promiscuous breeding systems or continuous sexual receptivity); and (4) other forms of normal uterine bleeding—proestrous, periovulatory, implantation, and postpartum—also have an anti-pathogen function.

The hypothesis presented in this article has implications for the diagnosis, treatment and prevention of uterine infection and, therefore, for the prevention of pathogen-induced infertility. The uterus appears to be designed to increase its bleeding if it detects infection: Human uteri that become infected (or otherwise inflamed) bleed more profusely, bleed on more days per cycle, and often bleed intermittently throughout the cycle. Thus artificially curtailing infection-induced uterine bleeding may be contraindicated.

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INTRODUCTION

MENSTRUATION is the phenomenon of uterine bleeding and shedding between successive ovulations. Its function has remained elusive because it has never been subjected to an adaptationist analysis. To demonstrate that a physiological phenomenon is an adaptation — that is, a functional mechanism — one must, first, identify the problem that the candidate mechanism was designed to solve, and, second, elucidate design — that is, show there is an adaptive fit between the mechanism and the problem that is too close to be merely the product of chance or the by-product of other mechanisms (see G. C. Williams, 1966; Mayr, 1983; G. C. Williams and Nesse, 1991).

In the absence of such an approach to physiology, functional mechanisms, such as menstruation, are sometimes even viewed as defects. The Seventeenth-Century anatomist Regnier de Graaf (for whom the Graafian follicle of the ovary was named), hypothesized that "The menstrual blood escapes by the feeblest parts of the body, in the same way that wine or beer undergoing fermentation escapes by the defective parts of the barrel" (quoted in Fluhmann, 1939: 20). Although researchers and menstruating women in modern industrialized societies may find this particular hypothesis absurd, they have not abandoned its underlying theme: that menstruation is a process of an inefficient body that repeatedly wastes, rather than recycles, its nutritious blood-filled uterine lining.

Current scientific hypotheses about menstruation treat it as a constraint or nonfunctional by-product of reproductive cycling. Finn (1987), for example, views menstruation as the necessary sloughing in nonpregnant cycles of cells of the endometrium (the uterine lining that is shed at menstruation) that have differentiated irreversibly into a type of cell known as "decidual" or "predecidual." He notes that in humans and a couple of other menstruating species this uterine predecidualization takes place before implantation, whereas in some species not known to menstruate, it takes place only in the presence of an implanting blastocyst (an early-gestation embryo), or not at all. This leads him to suggest that "menstruation would be the penalty women pay for a greater state of readiness for the implantation of embryos in their uteri" (p. 570).

Preimplantation predecidualization, however, is not a prerequisite for either menstruation or reproduction. The uteri of many overtly menstruating species, such as rhesus monkeys and baboons, do not undergo predecidualization at the preimplantation stage (Ramsey et al., 1976; Enders, 1991). In fact, according to Enders (1991), the human and chimpanzee are the only primates that have been shown to undergo these changes in the absence of implantation. And, as Finn (1987) mentions, the uteri of many species do not undergo decidualization during any stage of pregnancy. The uteri of all species are, nonetheless, sufficiently "ready" for implantation. Furthermore, Finn's hypothesis does not explain why tissue that becomes decidualized in nonpregnant cycles is shed rather than maintained. Thus it does not explain menstruation.

Nor is menstruation a by-product of endometrial preparation for any particular type of placentation. (Mammalian placentas are classified according to the type of membranes that separate maternal from fetal blood.) Kleine (1931) concluded that menstruation is limited to species with "hemochorial" placentas, in which maternal blood is in direct contact with fetally derived trophoblast tissue. But among mammalian species that are well documented to menstruate (see Appendix) are examples to the contrary. For example, the placentas of slender lorises are "epitheliochorial" (Mossman, 1987: 200), the placentas of tree shrews are "endotheliochorial" (Mossman, 1987: 180), and the placentas of leaf-nosed bats and long-tongued bats appear to be "endotheliochorial" (Mossman, 1987: 194).

A basic problem with by-product hypotheses about menstruation is that they fail to account for its costs. None of the known features of female mammalian reproductive physiology require menstruation as an ineluctable by-product. If menstruation were both costly and functionless, natural selection surely would have eliminated it long ago. Menstruation is nutritionally costly. Women lose, on average, about 40 milliliters of blood and an equal volume of tissue per cycle, and some women lose enough blood to significantly decrease their iron stores (Smith et al., 1985; Andrade et al.,

1991). Even covert menstruation—in which all the menstrual blood is resorbed in the uterus or discharged inconspicuously through the vagina via mucus—is costly because it involves tissue degeneration, phagocytosis, and tissue regeneration. (Covert, rather than overt, menstruation occurs if the quantity of blood is small or the resorption mechanisms are especially efficient.)

Menstruation is also reproductively costly. It lengthens the female reproductive cycle, because the process of degeneration and regeneration of endometrial tissue is necessarily time-consuming. This endometrial flux narrows the window of fertility, resulting in long intervals between reproductive opportunities within a single breeding season. The occurrence of menstruation during short breeding seasons may significantly limit the total number of days during which conception is possible.

Since the costs of menstruation are not negligible, the question that needs to be resolved is why the body does not simply maintain its uterine lining or, at least, resorb rather than discard uterine nutrients. Even overtly menstruating mammals have mechanisms to resorb uterine nutrients; rhesus monkeys, for example, resorb a significant amount of fluid from the endometrium at the end of the menstrual cycle (Markee, 1940). In sum, the persistence of the mechanisms of menstruation, in the face of significant costs, implies the existence of some selective advantage(s).

Although no functional hypothesis of menstruation has ever been developed, the scientific literature contains several brief speculations on possible benefits or functions of menstruation. Shaw and Roche (1985) suggest that menstrual blood helps to cleanse the uterus of cellular debris and necrotic tissue after the breakdown of the endometrium. Garey (1990) proposes in an abstract that menstruation may function to cyclically rid the uterus of dietary phytoestrogens (natural plant toxins that, once ingested, can interfere with reproduction by binding to hormone receptors). [One might also hypothesize that menstruation sloughs off endometrial cells that are contaminated by teratogens (plant and bacterial toxins that can interfere with embryonic or fetal development).] Haig (in press) suggests that menstruation may enable the uterus to expel fetal cells that might otherwise manipulate maternal metabolism and behavior. Ravenholt (1966) notes that "menstruation may be regarded as a physiological eraser of endometrial neoplasia" (p. 525). And Sullivan (1989) emphasizes the cardiovascular benefits of cyclic iron depletion caused by menstruation.

None of these putative benefits of menstruation, however, is likely to have led to its evolution. The suggestion that blood washes out debris from the uterus does not account for covert menstruation or for the extensive endometrial breakdown itself. The sloughing of endometrial tissue without the bleeding would generally be sufficient for shedding toxin-contaminated or mutated cells of the uterus, just as the sloughing of epithelial tissues is generally sufficient for shedding such cells in other organs. The profuse and lengthy bleeding that occurs postpartum should normally be sufficient for discarding remnant fetal cells. Although there may be cardiovascular benefits from menstrual iron loss among women living in industrialized societies, hunter-gatherer women and, by extension our Pleistocene ancestors, rarely suffer from heart disease (Eaton et al., 1988: 251) (in part because of their diet and excercise and in part because they rarely live long enough to suffer degenerative diseases of old age). The existence in the human body of exquisite mechanisms to store and recycle iron and to facultatively regulate the intestinal absorption of dietary iron—thereby avoiding both iron deficiency and overload (see U. S. Department of Health and Human Services, 1988; Wadsworth, 1992)—implies that ancestral humans are unlikely to have evolved a mechanism whose purpose was to cyclically eliminate substantial stores of iron. Furthermore, if cyclic bleeding functioned to eliminate iron, one would expect it to occur in both sexes.

In trying to identify the function of a mechanism, it is important to distinguish between adaptation and benefit. As G. C. Williams (1966: 12) points out, "A benefit can be the result of chance instead of design. The decision as to the purpose of a mechanism must be based on an examination of the machinery and an argument as to the appropriateness of

the means to the end." An adaptation, once in place, however, can be subsequently modified to produce additional benefits that did not provide the original selection pressures for its evolution (G. C. Williams, 1992). But any claim that a benefit of menstruation constitutes a function must be supported by evidence that some aspect of the machinery of menstruation has been modified by natural selection specifically to produce this benefit.

In this article I argue that the function of menstruation is to defend against pathogens transported to the uterus by sperm and that menstruation occurs at least covertly in most, if not all, mammalian species. I support this hypothesis with three complementary kinds of evidence: adaptive design, comparative mammalian data, and clinical studies. The article is structured as follows. I begin by arguing that the machinery of menstruation is appropriately designed to perform the function of pathogen defense. I show that sperm are vectors for pathogens and that natural selection has produced an array of mechanisms in the female reproductive tract to hinder the sexual transmission of pathogens. I discuss the ways in which menstruation and other types of uterine bleeding (proestrous, periovulatory, implantation, and postpartum) protect against pathogens. Then I offer predictions relating the likelihood and degree of menstruation in different species to various features of physiology and social behavior that influence the costs and benefits of menstruation, and I discuss the comparative mammalian data on menstruation in relation to the predictions of the antipathogen hypothesis. Finally, I discuss the clinical data and the medical implications of the hypothesis.

Throughout the article I refer to the phases of the menstrual or estrous cycle, which are generally defined as follows. In higher primates, the menstrual or estrous cycle is divided into two main parts: the follicular, or proliferative, phase, during which estrogen levels rise; and the luteal, or secretory, phase, during which estrogen levels fall and progesterone levels rise and then fall. The follicular phase is characterized by menstruation (day one of the cycle is the first day of menstrual bleeding), and then by proliferation of the endometrial tissue. Separating the follicular from the luteal phase is ovulation, during which, in women at least, endometrial proliferation temporarily stops. Estrus, the primary period of sexual receptivity in nonhuman mammals, immediately precedes or coincides with ovulation. The luteal phase is characterized by the continued proliferation of endometrial tissue, in preparation for blastocyst implantation, and, in unsuccessful cycles, by the subsequent resorption of uterine fluid and the degeneration of endometrial tissue. In nonprimate mammals, the estrous cycle is traditionally divided into four parts: proestrum, the period that precedes estrus and corresponds to the late follicular phase in primates; estrus, which immediately precedes or coincides with ovulation; metestrum, the period that immediately follows ovulation and corresponds to the early luteal phase in primates; and diestrum, the period characterized by endometrial degeneration and quiescence, which corresponds, more or less, to the late luteal and menstrual phases in primates. In most mammals, following ovulation the corpus luteum of the ovary secretes the hormones necessary to maintain the endometrium for blastocyst implantation. In unfertile cycles, the period during which the corpus luteum maintains the endometrium is referred to as "pseudopregnancy"; it can last several weeks in species that normally have high pregnancy success rates per cycle.

THE PHYSIOLOGY OF MENSTRUATION SHOWS ADAPTIVE DESIGN

The mechanisms that collectively constitute menstruation appear to manifest adaptive design in the precision, economy, efficiency, and complexity with which they achieve the goal of producing menstruation [see G. C. Williams's (1966) criteria for detecting adaptive design]. If menstruation were merely a functionless by-product of cyclic hormonal flux, there would be no mechanisms specifically designed to cause it, nor would the constituents of menstrual and venous blood differ significantly. Menstruation would have essentially the same etiology as the phenomenon of "vicarious menstruation," a rare disorder in which tissues of nonreproductive organs, such as the kidneys, stomach, or retina, bleed cyclically due to a hormone-induced increase

in the permeability of capillaries (see Dunn, 1972). I argue that the uterus is designed to bleed at the end of nonpregnant cycles and that evidence of adaptive design is demonstrated by the following physiological features of menstruation: (1) specialized spiral-shaped arteries constrict and dilate in a sequence timed to induce menstruation; and (2) menstrual blood differs from venous blood in ways that promote blood flow rather than clotting.

The uteri of most species that are known to menstruate overtly have prominent spiral arteries and arterioles (named for their corkscrewlike appearance) that supply blood to the superficial two-thirds of the endometrium. As end arteries, they can bleed directly into the uterine cavity (Christiaens et al., 1982). According to van der Horst (1950), the spiral arteries in the uterus differ in form and function from coiled arteries in other organs. During pregnancy, the spiral arteries are important conduits of blood for the placenta (Kaiserman-Abramof and Padykula, 1989); in fact, in the Transvaal elephant shrew *Elephantulus myurus*, the three spiral arteries controlling menstruation are located at the site of blastocyst implantation (van der Horst, 1950). But the role of spiral arteries in menstruation is not merely a by-product of their role in pregnancy. Rather, at the end of nonpregnant cycles they undergo specialized changes to induce menstruation.

The sequence of uterine events that characterize menstruation were discovered by Markee (1940) in a classic study that involved transplanting wedges of rhesus monkey endometrial tissue into the anterior chambers of the monkeys' eyes, and observing the changes in the transplants in response to hormonal fluctuations during the menstrual cycle. From day five to day one before the onset of menstruation, the spiral arteries grow longer and become increasingly coiled, resulting in increased resistance to blood flow and consequent slowed circulation or stasis. Large concentrations of leukocytes (white blood cells) infiltrate the endometrial tissue at this stage. Approximately 24 hours before the onset of menstruation the spiral arteries constrict, which prevents blood from flowing to the endometrial tissue and thereby causes ischemia (deprivation of blood and thus of oxygen), killing the affected tissue. Menstruation occurs when the spiral arteries temporarily and abruptly relax, allowing blood to flow through them and to rupture the ischemic arteriole walls.

Most menstrual bleeding occurs from *hematomas* (pockets of blood) beneath the uterine epithelium, which are formed when individual spiral arteries hemorrhage. According to Markee (1940), the hematomas expand, lifting and stretching the uterine epithelium, then rupture, pouring blood over the uterine surface. (This process is commonly referred to as the *extravasation* of blood.) Endometrial tissue fragments begin breaking off near the end of the first day of menstruation, usually in regions of the epithelium where the bleeding has ceased. Except during hemorrhage, each spiral artery remains constricted throughout menstruation and usually is shed along with other endometrial tissue. Menstruation ends when the endometrium revascularizes and blood is diverted away from the endometrial surface.

Although it is clear that the spiral arteries are adapted to induce menstruation, it is not clear whether the coiling of the arteries per se is an essential part of this machinery and whether spiral arteries are part of the machinery of menstruation in all menstruating species. Since spiral arteries appear to constitute the main mechanism of menstruation and have been prominent subjects of menstruation research throughout this century, the following discussion elaborates on these issues. Uterine arteries that are straight early in the menstrual cycle often become highly coiled toward the end of the cycle because they grow faster than the endometrial tissue and are forced to coil in order to fit into a restricted space (Markee, 1950). In rhesus monkeys, for example, the ratio of artery length to endometrial thickness changes from about 2 in the early proliferative phase of the cycle to about 15 shortly before menstrual bleeding (Markee, 1950). Markee (1950) concludes that the coiling of the arteries is important in causing menstruation because it causes the premenstrual arterial stasis that facilitates hemorrhage. He notes that in any particular rhesus menstrual cycle, the amount of tissue shed is positively correlated with the extent of development and coiling of the spiral arteries. Bartelmez (1956),

however, argues that the coiling of the arteries is not essential for menstruation because the same degree of bleeding and tissue sloughing occurs in areas of the rhesus monkey endometrium where the coiling of the arteries is minimal as occurs in areas where the coiling is tortuous.

Kaiser (1947), on the other hand, believes that the degree of coiling partly determines the degree of bleeding and shedding of the endometrium, but he assumes the following: first, that gross external bleeding occurs in Old World monkeys and apes, whereas only microscopic bleeding occurs in New World monkeys; and, second, that Old World monkeys and apes have spiral arteries, whereas New World monkeys lack them. As shown in the Appendix, however, although many Old World monkeys and apes menstruate to a greater degree than do most New World monkeys, many Old World monkeys and apes have scant bleeding, resembling that of New World monkeys. Furthermore, as van der Horst (1950) points out, although Kaiser did not find coiled endometrial arterioles in New World monkeys, one type of arteriole he described is likely to be homologous to the spiral arteries of Old World monkeys because, like the spiral arteries, it runs without branching almost to the superficial epithelium of the endometrium. Since the coiling of spiral arteries of Old World monkeys increases significantly as the menstrual cycle progresses, the straightness of the endometrial arteries that Kaiser observed in New World monkeys may simply have reflected an early stage of the menstrual cycle (Kaiser does not specify the cycle stage of the monkeys he dissected). On the other hand, Rasweiler (1991) notes that the spiral arterioles of the menstruating bat *Mollosus ater* do not increase their coiling as menstruation approaches. In sum, although the spiral arteries (and their straighter apparent homologues) are part of the machinery of menstruation, it has not been demonstrated that coiling per se is necessary for menstruation.

If the spiral arteries (and their homologues) are adaptations for menstruation, they are likely to be present in all menstruating species. The menstruating Transvaal elephant shrew *Elephantulus myurus*, for example, bleeds vigorously from its spiral arteries (van der Horst, 1950), as does the black mastiff bat *Molossus ater* (Rasweiler, 1991). Rasweiler and Bonilla (1992) note that two menstruating bats of the family Phyllostomidae, *Carollia perspicillata* and *Glossophaga soricina*, appear to lack spiral arterioles, but whether they have homologous arterioles has yet to be investigated. Most nonprimate species have not been investigated for the presence of spiral arteries, but no menstruating mammals are known with certainty to lack them. Spiral arteries have been found in the uteri of many mammals not yet documented to menstruate, including the tenrec *Hemicentetes semispinosus* (Goetz, 1936, 1937), the two-toed sloth *Choloepus hoffmanni* (Turner, 1873), the galago *Galago senegalensis* (H. Butler, 1967), and the slow loris *Nycticebus coucang* (H. Butler, 1967).

Spiral arteries may exist in the uteri of all mammals, but detecting them is often difficult. In order to detect spiral arteries in the rat uterus, for example, P. A. W. Rogers and Gannon (1981) used a scanning electron microscope after vascular casting of the uterus. As in Old World primates, the rat arteries were tortuous late in the cycle (during diestrus) but much straighter early in the cycle (during proestrus). Although the mouse has not yet been shown to have spiral arteries, it can be artificially induced to menstruate visibly if treated with a sequence of hormones, a uterine stimulus to induce decidualization, followed by hormone withdrawal (Finn and Pope, 1984). [The reason this stimulus is needed to trigger mouse menstruation is not clear. If, as Finn and Pope (1984) believe, the stimulus mimics blastocyst implantation, then the subsequent bleeding may actually represent abortion. If, instead, it mimics copulation—which in mice is needed to induce corpus luteum formation—then the bleeding may represent true menstruation.] The presence of uterine spiral arteries in the rat implies that it may have the capacity to menstruate; the discovery of such arteries in the mouse would explain why it can be induced to menstruate and might indicate that it menstruates naturally to some degree.

One of the most salient features of menstruation indicating adaptive design is the fact that menstrual blood—unlike most blood issuing from wounds—lacks many of the normal clot-

ting factors (Beller, 1971; Christiaens et al., 1985). Thus, when the constricted spiral arteries begin to relax, the menstrual blood flows easily from them. The low coagulability of menstrual blood has been one of its most conspicuous characteristics throughout decades of menstruation research (Bartelmez, 1937). In a normal human skin wound, the surrounding blood vessels are occluded by hemostatic plugs that contain platelets and fibrin, which prevent large quantities of blood from escaping. In the human menstrual wound, however, the hemostatic plugs are smaller and transient, being present for only a short period during the early part of menstruation (Christiaens et al., 1980; van Eijkeren et al., 1991). Furthermore, after the first 20 hours of menstruation hemostatic plugs are apparently absent; bleeding ultimately is stopped by arterial vasoconstriction (van Eijkeren et al., 1991).

Rees et al. (1984) note that the quantity of platelets found in human menstrual blood is only one-tenth of that found in venous blood and that the platelets in menstrual blood, in contrast to the platelets obtained from the uterine vein during menstruation, do not aggregate normally. Rees et al. (1984) suggest that menstrual blood platelets do not aggregate because they are "spent," that is, because they have already released their clot-promoting chemicals (cyclooxygenase products) at the site of the menstrual wound. But blood emanating from a normal skin wound coagulates; therefore, this hypothesis fails to account for the difference between a menstrual and a nonmenstrual wound. In summary, menstrual blood appears to be designed to have low coagulability. Because menstruation is a process of shedding, its function is likely to be revealed by investigating what is shed from the uterus via endometrial tissue and blood.

SEXUAL INTERCOURSE TRANSMITS PATHOGENS TO THE UTERUS

Sperm are vectors of disease. Bacteria frequently are transported from the vagina or cervix to the uterus by attaching to the heads or tails of sperm (Toth et al., 1982; Friberg and Fullan, 1983; Keith et al., 1984). The vagina and cervix of a healthy woman normally harbor a significant number of bacteria, ranging from roughly 100 million to 10 billion organisms per milliliter of vaginal or cervical fluid (Bartlett et al., 1978; Lindner et al., 1978). Although vaginal bacterial counts fluctuate to some extent with the stage of the menstrual cycle, they remain significant throughout the cycle (Bartlett et al., 1978; Onderdonk et al., 1986; Domingue et al., 1991) because the vagina is exposed to the external environment. Electron microscopy has shown that human sperm can be exploited as vehicles of transport by a wide spectrum of bacteria, including *Chlamydia trachomatis* (Friberg et al., 1985), *Escherichia coli* (Friberg and Fullan, 1983; Keith et al., 1984), *Streptococcus viridans, Staphylococcus aureus* (Toth et al., 1982), and *Neisseria gonorrhoeae* (James-Holmquest et al., 1974). In the mouse uterus one day after mating, bacteria are invariably present, the number of bacteria greatly exceeds the number before mating, and the kinds of bacteria correspond reasonably well to those cultured from the vagina before mating (Parr and Parr, 1985). (Since the male mouse ejaculates directly into the uterus rather than the vagina, vaginal pathogens that end up in the uterus probably attached to the male's penis during intromission.) Seminal fluid also acts as a vector for pathogens, transmitting certain viruses, such as cytomegalovirus, from the male to the female reproductive organs (Lang and Kummer, 1972). Sperm, rather than seminal fluid, however, appear to be the primary vectors in the ejaculate for pathogens.

Pathogens that are relatively innocuous as flora of the lower reproductive tract can become pernicious in the upper reproductive tract, causing spontaneous abortion or infertility. In a study of women visiting a gynecology clinic, for example, Stray-Pedersen (1979) found that infections of the endometrium by *Ureaplasma urealyticum*, an organism that commonly inhabits human cervical mucus and that can attach to the neck of a sperm, are associated with both habitual spontaneous abortion and infertility. *U. urealyticum* was found in the endometrium of 28% of the 46 habitual abortion patients, compared to only 7% of the fertile control women, and in the endometrium of 26% of the 18 unexplained infertility patients, compared to only 8% of the fertile control women. It is of particular interest that this organism was not present in the endome-

trium of any of the nine women whose husbands had azoospermia (absence of sperm in semen), even though it was present in the cervix of five of these women.

Sperm are also vectors for pathogens that infect the oviducts (fallopian tubes) and that thereby cause pelvic inflammatory disease, a major risk factor for infertility (Keith et al., 1984). *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, the most common pathogens of pelvic inflammatory disease in the United States, can be transported by sperm (James-Holmquest et al.,1974; Friberg et al., 1985). Pathogens are known or suspected culprits in many cases of infertility, including male infertility, which is often associated with the presence of pathogens in the seminal fluid (Fowlkes et al., 1975; Dahlberg, 1976; Toth and Lesser, 1981). In sum, the vagina, the cervix, and sometimes the seminal fluid are reservoirs of bacteria that can attach to incoming sperm and ascend the female reproductive tract.

ALL FEMALE MAMMALS HAVE DEFENSES AGAINST SEXUALLY TRANSMITTED PATHOGENS

All female mammals have a set of adaptations designed to protect their reproductive organs from sexually transmitted pathogens. For each female reproductive organ that comes into contact with pathogen-bearing sperm, there is a trade-off between providing an environment hostile to pathogens and providing one hospitable to eggs, sperm, and zygotes or blastocysts. The reproductive organs therefore must be designed to alter their environment throughout the menstrual cycle in ways that optimally achieve these conflicting ends. The timing of maximal recruitment of defenses during the menstrual cycle is different for each reproductive organ, depending on the timing of its exposure to pathogens and the timing of its need to protect eggs, sperm, zygotes, or blastocysts.

Defenses of the vagina, cervix, uterus, and oviducts that vary with the menstrual cycle are discussed in the following paragraphs. (This discussion of defenses excludes rodent studies for two reasons: rodents have not yet been shown to menstruate under natural conditions; and the mice and rats in most of the studies are unmated, which means they do not necessarily recruit the normal level of uterine defenses, since corpus luteum formation in rodents is induced by copulation.) The defenses include: (1) *Shedding epithelial tissue*. This is an important defense against pathogens and toxins for all organs exposed to the external environment, including the skin, gastrointestinal tract, lungs, eyes, and genitourinary tract (N. A. Wright and Alison, 1984). For each reproductive organ, tissue shedding would be expected to occur following exposure to sperm, but not until the need of that organ to protect eggs, sperm, or zygotes had been fulfilled. (2) *Secreting immune cells and antibodies*. The body's primary network of defenses against pathogens is the immune system. (3) *Reducing pH*. An acidic environment generally is more hostile to pathogens. (4) *Increasing lactoferrin levels*. The protein lactoferrin is bactericidal because it binds iron very efficiently, thus depriving bacteria of this essential element (Oram and Reiter, 1968; Arnold et al., 1977). Lactoferrin is present in most external secretions, and unlike transferrin (a major iron-binding protein in serum), it binds iron under highly acidic conditions (down to pH 2) (Masson et al., 1968). A cyclic increase in lactoferrin would be expected in reproductive organs that need to sequester the iron of menstrual blood from pathogens.

Vagina. During estrus, which in nonhuman mammals is the period of sexual receptivity, the vagina is exposed to semen and to pathogens from the male genitalia. At no time during the cycle does the vagina need to protect a potentially implanting blastocyst, but at estrus it should not be excessively hostile to sperm. Most vaginal defenses, therefore, would be expected to be greatest during or immediately following estrus, and this appears to be the case. The vaginal epithelium of virtually all mammals becomes cornified (scalelike) at estrus and begins to shed (for numerous examples see Asdell, 1964), thus hindering sexually transmitted pathogens from colonizing vaginal tissue. Toward the end of and immediately following estrus (ovulation in women) large numbers of leukocytes invade the vaginal tissue and secretions (Hamlett, 1939; Larsson and Platz-Christensen, 1990; for numerous mammalian examples see Asdell, 1964). In addition, the vagina becomes more acidic during estrus (ovulation in women) (Nalbandov,

1976: 125; B. R. Møller and Kaspersen, 1991) and thus more hostile to pathogens. J. A. Hill and Anderson (1992) point out that low pH is one of the vaginal defenses against pathogens. The level of vaginal bacteria, accordingly, is lowest following ovulation. Bartlett et al. (1977) measured a 100-fold decrease in aerobes following ovulation, although they did not find major fluctuations in anaerobes throughout the cycle. Since the vagina is constantly reexposed to and colonized by bacteria in the external environment, fluctuations in vaginal bacterial counts would be expected to be relatively slight.

Among overtly menstruating mammals, a high level of iron-binding proteins is needed in the vagina during menstruation to sequester iron from bacteria. Cohen et al. (1987) report that the concentration of lactoferrin in human vaginal mucus is more than an order of magnitude higher during the week following the cessation of menses than it is at three weeks following the cessation of menses (levels during menses were not measured). The fluctuations in levels of vaginal lactoferrin appear to be hormonally regulated, since fluctuations do not occur during the cycles of women taking oral contraceptives (Cohen et al., 1987); thus these fluctuations appear to be adaptive responses to the cyclically changing needs of the vagina.

Cervix. The cervix, like the vagina, is exposed to sperm at estrus. The primary cervical defenses against sperm-borne pathogens involve changes in the cervical mucus, which is the gel that fills the narrow cervical tunnel through which sperm and pathogens must travel in order to reach the uterus from the vagina. These defenses would be expected to be: minimal during estrus (ovulation in women), in order to enable the passage of sperm to the uterus; maximal following estrus and the associated period of sperm transport through the cervix, in order to eradicate sperm-borne pathogens; and formidable throughout the rest of the cycle, in order to inhibit pathogen ascent.

The characteristics of cervical mucus change with hormonal flux, ensuring a hostile environment throughout the menstrual cycle except during the periovulatory phase (Chantler et al., 1989). As estrogen levels rise, cervical mucus becomes profuse, watery, and increasingly penetrable by sperm; as progesterone levels rise, it becomes viscous, dense, and increasingly impenetrable by sperm (Chrétien, 1978; Chantler et al., 1989). Thus, it is most receptive to sperm and sperm-borne pathogens during the estrogen peak coinciding with estrus, and most hostile to sperm and pathogens during the progesterone peak following estrus. The cervical mucus is also typically very acidic (pH of 4.5) before the 10th and after the 18th days of a menstrual cycle, creating a hostile environment for sperm and pathogens, but it is alkaline (pH of 7.5) in the periovulatory period (Shettles and Guttmacher, 1940), permitting sperm survival.

Since the cervix of overtly menstruating mammals is exposed to menstrual blood, it would be expected to have defenses to sequester the iron of menstrual blood from pathogens. The cervix synthesizes lactoferrin, and, in a preliminary study involving two women taking sequential hormonal contraceptives (which mimic the sequence of hormones in the natural menstrual cycle), lactoferrin levels in cervical mucus increased dramatically at the end of the luteal phase of the cycle, immediately preceding menstruation, and subsided by the next midcycle (Schumacher, 1973).

Uterus. Since the time between ovulation and implantation is at least several days, the uterus usually is exposed to pathogen-bearing sperm several days before it is exposed to a blastocyst. Uterine defenses would be expected to be greatest between cycles, when there is no possibility of an implanting blastocyst, but heightened defenses might also be expected between ovulation and (potential) implantation.

All female mammals shed their uterine lining between successive ovulations. Nalbandov (1976) points out that midway between ovulations various farm mammals slough off large parts of the uterine epithelium, which resemble casts of the uterine horns. Bullough (1961) points out that the amount of uterine sloughing in mammals almost seems to form a continuum, with one extreme being observable menstruation. In humans and all other primate species on which information exists, menstrual shedding and bleeding is preceded and accompanied by the massive infiltration of leukocytes into the endometrium (see Rao,

1932; Bartelmez, 1937; Markee, 1940; Ingerslev et al., 1982).

In a study of 74 women in various phases of the menstrual cycle (Masson et al., 1968), the endometrial concentrations of lactoferrin rose dramatically during the late luteal phase of the cycle, just prior to menstruation, whereas they fell and remained very low during the follicular phase. This apparent reversal of the timing of lactoferrin fluctuation in the vagina is viewed by Cohen et al. (1987) as paradoxical, but it can be explained by the different defensive needs of the uterus and vagina at different stages of the menstrual cycle and by the fact that the studies did not measure lactoferrin levels in either organ during menstruation. During the luteal phase the endometrium becomes swollen with blood, in preparation for either an implanting blastocyst or menstruation, and therefore it must increase its lactoferrin levels in order to sequester the blood's iron from bacteria. Much of this lactoferrin is probably shed along with endometrial tissue during menstruation, which would account for the sharp decrease in levels following menstruation. The vagina, on the other hand, needs to guard against bacterial utilization of iron primarily during overt menstruation. Since the vagina does not shed its tissue at this time, its lactoferrin levels would be expected to decrease more gradually than uterine lactoferrin levels do following menstruation. The antipathogen hypothesis predicts that in overtly menstruating mammals lactoferrin levels are high in both the vagina and the uterus during menstruation. Masson et al. (1968) suggest that the adaptive significance of the luteal-phase rise in lactoferrin levels of the endometrium is to prepare for the maternal-fetal exchange of iron, but they were unable to detect lactoferrin in the placenta or amniotic fluid. They overlooked the need of the uterus to sequester the iron of menstrual blood.

Oviducts. The oviducts are exposed to pathogen-bearing sperm at the same time they are conveying newly ovulated or fertilized eggs. Therefore, antipathogen defenses would be expected to be greatest immediately after the potentially fertilized ovum descends the oviducts and enters the uterine cavity, which in humans occurs several days after ovulation. The epithelial tissue of the oviducts does indeed undergo considerable cell death and sloughing during the luteal phase of the menstrual cycle. In women and macaques, for example, the oviductal epithelium begins to regress within several days after ovulation, so that by the onset of menstruation it has decreased to about two-thirds of its thickness at ovulation (Brenner et al., 1983; Kim-Bjorklund et al., 1991). Thus the shedding of the oviductal epithelium takes place a phase ahead of the shedding of the endometrial epithelium and a phase behind the shedding of the vaginal epithelium.

The oviducts are most acidic during the follicular phase, when they are not helping to transport eggs, sperm, or zygotes. In rhesus monkeys the pH of the oviducts increases sharply at ovulation, from 7.1 to 7.3 during the follicular phase to 7.5 to 7.8 during the luteal phase (Maas et al., 1977). As the authors of this study point out, this rise in pH appears to be timed to provide an optimal environment for fertilization and development of the egg. (Why the oviductal pH in this study remained high throughout the luteal phase, rather than decreasing when the oviductal epithelium began to shed, still needs to be explained.) In sum, the female reproductive organs have a cascade of defenses designed to protect them against sexually transmitted pathogens. I propose that menstruation is one such defense.

Each cycle the uterus prepares for implantation by building a nutritious lining, which is also a favorable environment for many types of pathogen. The question of whether the healthy uterus normally contains bacteria has been debated for decades. B. Butler (1957) and Ansbacher et al. (1967), for example, detected bacteria in only about 5% of uteri, whereas Bollinger (1964) detected bacteria in 60% of uteri. It is not clear in the older literature, however, whether the subjects had been sexually active during the cycles in which cultures were obtained, or whether the methods used to detect bacteria were sufficiently sensitive to detect low levels. In a recent study by Hemsell et al. (1989) of healthy, sexually active women, 89% of uteri contained bacteria, but many fewer bacterial species were present in the uterus than in the cervix (or than are typically present in the vagina, which is essentially an external organ that does not

directly protect delicate eggs, zygotes, or embryos). That many uteri have low or undetectable levels of bacteria underscores the fact that uterine defense mechanisms are designed to rapidly clear bacteria. As B. Butler (1957) emphasizes, endometrial infection interferes with fertility.

Menstruation cyclically destroys the nutritious endometrium, wreaking havoc on the bacteria infecting it (discussed below). Uterine pathogens in sexually active females therefore would be expected to be more prevalent before menses than they are between the end of menses and the first postmenstrual copulation. But the invasive studies that would be needed to test this hypothesis (which would entail inserting probes into the uterus at successive stages of the menstrual cycle over several cycles) are not performed on healthy humans and have not been performed yet on nonhuman mammals. Although some studies of humans (e.g., Sweet et al., 1986; Rosenthal and Landefeld, 1990) have compared rates of reproductive tract infection in the various phases of the menstrual cycle, the results do not shed light on the effect of menstruation on uterine pathogens, for several reasons. First, each species of pathogen has its own distinctive incubation time, which is usually represented by a range rather than by a discrete interval, so that the initial infection and the clinically apparent infection occur at different times during the cycle. Second, studies of reproductive tract infection usually involve the cervix or the oviducts rather than the uterus; in cases of ascending infections, it is not clear when the infection of the uterus took place. And third, such studies do not control for the timing of sexual intercourse.

HOW MENSTRUATION PROTECTS AGAINST PATHOGENS

It might seem reasonable that blood loss would occur as an incidental by-product of extensive uterine shedding, since the luteal-phase uterus is highly vascularized. The existence of mechanisms designed to promote bleeding, however, indicates that bleeding per se is an adaptation and not simply a concomitant of uterine shedding. Menstrual bleeding appears to augment the uterine defense against pathogens through two main means: mechanical and immunological.

Mechanical. Menstrual blood helps to shed thick layers of potentially infected uterine tissue. Pockets of menstrual blood form hematomas at the base of the endometrium, which lift, stretch, and help to shed it (Markee, 1940). This enables the uterus to expel the tissue through mucosal discharge or, in overtly menstruating mammals, through menstrual blood flow. But if mechanical expulsion were the only function of menstruation, menstrual fluid would be expected to be composed almost entirely of water in order to spare the valuable components of blood. Yet the nonwater content of menstrual blood (12%) is almost two-thirds that of venous blood (19.5%) (Büssing, 1957). The important question, therefore, is why blood is advantageous. The answer may lie in the immunological components of blood.

Immunological. Menstrual blood delivers large concentrations of leukocytes to bacteria-infested endometrial tissue. Leukocytes directly combat pathogens and also phagocytize potentially infected necrotic tissue. In a study by De Merre et al. (1967), the number of leukocytes per cubic millimeter of menstrual blood (collected from intravaginal cups) was about three times as high as that of venous blood on the first day of menstruation, and twice as high on the third day. (It is not clear, however, whether the venous blood samples were collected during menstruation.) Massive leukocytic infiltration is a salient characteristic of the late luteal-phase human uterus (Ingerslev, 1982), and microscopic observations of various menstruating mammals have demonstrated significant leukocyte activity in the menstrual discharge in the uterus (Rao, 1932; Bartelmez, 1937; Markee, 1940). Venous levels of B lymphocytes and T lymphocytes (types of leukocytes) decrease significantly on the second and third day of menstruation, which may reflect the loss of such cells to menstrual blood (Tumbo-Oeri, 1985). Raptopoulou and Goulis (1977) point out, however, that the decrease in venous T lymphocytes precipitated by menstruation may be in part a response to hormonal flux rather than a consequence of menstrual blood loss. Rao (1932) noted in his meticulous observations of the menstruating uterus of the slender loris that many leukocytes in uterine blood appear to reenter the revascularized uterus rather than being dis-

charged through the cervix and vagina. One would therefore expect menstrual blood in the uterus to contain even larger concentrations of leukocytes than menstrual blood in the vagina.

Menstrual blood also delivers complement —a component of blood that destroys a wide spectrum of pathogens—to the uterus. In mammals with overt menstruation, complement in menstrual blood also would benefit the cervix and vagina. Demeš, Gombošová, Valent, Fabušová, and Janoska (1988) and Demeš, Gombošová, Valent, Janoska, Fabušová, and Petrenko (1988) have shown that although the complement activity of human menstrual blood discharged from the vagina is lower than that of venous blood, it is nonetheless often sufficiently high to kill the common vaginal parasite *Trichomonas vaginalis* in vitro. In their studies, the number of trichomonad parasites in the vagina decreased dramatically during menstruation, increasing again within days after the cessation of bleeding. Menstrual blood pouring into the uterus probably has a higher level of complement than that discharged from the vagina: Since menstrual blood encounters a trail of bacteria through the uterus, cervix, and vagina, some of the complement presumably is consumed along the way.

Menstrual blood differs in many ways from normal circulating blood, and the electrophoretic pattern of menstrual bloodstain indicates that it contains many more compounds (Alsawaf and Tu, 1985). Most of these other compounds have yet to be identified, but their possible antipathogen activity should be investigated.

Although menstrual blood would primarily protect the uterus, it may also help to protect the oviducts. Retrograde menstruation, in which menstrual blood flows from the uterus through the oviducts and into the pelvic cavity, appears to be a common phenomenon among humans; in one study, it was observed in 57 of 75 women (76%) (Liu and Hitchcock, 1986). Although there is no evidence that the oviducts themselves bleed, they are so narrow that bleeding would be difficult to detect.

Menstruation need not be overt in order to perform an antipathogenic function, because the direct expulsion of infected tissue from the body is not necessary for eradicating pathogens. Destruction of pathogens and phagocytosis of infected tissue by leukocytes should be sufficient for combatting moderate levels of pathogens. Even covert menstruation can deliver large quantities of blood (see Rasweiler, 1991) and, therefore, leukocytes throughout the uterine cavity. It is probable, however, that even in covertly menstruating mammals some of the infected tissue shed at menstruation is subsequently discharged via uterine, cervical, and vaginal mucus.

It might be argued that menstruation could not be an antipathogen adaptation because it would promote infection by delivering iron to pathogens. Almost all bacteria need iron to thrive (Weinberg, 1989), and exogenous iron can indeed promote infection (Payne and Finkelstein, 1978). Host iron is so important for bacterial growth that mammals have evolved various defenses to deprive bacteria of iron. Cellular recognition of signals indicating bodily infection triggers a set of facultative adaptations to prevent pathogens from obtaining iron: macrophages, which acquire iron from decaying erythrocytes for recycling, sequester the iron rather than releasing it to plasma; and neutrophils (types of immune cells that accumulate in infected areas) secrete lactoferrin to bind iron (Weinberg, 1984). Nevertheless, some bacteria can exploit wounds and utilize iron from some of the hemoglobin of the escaping blood (Weinberg, 1984). Thus, the menstrual wounds in the uterus would seem to be potential breeding grounds for pathogens (although menstrual wounds are not as exposed to the external evironment as are skin wounds, and therefore would not be as susceptible to exploitation by pathogens).

In order for menstruation to be an effective defense against pathogens, therefore, the reproductive tract must have concomitant mechanisms to sequester the iron of menstrual blood away from pathogens. As discussed above, lactoferrin concentrations in the human endometrium increase sharply prior to menstruation, and menstrual blood itself would be expected to contain high levels of lactoferrin. In a study by Cohen et al. (1987) involving three women, plasma levels of lactoferrin were found to be more than twice as high just before or during menses than during midcycle. This implies that lactoferrin levels in menstrual blood are also likely to be elevated. Furthermore, if

menstrual wounds, like other wounds, signal potential infection, then neutrophils migrating there would be expected to secrete high levels of lactoferrin.

Although lactoferrin generally causes bacterial death, it nevertheless is not able to inhibit all bacterial species from acquiring iron. Certain strains of *Neisseria gonorrhoeae*, for example, have evolved ways of acquiring iron from lactoferrin (Mickelsen et al., 1982). The finding that infections of the oviducts by *N. gonorrhoeae* usually occur within a week of a woman's onset of menses (Eschenbach et al., 1977; Sweet et al., 1986) might be explained by the ability of these pathogens to exploit the lactoferrin in menstrual blood for iron.

Another way the body could prevent menstruation from delivering much iron to pathogens would be simply to decrease the level of iron in menstrual blood, by, for example, decreasing the level in venous blood during menstruation. Vartiainen and Zilliacus (1968) note that venous levels of hemoglobin, to which most iron in women is bound (U. S. Department of Health and Human Services, 1988: 470), fluctuate with the menstrual cycle, reaching their peak at midcycle, declining in the luteal phase before menstruation, and reaching their lowest levels during menstruation. De Merre et al. (1967) found that levels of hemoglobin and of erythrocytes (which contain hemoglobin) were dramatically lower in menstrual blood than in venous blood, but they did not mention whether the measurements of venous blood were made during menstruation. A decrease in the hemoglobin content of menstrual blood would be expected to be accompanied by a corresponding decrease in iron. Furthermore, the numerous macrophages that accumulate at menstrual wounds may sequester the iron from the erythrocytes they phagocytize rather than release it to menstrual blood.

Whether the iron content of menstrual blood is indeed lower than venous blood, however, has not been experimentally determined. Most studies investigating iron loss through menstruation (e.g., Hallberg and Rossander-Hultén, 1991) simply assume that iron levels in venous and menstrual blood are the same, and infer a specific quantity of menstrual iron loss from measurements of blood loss. Other investigators have assumed that a significant amount of iron is lost through menstruation after they measured low venous serum levels of iron or ferritin (an iron-storage protein) at the cessation of menses (Ji et al., 1987; Andrade et al., 1991). But if venous iron is temporarily sequestered in cells during menstruation, such measurements overestimate actual iron loss. In a study by Zilva and Patston (1966), serum iron levels began decreasing significantly three days before the onset of menstrual bleeding, which may indicate that iron is being sequestered in preparation for menstrual bleeding. The authors of the study suggest that this cyclic variation in iron levels is a consequence of hormonal variation, since steroid hormones affect serum iron levels in other mammals that have been studied. The percentage of dietary iron absorbed by the intestines fluctuates according to the individual's need for iron (Wadsworth, 1992); perhaps iron absorption is also regulated in part hormonally, as an adaptation to reduce levels of iron in blood during menstruation.

No recent studies to my knowledge have measured the iron content of menstrual blood to determine how much iron is actually lost during menstruation, and two older studies appear to be contradictory. Büssing (1957) measured a 25% increase in the levels of iron in menstrual blood compared to venous blood, which he attributed to the destruction of erythrocytes and the release of their contents in menstrual discharge. Thomas (1970), on the other hand, obtained a measurement of the iron content of menstrual blood that corresponds to a 15% decrease compared to the iron content of venous blood (assuming an average menstrual blood loss of 40 milliliters). Measurements of iron content are difficult to interpret because they are necessarily indirect or incomplete; iron binds to many different kinds of protein in cells or in serum and can be stored at a wide range of levels inside cells. In any case, the reduced levels of hemoglobin and erythrocytes in menstrual blood indicate that iron is spared to some extent during menstruation, and the increased levels of lactoferrin in the premenstrual endometrium and in the venous blood during menstruation indicate that much of the iron in menstrual blood is rendered unavailable to most pathogens.

Although it may not seem intuitively obvious that pouring blood on uterine pathogens helps to eradicate them, blood is important for fighting infections in all organs. When an eye or an area of skin becomes infected, for example, it reddens because its blood vessels expand, enabling large numbers of immune cells to reach the infected area. Periodic nonpathological bleeding is probably unique to the uterus because it is the only truly internal organ that is regularly exposed to vectors of disease. Although the gut and lungs are sometimes exposed to vectors of disease in the form of food or pollen, they are essentially extensions of external organs, because they function to directly filter substances from the external environment. The uterus, by contrast, does not function as an interface between the external and internal environments. Furthermore, as D. Symons (pers. commun.) points out, unlike most other organs, which need to perform vital functions continuously, the uterus only needs to perform a function episodically, and thus can afford the "time out" to shed extensively and to bleed.

In sum, menstruation appears to protect the uterus by killing, dislodging, and either phagocytizing or discharging pathogens and potentially infected tissue. Menstruation directly protects the uterus and, possibly, the oviducts. Menstruation indirectly protects the ova from pathogens that otherwise would ascend the reproductive tract. Any benefits of menstrual blood to the vagina, however, are probably incidental.

OTHER FORMS OF UTERINE BLEEDING

Nonmenstrual forms of normal uterine bleeding may also perform an antipathogen function. Overt proestrous or periovulatory bleeding has been documented in various mammals, including some that also menstruate overtly. Bleeding during and following implantation, spontaneous abortion, and parturition is known to occur in many mammals and may occur in all of them. Menstrual bleeding has traditionally been viewed as having a different etiology from other forms of normal uterine bleeding, none of which has been thought to have a function per se. Determining whether these other forms of uterine bleeding have essentially the same function as menstruation would ultimately entail investigating whether they employ the same mechanisms as menstruation and whether the blood discharged has the same composition as menstrual blood. Low concentrations of clotting factors and high concentrations of leukocytes and lactoferrin would imply an antipathogen adaptation.

Periovulatory bleeding. Periovulatory, or midcycle, bleeding has been documented to occur overtly or covertly in several primates, including humans (Shaw and Roche, 1985), vervet monkeys (Rowell, 1970), Sykes monkeys (Rowell, 1970), and, possibly, cottontop tamarins (Brand, 1981) (see Appendix). In women, the endometrium undergoes slight regression and bleeding during ovulation and resumes growth after ovulation. Shaw and Roche (1985) interpret this fluctuation as a by-product of the temporary decline in estrogen levels associated with the ovulatory surge in follicle-stimulating and luteinizing hormone levels. Midcycle bleeding in response to the hormones that signify ovulation (and possible conception), however, may be an adaptation to clear bacteria from the uterus in preparation for blastocyst implantation.

Periovulatory bleeding would defend against pathogens most effectively if it occurred immediately following the period of sexual receptivity, which is the period of sexual transmission of pathogens. Ovulation marks the end of sexual receptivity in the cycles of most nonhuman mammals. In most domestic cattle, for example, bleeding occurs within 48 hours after the end of estrus, or about 15 to 20 hours after ovulation; it is caused partly by the destruction of the endometrial epithelium and partly by diapedesis (bleeding of capillaries directly into the uterine cavity) (Nalbandov, 1976: 142). (Although domestic and laboratory mammals are not the most appropriate models of adaptation by natural selection, their close association with humans makes them the most well-studied mammals.) Periovulatory uterine shedding and bleeding would not be expected to be as extensive as menstrual shedding and bleeding (except in mammals with long intervals between estrus and implantation) because the postestrous uterus must prepare a thick endometrium for implantation. Periovulatory bleeding following

estrus may well turn out to be a general mammalian phenomenon.

Proestrous bleeding. In some wild mammals, such as the slender loris (Rao, 1932) and the northern coyote (Whiteman, 1940), uterine bleeding precedes estrus (as it does in the domestic dog). The purpose of this proestrous bleeding may be to eradicate pathogens in the uterus that survived the last episode of uterine bleeding and that replicated in the intervening span of time. If not eliminated prior to estrus, these tenacious pathogens might otherwise attach to incoming sperm during estrus and ascend the oviducts. Since data on nonmenstrual uterine bleeding are sparse—possibly because such bleeding in most mammals is covert—it is not clear if proestrous and periovulatory bleeding are mutually exclusive. If they are, whether uterine bleeding precedes or follows estrus may depend on the length of the interval between estrous cycles.

Proestrous bleeding might be less adaptive in polyestrous mammals (which can experience at least several consecutive cycles in a year), such as Old World monkeys and apes, since in consecutive cycles it would immediately follow menstruation without any intervening copulation and consequent exposure to pathogens. Proestrous bleeding would be more likely to occur in species, such as the slender loris or the coyote, that consistently have long intervals between the end of one cycle (marked by menstruation or parturition) and the onset of the next estrous period. Both of these mammals are basically monestrous (although the slender loris may have up to two consecutive cycles per season and possibly two sexual seasons per year) (Rao, 1932; Whiteman, 1940; Ramaswami and Kumar, 1965).

Polyestrous or seasonally polyestrous mammals, however, would also benefit from uterine bleeding prior to an estrous period that followed a long interval without bleeding, such as the interval between parturition and the weaning of offspring or between the end of one breeding season and the beginning of the next. The phenomenon of "silent ovulation," which has been documented in rhesus monkeys during the nonbreeding season (Herndon et al., 1987), may have a function in polyestrous mammals analogous to that of proestrous bleeding in monestrous mammals. During the nonbreeding season, rhesus monkeys often ovulate without exhibiting estrus. Markee (1940) documented menstruation in rhesus monkeys during the nonbreeding season, but noted that it is less frequent and that the degree of tissue shedding and bleeding is usually significantly less than during the breeding season. During the nonbreeding season, it may be important to continue to regularly disinfect the uterus to prevent its recolonization by tenacious strains of pathogens that survived the previous episode of uterine bleeding. Ovulation would be induced as a low-cost by-product of the sequence of hormonal changes necessary to induce menstruation. Whether silent ovulation is a common mammalian phenomenon is not yet known. It would seem to be adaptive to undergo at least covert bleeding immediately preceding the first postpartum estrous period, but whether such bleeding actually occurs in mammals that do not have overt proestrous bleeding needs to be investigated. Among women who breastfeed for prolonged periods, the first postpartum menstrual cycle is often anovulatory, which means that in many women overt bleeding necessarily precedes postpartum conception (Howie and McNeilly, 1982; Brown et al., 1985).

Implantation bleeding. In many mammals, uterine bleeding accompanies or follows implantation of the embryo. When overt, such bleeding even fools some newly pregnant women into believing they are menstruating. Implantation bleeding (also called "postconceptional bleeding") has been documented in various mammals, including the West European hedgehog *Erinaceus europaeus* (Deanesly, 1934), the Sykes monkey, the vervet monkey, the Barbary macaque (Küster and Paul, 1984), the stumptail macaque (Brüggemann and Dukelow, 1980), and the common chimpanzee (Elder and Yerkes, 1936). In the latter three species, overt bleeding begins more than a week after the start of implantation (Elder and Yerkes, 1936; Küster and Paul, 1984), at about the time that the embryonic placenta begins to absorb maternal blood. It is possible that the uterine spiral arteries that are tapped by the newly forming placenta are designed to divert some blood to the uterine cavity at im-

plantation to defend the embryo against bacteria that have persisted since estrus. This hypothesis would be supported by evidence that blood discharged from the uterus at implantation differs in composition from that which nourishes the implanting embryo. Data are as yet sparse, but the antipathogen hypothesis predicts that covert or overt implantation bleeding must occur in mammals generally.

Postpartum or postabortion bleeding. In humans, the uterus bleeds for many days and sometimes for weeks after parturition. In Barbary macaques, uterine bleeding after parturition or abortion lasts longer than one week and is more intense than menstrual bleeding (Küster and Paul, 1984). The fact that the wound at the site of uterine hemorrhage does not clot promptly implies that it is designed to bleed for prolonged periods. Bacteria colonize the uterus immediately after parturition (Hirsch, 1979) because the cervix is widely dilated, exposing the uterus to the pathogens of the lower reproductive tract. Postpartum or postabortion bleeding may be especially important in combating pathogens.

The existence of one form of uterine bleeding does not obviate the need for the other forms, even if all function to combat pathogens, because each type responds to a different reproductive event. A mammal that experiences several forms of uterine bleeding may exhibit some overtly and others covertly. If uterine bleeding functions to defend the upper reproductive tract and the implanting embryo against pathogens, then the optimal bleeding strategy for most mammals would be: (1) to bleed and shed extensive amounts of tissue at the end of the cycle (true menstruation) in order to prevent sexually transmitted bacteria from multiplying extensively and colonizing the uterus and oviducts (in monestrous mammals, which lack the periodic cleansing of consecutive cycling, additional bleeding preceding estrus would help to prevent tenacious pathogens in the uterus from attaching to sperm at estrus and ascending the oviducts); (2) to bleed and shed as much tissue as can be spared between copulation and potential implantation and to bleed during implantation, in order to prevent bacteria introduced during copulation from interfering with implantation, embryonic development, and subsequent reproductive ability; and (3) to bleed and shed tissue extensively following parturition or abortion in order to prevent infection after the exposure of the upper reproductive tract to the pathogens of the lower reproductive tract.

As shown in the Appendix, at least three species of bat—the Seba's short-tailed bat, the common vampire bat, and the Palla's long-tongued bat, all of which are in the family Phyllomostidae—combine (1) and (2) above by menstruating at or shortly after ovulation. The close temporal association of these two events is possible in these species because the interval between ovulation and implantation is at least two weeks (the fertilized ovum is retained in the oviducts), and the uterus thus has sufficient time after exposure to sperm-transported pathogens for extensive shedding, bleeding, and rebuilding before implantation.

Another form of normal bleeding in the reproductive system that may perform a similar antipathogen function is ovarian bleeding, which occurs at ovulation from the ruptured follicle. Ovarian bleeding has been demonstrated in many mammalian species (see, e.g., Asdell, 1964) and may occur in all of them. Ovulation briefly exposes inner tissues of the ovary to pathogens that have ascended the oviducts on sperm. Some sperm travel the full length of the oviducts and even escape into the peritoneal cavity (Blandau, 1969), and in nonhuman mammals most such sperm would arrive in the vicinity of the ovary at about the time of ovulation. A small flow of blood from the ruptured area of the ovary containing a large concentration of immune cells may destroy nearby pathogens.

PREDICTIONS FOR THE LIKELIHOOD AND DEGREE OF MENSTRUATION AMONG MAMMALS

The degree of menstruation among mammals may comprise a continuum, from microscopic to profuse bleeding. The fact that mice, who are not generally thought to menstruate, can be artificially stimulated to do so suggests that many mammals not thought to menstruate may actually do so microscopically. The antipathogen hypothesis predicts that most, if not all, mammals menstruate, although many do so covertly (i.e., there is no obvious external flow). If menstruation is an adaptation,

then interspecific variation in the likelihood and the degree of menstruation should be a function of the factors determining menstruation's costs and benefits. The primary factors that I believe affect these costs and benefits are outlined below.

Menstruation Would Benefit Females of Some Species More Than Others

Selection Pressures to Menstruate Should Increase with Decreasing Probability of Pregnancy per Cycle (Fecundability)

Mammals with medium to low (<<100%) fecundability face strong selection pressures to menstruate, because a mammal that copulates without subsequent uterine bleeding risks infection of its uterus and oviducts. Since menstruation occurs only in the absence of pregnancy, mammals that virtually always become pregnant in a cycle during which they copulate have less need for menstruation. Such mammals, however, face strong selection pressures for uterine bleeding following ovulation, during implantation, and after parturition. Although no species has a fecundability of 100% some mammals, such as mice, have very high fecundability (about 98%) (Nalbandov, 1976), while others, such as humans, have relatively low fecundability (averaging well below 50%) (Wood, 1989). The major correlates of low fecundability are the following:

(1) *Polyestrous cycling.* Polyestrous mammals, which can experience consecutive cycles throughout the year or throughout a prolonged breeding season, by definition do not get pregnant every cycle. Monestrous mammals, by contrast, are able to cycle only once or twice per year and tend to have high fecundability. (Monestrous mammals usually have short breeding seasons because of dramatic seasonal fluctuations in food availability and the consequent need to time the birth or weaning of offspring to the ecologically optimal parts of the year.) Mammals that have only narrow windows within which to breed have therefore evolved mechanisms to ensure high fecundability.

Polyestry would be expected to be favored in mammals that could afford it as insurance against reproductive failure (including abortion, fetal malformation, and infant death). That many mammalian species (including monestrous and some polyestrous species) have high fecundability implies that the lower fecundability of many polyestrous species does not reflect inherent constraints on reproductive engineering. Rather, it may reflect the fact that female mammals not confined to short breeding seasons can afford reproductive adaptations that result in lower fecundability as a by-product. For example, polyestry may provide females with wider scope for sperm and zygote selection, which would be especially important in species with single births. [Mechanisms to discriminate against subtle or gross morphological defects in sperm, zygotes and blastocysts may be common in mammalian female reproductive tracts and ova (see Redi et al., 1984; Menkveld et al., 1991; Sonta et al., 1991; Roldan et al., 1992)]. Polyestry also may give females more facultative control over the timing of conception, in response to the availability of food, sleeping sites, desirable mates, female allies, or other factors that affect infant quality or infant survival. Lower fecundability itself might even be selected for in some polyestrous species (particularly those with monogamous breeding systems) as a form of extended courtship. One cost of low fecundability, however, is an increased number of copulations per viable pregnancy and, therefore, an increased exposure to sexually transmitted pathogens.

(2) *Monotocous birth.* Monotocous species (those bearing only one offspring per pregnancy) generally have lower fecundability than polytocous species (those bearing multiple offspring). Monotocous females ovulate enough ova to have a good chance of bearing one, or occasionally two, offspring, whereas polytocous females ovulate enough ova to bear a litter. According to Nalbandov (1976: 270), the fertilization rate of polytocous mammals that are inseminated at the proper time is almost 100% (the average for rabbits, guinea pigs, mice, and rats is

98.6%), whereas the rate for monotocous mammals is generally much lower. Although horses are monotocous, for example, artificially superovulated mares are twice as likely as single ovulating mares to produce viable embryos after artificial insemination (Squires et al., 1987). Monotocous species generally ovulate one or two ova per cycle, presumably because it would be energetically unfeasable and even dangerous to implant more embryos than the uterus could support. One exception, however, is the Transvaal elephant shrew *Elephantulus myurus*, which ovulates about 120 eggs per cycle (van der Horst, 1955), but apparently has mechanisms to ensure that only one or two of them implant.

(3) *Concealed ovulation*. In mammals with concealed ovulation, most copulation is decoupled from ovulation, which decreases fecundability. Ovulation can be considered to be concealed if it is unaccompanied by cues that signal female fertility to males. Although concealed ovulation necessarily implies more or less continuous female sexual receptivity, these two features are discussed separately. Concealed ovulation is expected to increase the likelihood of menstruation, and is discussed in this section, whereas continuous sexual receptivity is expected to increase the degree of menstruation, and is discussed in a following section. The time elapsing between copulation and ovulation is a crucial determinant of reproductive success, because the postovulatory age of the ova and the postejaculatory age of the sperm significantly influence the probability of fertilization and the viability of embryos (Nalbandov, 1976; Martin, 1992). (Although the fertilizable life span of ova and sperm are usually measured in hours or days, the sperm of some species are preserved in the uterus or oviducts for months before fertilization.)

Even different parts of a short estrous period may not be equally conducive to fertilization. Experiments with cows, rats, and guinea pigs show that rates of fertilization and pregnancy decline rapidly with the postovulatory age of the ova. A cow ovum 14 hours after ovulation has a 56% probability of being fertilized successfully, whereas 20 hours after ovulation it has only a 31% probability (Nalbandov, 1976). Furthermore, aged ova that do become fertilized are less likely to develop to the embryonic stage. Generally, as the age of the ova at fertilization increases, the size of the litter decreases and the number of abnormalities increases (Nalbandov, 1976: 241). In a study of mice, for example, delaying mating until the end of estrus significantly decreased the probability of fertilization and increased the risk of embryonic abnormalities (Sakai and Endo, 1988). As Nalbandov (1976: 243) points out, the problem of nonviability of embryos resulting from the fertilization of aged eggs may be a particularly significant cause of low fertility in monotocous species.

Almost all mammals experience a well-defined estrous period that immediately precedes or coincides with ovulation. The only mammal whose ovulation is known to be truly concealed is *Homo sapiens*. Although some studies have indicated that women accept male sexual advances or initiate sexual intercourse slightly more frequently around the time of ovulation than during other phases of the cycle (Udry and Morris, 1968; Adams et al., 1978), most human intercourse occurs outside the peak period of fertility. By contrast, even in nonhuman mammals that have been reported to copulate throughout the menstrual cycle, almost all ejaculatory copulations occur during the peak period of fertility (see below). The lack of synchrony between copulation and ovulation is probably one reason why healthy fertile women have such relatively low fecundability.

Although Andelman (1987) hypothesizes that ovulation is concealed in the vervet monkey *Cercopithecus aethiops*, as it is in humans, the supporting data are by no means conclusive. Data on the rates of copulation per week of breeding season

were pooled for three groups of monkeys over five breeding seasons and graphed in relation to the estimated dates of conception. Although the results might seem to suggest that copulation takes place throughout the menstrual cycle, hormonal analyses to accurately assess the stage of the females' menstrual cycles at copulation and the dates of conception were conducted only in one group over two seasons, and these data are not listed separately. The great majority of the data in the graph is based on dates of conception estimated from the individual dates of birth and the average gestation length for that species. Thus, while it is possible that the vervet monkey has concealed ovulation, this study does not demonstrate it.

Sexual activity outside of the female's fertile period occurs occasionally in some primates, but its frequency appears to have been exaggerated, as discussed in more detail in a following section. Female chacma baboons, for example, sometimes copulate on nonfertile days, but most ejaculations—and all ejaculations with adult males—occur during the female's peak period of fertility, which is the period of maximal swelling of her sexual skin (Saayman, 1970). Thus this nonfertile copulation does not represent concealed ovulation and does not reduce the female's fecundability. Copulation during early pregnancy has been documented in langurs and certain other mammals that mate with more than one male during an estrous cycle, and Hrdy (1977, 1979) has provided strong evidence that, at least in some species, such copulation may be a female strategy for confusing paternity and thereby preventing infanticide by males unrelated to the infant. Copulation during pregnancy, however, would not affect fecundability or the likelihood of menstruation in a given species.

(4) *Spontaneous ovulation.* A mammal that ovulates spontaneously does so independently of copulation, so that ovulation and copulation are not necessarily optimally synchronized. When ovulation is induced by copulation, by contrast, these two events are necessarily optimally synchronized, and fecundability increased. Daly and Wilson (1983: 219) point out that induced ovulation generally occurs in solitary species, such as camels, for whom the close proximity of potential mates at any given time cannot be guaranteed. (Induced ovulators cannot successfully mate at just any time, however; estrus—whether spontaneous or induced after a period of exposure to a male—is still a prerequisite.) The inducibility of ovulation among mammals appears to some extent to be a matter of degree. Copulation has been shown to hasten ovulation in various spontaneous ovulators, including, according to some researchers, humans (Jöchle, 1973, 1975). Jöchle (1975) points out that many spontaneous ovulators appear to be facultative reflex ovulators; that is, they ovulate more readily or more eggs in response to vaginal or cervical stimulation or to other neurohormonal mating stimuli, such as the olfactory or visual cues of cohabitation.

The selection pressures favoring menstruation would be expected to increase with decreasing inducibility of ovulation. Mammals with truly spontaneous ovulation—that is, with little or no inducibility—would have, on average, less precise synchrony between copulation and ovulation, lower fecundability, and greater need for menstruation. Menstruating mammals with either induced corpus luteum formation or induced ovulation (which induces corpus luteum formation) would be likely to menstruate only after unfertile matings, and not after abstinent cycles, because pseudopregnancy, which culminates in menstruation, does not occur in the absence of corpus luteum formation. This would prevent such mammals from incurring the nutritional costs of menstruation during cycles in which there was no sexual transmission of pathogens.

Even monestrous or polytocous mammals can have cycles of unfertile matings or suffer reproductive failure due to, for example, ado-

lescent infertility (Hartman, 1931) or uterine resorption of embryos (Wasser and Barash, 1983). Thus, selection may favor mechanisms to menstruate even in monestrous and polytocous species, although menstruation would occur much less frequently in these species than in polyestrous and monotocous species.

The Average Degree of Menstruation in a Species Should Be Positively Correlated with the Average Sexually Transmitted Pathogen Load of That Species

The costs imposed on females by sexually transmitted pathogens are likely to be a function of the following four factors: (1) the total number of pathogens transmitted to the uterus, which is likely to be positively correlated with the number of ejaculated sperm, since sperm are vectors for pathogens; (2) the diversity of pathogens transmitted to the uterus and the frequency of uterine exposure to pathogens previously unencountered by the female's immune system (these factors increase the risk that at least one of the pathogen species will replicate to high levels and cause significant harm); (3) the virulence of the pathogens transmitted [Ewald (1991) points out that an increase in sexual promiscuity favors an increase in the virulence of sexually transmitted pathogens because it shortens the intervals between the pathogens' opportunities to spread to new hosts and therefore favors pathogen strains with shorter latency periods and faster rates of replication]; and (4) the extent of colonization of the uterus by pathogens within a menstrual cycle, which is determined in part by the amount of time that elapses between copulation and menstruation. The major correlates of high pathogen load per estrous cycle are the following:

(1) *Promiscuous breeding systems*. Species differ greatly in their breeding systems; that is, in the extent of male and female promiscuity. (In this article, the extent of promiscuity in a species is defined by the number of different sexual partners, not by the number of copulations.) Menstruation would be especially adaptive among promiscuous mammals because promiscuity increases the sexual transmission of pathogens. Both male and female promiscuity should increase the diversity and virulence of pathogens transmitted sexually to females, but female promiscuity should also increase the total number of sexually transmitted pathogens, because female promiscuity selects for high sperm volume (i.e., high sperm number) in males. When estrous females regularly mate with more than one male, males compete to fertilize females by producing large quantities of sperm (Short, 1981). If sperm are vectors for pathogens, then an increase in the number of sperm ejaculated would be likely to lead to a greater pathogen load in the uterus (D. Symons, pers. commun.). The type of breeding system of a species, therefore, should dramatically influence the average degree of menstruation in that species. [Breeding system, rather than social system, is the crucial variable determining the degree of sexual transmission of pathogens. Female hamadryas baboons, for example, often congregate at night in large multimale groups, but they breed in harem groups (Kummer, 1984).] Breeding systems can be ranked according to the extent to which they facilitate the sexual transmission of pathogens. These rankings, from highest to lowest, are as follows:

(a) *Multimale breeding systems*. Estrous females in multimale breeding systems often mate with more than one male per cycle. The males tend to have very large testes for their body size and correspondingly high sperm volumes (Short, 1981; A. P. Møller, 1988; Harvey and May, 1989). In the chimpanzee, which has a multimale breeding system, the testis weight as a proportion of body weight is almost 16 times greater than that of the gorilla, which has a unimale breeding system (Short, 1981). Chimpanzee males also mate much more frequently than gorilla males, manufacturing enough sperm for four full-strength ejaculations per day (Short, 1981). In general, the ejaculates of primates with large testes are characterized by relatively large sperm volumes, high sperm counts, high sperm motility, and a large percentage of motile sperm (A. P. Møller, 1988). Hence, in such species many more vectors of sexually transmitted pathogens (sperm) can be expected to reach the uteri. The degree of menstruation in a given species may be to some extent a function of male testis weight (D. Symons, pers. commun.). The

transmission of pathogens from male genitalia to the female reproductive tract may also be greater in multimale breeding groups because copulations in such groups frequently involve prolonged or multiple intromissions (see Dixson, 1991), which increases male-female genital contact. Furthermore, the combination of male and female promiscuity in multimale breeding systems should promote greater pathogen virulence. In sum, copious menstruation is expected to be especially strongly selected for (other things equal) among females of multimale breeding systems.

(b) *Polyandry*. Polyandrous breeding systems (in which one female has more or less exclusive sexual access to two or more males) should favor intense sperm competition and, thus, relatively copious menstruation (D. Symons, pers. commun.). Field studies suggest that several species of Callitrichidae, including the cottontop tamarin *Saguinus oedipus*, mate polyandrously (Sussman and Kinzey, 1984). Although this species and another callitrichid, the common marmoset *Callithrix jacchus*, are listed as monogamous by Harcourt et al. (1981), the exceptionally large testis weight in relation to body weight in males of these species (Harcourt et al., 1981) implies that the females are indeed likely to be polyandrous and to menstruate copiously compared to nonpolyandrous mammals of the same body size.

(c) *Breeding systems of solitary mammals*. The degree of menstruation in species with solitary social systems should vary directly with the degree to which males are able to maintain exclusive sexual access to females during a typical cycle. Females living in solitary social systems sometimes mate with more than one male during a given cycle, but since matings between solitary mammals tend to be relatively opportunistic and sporadic, their degree of promiscuity and menstruation typically should be less than that of mammals living in multimale breeding systems. In species in which solitary males form temporary consortships with females and successfully exclude other males from their territories, male testis weight would be expected to be correspondingly low and females would be expected to exhibit scant menstruation.

(d) *Harems*. In harem breeding systems, one male has more or less exclusive sexual access to a group of females (until he is ousted by a rival). (Multimale and harem breeding systems are end points of a continuum; the degree to which a breeding system is truly a harem system depends on the degree to which the harem male is able to exclude other males from sexual access to his females.) Males in species with obligate harem breeding systems tend to have much smaller testes than do males in species with multimale breeding systems (Short, 1981; A. P. Møller, 1988); hence, harem males ejaculate fewer vectors of disease into female reproductive tracts. Although testis weights and sperm volumes are no greater in harem than in monogamous males, harem males are promiscuous and therefore more likely to transmit a greater diversity of pathogens. Therefore, a slightly greater degree of menstruation should be favored in harem than monogamous females. Although some females of harem and monogamous breeding systems "sneak" copulations with males other than their primary mates (Baker and Bellis, 1989), they do not exhibit the degree of promiscuity that females of multimale breeding systems do, and thus would not need the same degree of menstruation.

(e) *Monogamy*. Of all the breeding systems, monogamy provides the lowest selection pressures for overt menstruation. Mammals in monogamous systems generally copulate less frequently, have lower sperm volumes, and are by definition less promiscuous than mammals in other breeding systems (even though they are not always strictly "faithful" to their mates). Monogamous gibbons, for example, have small testis weights (Harcourt et al., 1981) and very low sperm motility (9% of the sperm in the monogamous gibbon *Hylobates lar* are motile compared to up to 94% in the promiscuous macaque *Macaca mulatta*) (A. P. Møller, 1988).

The presence of a relatively large number of sperm in the ejaculate, however, does not necessarily indicate that a correspondingly large number of sperm reach the uterus and oviducts. Baker and Bellis (1988, 1989) hypothesize that different sperm morphs within a single ejaculate serve different functions: the highly motile morph to fertilize ova; and the seemingly deformed morphs to serve as "kamikazes," which aggregate to block the sperm of other males. Harcourt (1991), however, counters this hypothesis by pointing out that males of multimale breeding systems do not produce a greater proportion of deformed sperm. But if kamikaze sperm aggregate, as Baker and Bellis (1988) suggest, at the strategically important cervico-utero and utero-tubal junctions, the uterus would still be exposed to significant numbers of bacteria-laden sperm, even though the function of these sperm would not be to

target ova. Also, in estimating the number of sperm that reach the uterus and oviducts, it is important to subtract sperm that the female expels. Immediately following copulation, females of at least some multimale breeding systems expel a large volume of semen (Ginsberg and Rubenstein, 1990).

D. Symons (pers. commun.) suggests that the degree of menstruation exhibited by individual females may facultatively track their degree of copulation and promiscuity. Dominant females in some polygynous and polyandrous species successfully copulate more often than subordinate females (see Silk and Boyd, 1983; Wasser, 1983; Smuts, 1986). Dublin (1983), for example, notes that dominant females in African elephant herds may deliberately limit the access of subordinate females to mates. Such dominant females should benefit from a more copious menstrual flow. It is possible, for example, that in some species extensive or repeated stimulation of the vagina, cervix, or clitoris increases the degree of menstruation in that cycle via neuropathways to the uterus.

Changes in the composition of males in the group would be likely to influence the degree of female promiscuity and might lead to facultative adjustments in the degree of menstruation. Red colobus monkeys *Colobus badius* of the Kibale Forest in Uganda, for example, tend to live in multimale groups, whereas at least one population of red colobus along the Tana River in Kenya lives in unimale harems (Struhsaker and Leland, 1985). Facultatively greater degrees of menstruation might be expected in females at the former location, especially if the males of these species can facultatively adjust their mating frequency and sperm volume. An abrupt increase in promiscuity by individual females might also precipitate a facultative increase in menstrual flow. Red colobus females, for example, solicit copulations with a greater number of males per estrous cycle during periods of frequent infanticide committed by males unrelated to the victimized infants (Struhsaker and Leland, 1985); it might be worth investigating whether these females exhibit correspondingly increased menstrual flow during such episodes.

(2) *Extended estrus or continuous sexual receptivity*. A greater degree of menstruation would be favored in mammals with significantly extended estrus or continuous sexual receptivity than in mammals with highly restricted estrous periods. Continuous sexual receptivity lengthens the interval between the first postmenstruation exposure to sexually transmitted pathogens and the next uterine bleeding and consequent clearing of these pathogens from the uterus (assuming ejaculation accompanies copulation). This probably enables pathogens to replicate and colonize the uterus more extensively, necessitating a greater degree of menstrual shedding and bleeding. Although large numbers of sperm do not necessarily succeed in reaching the uterus during nonfertile parts of the cycle, when the cervical mucus is hostile to sperm (Chantler et al., 1989), some of the sperm that do penetrate the mucus undoubtedly are vectors for pathogens. In humans, according to Katz (1991), sperm can penetrate the viscous cervical mucus early in the proliferative phase of the menstrual cycle, when estrogen is the dominant hormone, although the rate of penetration is not as high as during the periovulatory phase. Repeated parasitization of the uterus by sperm-borne pathogens at an early phase of the cycle should select for a copious menstrual flow.

Continuous sexual receptivity has been documented unambiguously only in humans. In captivity, however, some mammals display mating behaviors that are unnatural to their species, including frequent copulation outside of fertile periods. Although some researchers (such as Martin, 1992) argue that various nonhuman primates exhibit continuous sexual receptivity even in the wild, the primary literature cited in favor of this argument does not seem to support it.

In a study of wild chimpanzees *Pan troglodytes*, for example, Tutin and Mc-

Ginnis (1981) note that of the 1137 copulations they witnessed, 97.2% (all but 32) took place when the female was maximally fertile (i.e., when her sexual skin was maximally swollen). Although the researchers did pay most attention to maximally swollen females, they did so because these females were by far the most sexually active. By contrast, most human copulation takes place outside of maximally fertile days (see Adams et al., 1978). In a study of wild redtail monkeys *Cercopithecus ascanius*, Cords (1984) indicated that estrus was not necessarily restricted to a particular phase of the menstrual cycle; however, her definition of estrus was the female's participation in at least two of four behaviors, of which only one of the four included copulation (and not necessarily ejaculation). Had estrus been defined as copulation with ejaculation, a distinct cyclical pattern probably would have been revealed. Bonobos *Pan paniscus* (Pygmy chimpanzees) have also been characterized as continuously sexually receptive. But in a study of wild bonobos, Furuichi (1987) reports that almost all copulations involved maximally swollen females, which, as Furuichi notes, contradicts the reports that bonobos copulate frequently outside of fertile periods. Other studies relevant to this discussion, by Andelman (1987) on vervet monkeys and Saayman (1970) on chacma baboons, have been discussed above. In summary, the extent of copulation during nonfertile periods of the menstrual cycle is likely to affect the degree of menstruation, but humans may be the only species to exhibit truly extended estrus.

Factors that influence the overall pathogen load of a species, such as the latitude of its habitat, might also affect the sexually transmitted pathogen load and, accordingly, the degree of menstruation. Although the diversity of pathogens and other organisms generally increases with decreasing latitude, it is not known whether sexually transmitted pathogens show the same gradient of diversity. In investigating the relationship between latitude and menstruation, however, one should distinguish the degree of menstruation from the likelihood of menstruation. A positive correlation between low latitude and likelihood of menstruation might be spurious: Although low latitude is positively correlated with higher overall pathogen loads, mammals living at low latitudes are more likely to be polyestrous, because they are less likely to experience significant seasonal variations in food availability, and, as discussed above, polyestrous mammals are more likely to menstruate.

Menstruation Would Be More Costly for Females of Some Species than Others

Selection Pressures for Menstruation and Degree of Menstruation Should Decrease with Decreasing Body Size

Mammalian body size should influence the likelihood and the degree of menstruation. Small mammals cannot afford to menstruate as copiously as large mammals can. Menstruation entails bleeding a volume of blood from a surface area of uterus (the area of the endometrium, which forms the surface of the uterine cavity). Increasing the size of an object, while keeping its shape constant, increases its volume by the third power of its linear size, but its surface area only by the second power. If uterine size among mammals generally scales allometrically, then large mammals contain a larger bodily volume of blood per surface area of endometrium than do small mammals, which means that they can afford to menstruate a larger volume of blood relative to body size. Some mammalian species, however, may have large or small uteri for their body size and blood volume, depending on such factors as the maximum number and size of the fetuses that their uteri are designed to hold. Polytocous mammals, in particular, may have relatively large uteri, in which case they would face relatively large costs if they menstruated copiously.

Selection Pressures for Overt Menstruation Should Decrease with Increasing Reliance on Cryptic Behavior

Menstrual blood in humans (and presumably in other mammals as well) has a strong and distinctive odor that could potentially attract predators. This should result in selection pressures against overt menstruation in some

prey species. Bears have been reported to react to the smell of human menstrual blood with an aggressive curiosity and a disposition to attack (March, 1980), although the alleged cause-and-effect relationship between menstrual odor and bear attacks has been disputed by some researchers (L. L. Rogers et al., 1991). Because certain mammals, such as slow lorises and sloths, avoid predation largely by avoiding detection—that is, by either remaining stationary or moving cryptically—menstrual discharge might compromise their safety. Therefore, such mammals are less likely to menstruate overtly.

COMPARATIVE MAMMALIAN DATA

Methods of Data Collection

The Appendix lists the nondomesticated, nonlaboratory mammals that have been documented in the primary literature to menstruate or to exhibit proestrous, periovulatory, or implantation uterine bleeding. Domesticated and laboratory animals are excluded from the appendix because their adaptations have been grossly altered by artificial selection. The comparative literature on menstruation was located by extensively searching biological, medical, and zoological databases, by surveying bibliographies of books on mammalian reproduction, and by eliciting the database services of the Seattle Primate Information Center of the University of Washington. Although a reasonable amount of information on female reproductive cycling exists, menstruation has yet to be investigated in the vast majority of species.

The Appendix does not include a section with references to studies that claim a particular species does not menstruate, because such claims have been based solely on the lack of external signs of menstruation, and, in most cases, contradictory evidence is available. Menstruation cannot be ruled out in a species that lacks overt bleeding unless the possibility of covert menstruation has been investigated. Data on the slender loris *Loris tardigradus* illustrate this point. Ramaswami and Kumar (1965) stated that the slender loris does not menstruate even microscopically because they saw no evidence of sanguineous discharge at any time of the estrous cycle or of erythrocytes in the dissected uteri of estrous females. Females in estrus, however, would not be expected to be menstruating, and any midcycle uterine bleeding would be likely to precede or follow estrus, not coincide with it. Rao (1932), by contrast, found incontrovertible evidence of menstruation in dissected uteri of the slender loris, describing in great detail a complex process involving the degeneration of tissue, the breaking of congested capillaries, the extravasation of blood, the infiltration of leukocytes, and other events that resemble Markee's (1940) subsequent classic description of menstruation in macaques.

Similar examples include the following. P. C. Wright et al. (1986) concluded that tarsiers do not menstruate because no evidence of menstruation was found in any of the vaginal smears of *Tarsius bancanus* taken twice-weekly over a ten-month period. Van Herwerden (1925), however, observed evidence of menstruation in her dissections of numerous nonpregnant uteri of *T. spectrum*. Dixson (1983) concluded that the owl monkey *Aotus trivirgatus* does not menstruate because erythrocytes were never present in appreciable numbers in vaginal smears, but Hertig et al. (1976) noted occasional evidence of prior menstruation in their examinations of the genital tracts of 30 owl monkeys dissected during the inactive phase of the cycle.

The detection of menstruation in a species may require investigating a large number of individuals. In a study by Torii et al. (1987) of the common marmoset *Callithrix jacchus*, for example, one individual showed vaginal bleeding in each cycle coinciding with the decline in serum progesterone, indicating true menstruation, whereas three other individuals showed no external bleeding. Had the first marmoset not been included in the study, the phenomenon of menstruation in this species probably would have been overlooked. Studies of most species of prosimian would necessarily fail to detect menstruation unless invasive procedures were used, because the vagina of most prosimians remains imperforate throughout the cycle except at estrus and parturition (see Petter-Rousseaux, 1964; Manley, 1966; and H. Butler, 1967). Any menstrual blood would be resorbed in the uterus rather than discharged externally. To date, no wild mammals are known with certainty not to menstruate.

Menstruation in nonhuman mammals has yet to be studied systematically. In the studies listed in the Appendix, the authors detected overt uterine bleeding by visual observation of blood on the vulva or in vaginal smears; they detected covert bleeding by dissection, by chemical or microscopic evidence of erythrocytes in urine, or by visual observation of blood on swabs inserted deep into the vagina. The authors of many studies supported their assertions that the uterine bleeding they observed represented menstruation with hormonal analyses of venous blood, which identified the phase of the cycle in which the bleeding occurred. In none of the nonhuman studies, however, did the authors objectively quantify the amount of menstrual blood; rather, they estimated the amount subjectively, if at all. In the Appendix, I've divided the authors' estimates (when available) of the degree of menstruation into three categories: "overt" means that blood was easily detected externally by visual inspection, "slight" means that blood could be detected externally only by close visual inspection or a vaginal smear, and "covert" means that blood could not be detected externally even by close visual inspection. The terms overt, slight and covert are common in studies of mammalian menstruation, but it should be kept in mind that these terms describe the degree of menstrual flow relative to that of humans, who menstruate copiously. Thus, slight means slight only in comparison to the human menstrual flow, not in comparison to the flow of the average mammal.

These estimates should be considered rough approximations, because any noninvasive measurement of the degree of menstruation is inherently subjective. Measurements of the degree of external menstrual discharge do not necessarily reflect the degree of internal uterine bleeding, since blood extravasated from the uterus is often resorbed by the uterus rather than discharged through the vagina. In the bat *Molossus ater*, for example, menstruation involves a substantial amount of uterine blood, but most of it is resorbed by the uterus; only a trace amount flows through the cervix, and vaginal smears usually reveal no blood at all (Rasweiler, 1991). The longer the female genital canal, the less likely the extravasated uterine blood will reach the vaginal opening, and the less conspicuous menstruation will be. Because the reproductive tract of the nonpregnant adult African elephant, for example, spans on average 130 centimeters from the top of the uterus to the vulva (Balke et al., 1988), the quantity of menstrual blood observed in this species externally probably is only a fraction of that extravasated.

Furthermore, if the sample size in a study is small, even objective measurements of menstrual blood loss are to some extent unreliable, because the degree of menstruation can vary significantly among conspecifics. This intraspecific variation results from several factors, including genes, nutritional status, and parity, which are discussed below in the section on medical implications. Because the data for some of the species listed in the Appendix were compiled from small sample sizes, some of the estimates of menstrual blood volume probably do not precisely reflect the species' averages.

Data on menstruation are available for relatively few mammalian orders and genera. One reason for the paucity of comparative data is that menstruation traditionally has been assumed to be restricted to primates. The contributions of researchers who discovered menstruation among nonprimate mammals have received relatively little attention and have not spurred broad comparative investigations of menstruation. Another reason for the paucity of data is that even overt menstruation would not necessarily be noticed in all species. In aquatic mammals, for example, the water would quickly wash away the discharged menstrual blood, and in dark, furry mammals slight amounts of discharged blood might be absorbed by the surrounding fur and thereby escape researchers' notice.

Predictions Versus Data

Comparisons within the clusters of closely related species in the Appendix reveal a preliminary fit between the available menstruation data and the predictions outlined above relating specific variables to degree of menstruation. Comparisons are made within, rather than between, phylogenetic families or superfamilies, since comparisons between distantly related families would introduce more

unknown and uncontrolled variables. As discussed above, the antipathogen hypothesis predicts that the main selection pressures for a high degree of menstrual bleeding are promiscuous breeding system and continuous sexual receptivity, and the main selection pressures against a high degree of bleeding are small body size and cryptic behavior. For each species for which data are available, the Appendix includes the average degree of menstrual bleeding, the type of breeding system, and the adult female body size. Data on the duration of sexual receptivity are not included because humans are the only species known to have continuous sexual receptivity. Data on reliance on cryptic behavior also are not included, because this variable is difficult to quantify for most species, although it is probably correlated to some extent with body size.

A statistical analysis of the data in the Appendix, relating the estimated degree of menstrual bleeding to the predicted correlates, was not done because it would not be very meaningful, for the following reasons. First, none of the studies of menstrual blood loss in nonhuman mammals objectively quantified the amount of menstrual blood and tissue shed per cycle. Second, as discussed above, no systematic methodology was employed in obtaining data on menstrual blood loss. Most of the studies were not designed to measure menstrual blood loss, and only mentioned it incidentally in discussions of other aspects of the menstrual cycle or reproductive physiology. Different researchers employed various and incomparable techniques for measuring menstrual blood loss. Furthermore, data on uterine bleeding are lacking in most species of wild mammal. Nevertheless, the available data provide considerable support for the hypothesis that the function of menstruation is pathogen defense.

In the cluster of four closely related species from the families Pongidae (orangutan, gorilla, chimpanzee) and Hominidae (human), all species would be expected to menstruate overtly because all are polygynous to some extent and all are large enough to afford menstruation. [Species of the closely related family Hylobatidae (gibbons), which are much smaller in body size, are discussed below as a separate cluster.] The humans and chimpanzees, however, face stronger selection pressures favoring copious menstruation than do the gorilla and orangutan, and this difference is reflected in the menstruation data. Humans, but not the other three species, exhibit continuous sexual receptivity (because ovulation is concealed), which, as discussed above, should favor copious menstrual flow. Chimpanzees, but not the other three species, have multimale breeding systems and males with large testes and correspondingly high sperm volumes (Harcourt et al., 1981; Short, 1981), which, as discussed above, also should favor copious menstrual flow. [The ratio of testis weight to body weight in chimpanzees is 0.27%, compared to 0.05% in orangutans, 0.02% in gorillas, and 0.06% in humans (Harcourt et al., 1981).] Bleeding in the human and chimpanzee is overt and often profuse, whereas in the gorilla and orangutan it is slight and often barely visible externally (Appendix).

Data on the family Hylobatidae—the gibbons and the siamang—are preliminary but illuminating. Of the 9 species in the family, 8 have monogamous breeding systems and males with small scrotal sacs, and 1 (the black gibbon *Hylobates concolor*) has a polygynous breeding system and males with relatively large semipendulous scrotal sacs (Haimoff, Chivers, Gittens, and Whitten, 1982; Haimoff, Yang, He, and Chen, 1987). In their field study of the black gibbon, Haimoff et al. (1986, 1987) observed only unimale groups, but the testis weight of the males implies the females indulge in a significant number of extraharem copulations. It is even possible that the black gibbon, like the red colobus monkey discussed above, is facultatively multimale. Since polyestrous females in a single harem can become pregnant at different times throughout the year and remain pregnant or lactating for somewhat variable lengths of time, they would rarely all come into estrus simultaneously, and the harem male would not need to have testes significantly larger than those of a monogamous male in order to fertilize his females. Because of their large testis weights, *H. concolor* males presumably have larger sperm volumes than do males of other gibbon species, which means, according to the antipathogen hypothesis, that *H. concolor* females face stronger selection

pressures for a high degree of menstruation than do females of other gibbon species.

The sparse data on gibbon menstruation conform to these predictions. The Appendix lists data on three species of gibbon, including the polygynous *Hylobates concolor*. The two monogamous species of gibbon listed—*H. hoolock* and *H. lar*—have menstrual flows that are overt but slight (Carpenter, 1941; Matthews, 1946–1947; Breznock et al., 1977), whereas the polygynous gibbon has a flow that is profuse (Pocock, 1905). (An important caveat, however, is that the menstrual data on *H. concolor* and *H. hoolock* were based on only one individual each, so the data may not accurately represent the average degree of menstruation in these species.) Pocock (1905: 170) even compares menstruation of the polygynous *H. concolor* (formerly known as the "Hainan Gibbon") to that of the polygynous chimpanzee, whose menstrual discharge "is sanguineous in colour, profuse, monthly in occurrence, and three days in duration. In our Hainan Gibbon it is also sanguineous, stains the floor of the cage, and, according to her keeper, Mansbridge, who also looked after the Society's historic Chimpanzee 'Sally', is about the same in quantity relatively to the size of the animals as in that ape." By contrast, Matthews (1946–1947: 349) says of the monogamous *H. hoolock*, "On June 24, when the animal was about seven years old, menstruation occurred for the first time, the discharge being scanty and sufficient only to soil the skin in the neighbourhood of the vulvar cleft. It lasted for two days, practically no red blood corpuscles being found in the smear taken on the 26th. At none of the subsequent periods was the discharge more than slightly greater, though in some cases the period lasted up to four days." He later adds, "The quantity of the discharge in Pocock's specimen appears to have been greater than in the present one. . . . Compared with this the quantity in our example was scanty, and was not sufficient to do more than soil the circumvulvar area" (p. 358).

The menstruation data on New World monkeys are so sparse that interspecific comparisons are difficult to make. As a whole, the degree of menstruation in New World monkeys appears to be less than that in Old World monkeys, even after adjusting for body size. It is puzzling that New World female monkeys of multimale breeding groups, such as spider and howler monkeys, exhibit a less copious menstrual flow than do Old World female monkeys of multimale groups, such as rhesus monkeys. A related puzzle is why the New World monkey arterioles that appear to be the homologues of the Old World monkey spiral arteries are much less coiled and prominent. The key to these puzzles may lie in some as yet unidentified differences in reproductive physiology between New and Old World monkeys.

The only family of New World monkeys for which menstruation data on several species are available is the Cebidae. Comparisons among these species support the above predictions, but the data are too imprecise for the fit to be considered conclusive. Of the 7 species of Cebidae listed in the Appendix, the 5 species most likely to menstruate overtly are the mantled howler *Alouatta palliata*, the black-handed spider monkey *Ateles geoffroyi*, the Humboldt capuchin *Cebus albifrons*, the tufted capuchin *C. apella*, and the woolly monkey *Lagothrix lagotricha*, because all have multimale breeding systems and females of at least moderate weight (over 2 kg). These species do exhibit overt, albeit slight, menstruation. The two species of Cebidae least likely to menstruate overtly are the owl monkey *Aotus trivirgatus*, because it is monogamous as well as small (about 1 kg), and the squirrel monkey *Saimiri sciureus*, because, although it has a multimale breeding system, it is very small (about 580 g). Both of these species appear to menstruate covertly. When the data set on menstruation in New World monkeys is more complete, a comparison of closely related species will better test the predicted relationship between the degree of menstrual flow and the factors determining menstruation's costs and benefits. The woolly spider monkey *Brachyteles arachnoides*, whose sexual behavior resembles that of the highly promiscuous chimpanzee (Milton, 1985), would be an especially likely candidate to exhibit a comparatively high degree of menstruation.

Although the nonhuman menstruation data currently available are sparse, they support the antipathogen hypothesis. Most significantly, no anomalies have thus far surfaced when the

degree of menstrual bleeding of one species was compared with that of closely related species (taking into account all the factors that are predicted to influence the degree of bleeding). Because more data will surely be available in the future, it may be worthwhile to hazard some predictions. The antipathogen hypothesis predicts, for example, that different species of baboon (genus *Papio*) exhibit breeding system-dependent variations in menstrual blood volume. The Appendix lists four species of baboon, but data on the quantity of menstrual blood do not seem to be available for any of them. Of these 4 species, 3 have multimale breeding systems and males with large testes, and 1 (*P. hamadryas*) has a harem system and males with significantly smaller testes (Harcourt et al., 1981). The antipathogen hypothesis predicts that *P. hamadryas* females menstruate to a lesser degree (for their body size) than do females of the other species of *Papio*.

Differences in degree of menstruation are also likely to be found among the various species of bat. Of the four bat species listed in the Appendix, three are closely related, belonging to the family Phyllostomidae: the Seba's short-tailed bat *Carollia perspicillata*, the common vampire bat *Desmodus rotundus*, and the Palla's long-tongued bat *Glossophaga soricina*. *C. perspicillata* has a harem breeding system, although a relatively labile one (C. F. Williams, 1986). *D. rotundus*, on the other hand, appears to have a multimale system (Wilkinson, 1985a,b). According to Wilkinson (1985b: 129), in his study of a wild colony of *D. rotundus* in their roosts, "Although the males at the tops of trees spent more time near females than other males, they were not the only ones to mate. We observed 21 cases of mating between resident males and females. The top male got sixteen of these copulations, two went to the second highest male and three times a male lower in the tree succeeded in mating. One female copulated with a male in a low position on one day and then the top male on the succeeding day. At least one female also copulated with a male in a different tree when she changed roosts." Furthermore, in a study of one wild colony roost, the maximum paternity of offspring for top males was only 46 percent (Wilkinson, 1985b), which suggests a multimale breeding system. I have not found information on the breeding system of *G. soricina*. Although data on the quantity of menstrual blood in these species have not been published, the difference in breeding systems implies that *D. rotundus* is likely to have a greater menstrual flow, adjusted for species size, than does *C. perspicillata*.

Other mammals that are likely to menstruate overtly, but that have not yet been documented to do so, include elephants and zebras. African elephant females are polyestrous and monotocous (Dublin, 1983), and they sometimes mate with different males during the same estrous cycle, which would imply that males have high sperm volumes (Ginsberg and Rubenstein, 1990). As shown in the Appendix, the literature contains one anecdotal case of episodic uterine bleeding (based on urogenital smears) in the African elephant (Perry, 1952), but whether it represented menstruation is not known. The Grevy's zebra *Equus grevyi* is another likely candidate for overt menstruation. Both the Grevy's zebra and the sympatric plains zebra *E. burchelli* are large, polyestrous and monotocous; therefore, they are likely to menstruate to some degree. But the Grevy's zebra has a multimale breeding system, and the males have relatively large testes, whereas the plains zebra has a harem breeding system, and the males have relatively small testes (less than half that of the Grevy's) (Ginsberg and Rubenstein, 1990). The antipathogen hypothesis predicts that both species menstruate, and that the Grevy's zebra menstruates to a greater degree than does the plains zebra.

If, as I have argued, menstruation is an adaptation easily molded by specific selective circumstances, the presence or absence of overt menstruation is not a suitable tool with which to demonstrate phylogenetic relationships. P. C. Wright et al. (1986: 213), for example, point to the "fact" that tarsiers do not menstruate as partial evidence of phylogenetic position:

> Prior to this study, reproductive characteristics of tarsiers gave conflicting evidence on the phylogenetic affinities of *Tarsius*. . . . The absence of menstruation is a characteristic that tarsiers share with prosimians and most New World monkeys and do not share with Old World monkeys, apes, and humans. . . .

> Based solely on characteristics of reproductive cycles, tarsiers are best classified as prosimians. However, the shared similarities between tarsiers and prosimians cannot be shown at present to be shared derived features, and such a classification may reflect evolutionary "grade" rather than a monophyletic clade. No shared derived features of reproductive cycles link tarsiers to anthropoids.

Van Herwerden (1925), on the other hand, in her study of numerous tarsier uteri, concluded that tarsiers do menstruate. But even if they did not, the reasons for a specieswide absence of menstruation are more usefully sought in the species-specific set of selective circumstances, rather than in phylogeny. If future investigations identify mammals that lack even covert menstruation, these mammals will probably be found to possess several of the following characteristics: small body size, cryptic behavior, monestrous breeding season, polytocous pregnancy, and induced ovulation. Possessing several of these characteristics, however, does not necessarily mean that the mammal does not menstruate. The menstruating tree shrews studied by Conaway and Sorenson (1966), for example, are small, polytocous (the average litter size is 2), induced ovulators.

If menstruation is an adaptation to protect the uterus against sperm-borne pathogens, then virtually all mammals that can afford to menstruate are expected to do so, at least covertly. Heape (1900) listed a number of mammals, mostly domesticated, that had been documented to exhibit some form of uterine bleeding not related to parturition (since Heape confused menstruation with proestrous bleeding, it is unclear which type of uterine bleeding had been witnessed in each species). These species span many orders of mammal, and include the horse and donkey (Perissodactyla); the cow, sheep, goat, and pig (Artiodactyla); the dog and cat (Carnivora); the rabbit (Lagomorpha); and the mouse, rat, and gerbil (Rodentia). Although physiological differences exist between domesticated mammals and their wild progenitors, the fact that domesticated mammals of so many different orders exhibit uterine bleeding implies that their wild progenitors did as well. As Conaway and Sorenson (1966: 489–491) astutely remark in their study of menstruation among tree shrews, "Menstruation is often regarded as diagnostic of the primates and considered to be restricted to them. However, there does not appear to be any valid basis for this limitation. It is seemingly impossible to give any meaningful anatomical or physiological description of the post-luteal bleeding of primates which would not also be applicable to similar bleeding in widely unrelated mammalian groups. . . . Perhaps when adequate study has been made of many species, it will appear that 'menstruation' is the general phenomenon when non-pregnant cycles do occur and regression without tissue loss is less common."

CLINICAL DATA AND MEDICAL IMPLICATIONS

The hypothesis that menstruation functions to combat sperm-transported pathogens has implications for the diagnosis, treatment and prevention of diseases of the female upper reproductive tract. Understanding the function of this mechanism will enable researchers, clinicians and patients to more accurately distinguish its normal from its pathological expression. For example, because they fail to understand that menstruation is an adaptation, Beller and Schweppe (1979) were unable even to define a normal range of menstrual blood loss, remarking: "But what are normal values for a process which is not needed" (p. 232).

The great variability in the volume of menstrual blood loss among conspecific females would appear to be the biggest stumbling block to the acceptance of any adaptationist account of menstruation. The normal range of blood loss per cycle among healthy noncontracepting women is 10 to 80 milliliters (Rybo et al., 1985). [The extreme range reported in a study of 421 healthy noncontracepting Chinese women was 4.1 to 273.6 milliliters (Ji et al., 1987).] Genetic variation seems to account for some of this variability; the degree of menstrual blood loss is similar, for example, between monozygotic but not dizygotic twins (Rybo et al., 1985). If menstruation is an adaptation, it might be expected that selection would have favored one optimal degree of menstruation in each species. Why, then, has selection tolerated so much intraspecific variability?

The answer may be that both the benefits and the costs of menstruation vary directly

with the amount of menstrual blood loss. A greater degree of menstrual bleeding simultaneously confers greater antipathogen protection and inflicts greater nutritional costs. The net benefit—the benefits minus the costs—may be similar for a range of degrees of menstruation. If so, a specific range, rather than a specific degree, would be favored by selection. The extreme degrees of menstruation—chronic absence of bleeding or excessive continuous bleeding—would have zero or negative net benefit and, in menstruating species, would therefore represent or signal pathology. Currently there do not appear to be data correlating normal menstrual blood volume and susceptibility to uterine infection, presumably because researchers have not suspected a connection.

Selectional tolerance for wide intraspecific variability in the degree of menstruation would facilitate individual facultative adjustments. Individual women typically do not vary much in volume of menstrual blood loss over consecutive cycles (Hallberg and Rossander-Hultén, 1991). Changes in volume usually reflect facultative responses to changes in nutrition, parity, or uterine health. Nutritional deprivation, for example, can lead to a temporary nutrient-conserving state of anovulation (suppression of ovulation) and amenorrhoea (suppression of menstruation). As Frisch (1988) points out, in the preagricultural environment to which human physiology is primarily adapted, sudden caloric restriction, extensive loss of body fat, and strenuous physical excercise would have been reliable cues of nutritional stress. By contrast, giving birth generally leads to a permanent increase in the volume of menstrual blood loss among humans (Rybo et al., 1985). Although this increase probably is a by-product of the pregnancy-induced increase in uterine size and vascularization, it may help to combat tenacious strains of pathogens that can exploit the uterus during parturition.

Sudden dramatic increases in an individual's degree or frequency of uterine bleeding, however, are often diagnostic of uterine disease. If menstruation is adapted to defend against uterine infection, then such increases would seem to be adaptive responses to acute infection. If so, women should be alert to sudden increases in the volume of menstrual bleeding. I propose that the uterus is designed to increase its bleeding when it detects signs of infection. The following clinical evidence supports this hypothesis.

Menorrhagia (unusually heavy menstrual bleeding) and metrorrhagia (intermenstrual bleeding) are the primary symptoms of acute or chronic endometritis (infection of the endometrium), which is characterized by endometrial inflammation (Ingerslev et al., 1982). By bleeding heavily at menstruation the infected uterus sheds a more extensive layer of endometrium and distributes more immune cells throughout the uterine cavity, oviducts, and, in overtly menstruating mammals, cervix and vagina. By bleeding intermenstrually the uterus combats pathogens more frequently. Acute infection of the uterus is so commonly associated with a sudden, significant increase in bleeding that this symptom is recognized by some clinicians (such as Garland and Johnson, 1989) as one of the first indications of uterine disease.

Many species of microorganisms, such as *Gardnerella vaginalis* and *Chlamydia trachomatis*, have been shown to cause endometritis and associated menorrhagia and metrorrhagia (Ingerslev et al., 1982; Kristiansen et al., 1987). Sexually transmitted viruses can also cause acute endometritis. In one well-documented case, infection and inflammation of the endometrium by a herpes virus led to several months of abnormal uterine bleeding (Duncan et al., 1989). Ingerslev et al. (1982) point out that acute endometritis occurs most commonly after parturition or abortion, when the dilated cervix becomes a conduit for pathogens in the external environment. The special vulnerability of the uterus during these events underscores the adaptive significance of subsequent bleeding.

Infection of the oviducts, commonly called *pelvic inflammatory disease* (PID) or *salpingitis*, is thought to occur primarily from ascending infections of the cervix and uterus. One of the primary symptoms of PID is unusual uterine bleeding (Bowie and Jones, 1981; Ingerslev et al., 1982). Infection of the oviducts by *Chlamydia trachomatis*, for example, is commonly signaled by the sudden onset of irregular bleeding of the uterus, which is usually infected as well (Mårdh et al., 1981; Ingerslev et al.,

1982). [Mårdh et al. (1981) suggest that the reason chlamydial infections sometimes persist despite heavy menstrual shedding is that the infection spreads to endometrial crypts that do not shed or the woman simply becomes reinfected by her partner.] Because PID so often leads to infertility, Garland and Johnson (1989) emphasize that sudden abnormal uterine bleeding—indicating endometritis and the potential spread of infection to the oviducts—should be investigated promptly.

Infection of the endometrium leads to inflammation when large numbers of immune cells infiltrate the endometrium to defend it and release their inflammatory factors. Invasion of the uterus by substantial numbers of immune cells, particularly plasma cells (activated B lymphocytes), is commonly considered to be the distinguishing mark of endometritis (Ingerslev et al., 1982). Although the healthy uterus cyclically recruits a significant number of immune cells during the luteal phase of the menstrual cycle, the infected uterus recruits a much greater number and does so throughout all phases of the cycle (Ingerslev et al., 1982). Cromer and Heald (1987) note the association between abnormal uterine bleeding and hematological indexes of prolonged inflammation in *Chlamydia trachomatis* infection.

If an infection-induced increase in uterine bleeding is an antipathogen defense, it may be dangerous to curtail it artificially. Menorrhagia and metrorrhagia, as concomitants of endometritis, have not been recognized as adaptive responses to infection. On the contrary, they have usually been viewed as part of the pathology and even as possible causes of endometritis (Ingerslev et al., 1982). In failing to recognize uterine bleeding as an adaptive response to uterine infection, clinicians may try to minimize bleeding, through local or systemic clotting factors, and thereby interfere with this mechanism. Such "treatment" would undermine the body's defense against uterine infection. In the above-mentioned case of herpes-induced endometritis, for example, the initial treatment by physicians was to try to decrease the uterine bleeding with hormone therapy; only after this therapy failed was the possibility of uterine infection investigated, by which time the patient had become sick enough to require hospitalization. Although abnormal uterine bleeding can result from factors other than endometritis, such as ovarian or thyroid dysfunction (Beer, 1970), endometritis should be suspected.

Bleeding in response to infection may seem to be counterproductive, rather than adaptive, since blood contains iron that pathogens need in order to proliferate. As discussed on page 000, however, upon detecting infection, macrophages sequester iron from blood, and neutrophils secrete lactoferrin to bind much of the remaining iron and render it unusable by pathogens. It is possible, nevertheless, that pathogens that are able to obtain iron from lactoferrin, such as *Neisseria gonorrhoeae*, may thrive from increased uterine bleeding and may even have evolved ways to manipulate the mechanisms of uterine bleeding to increase their access to blood. Although to date there is no evidence that any organism can manipulate the machinery of menstruation, heavy bleeding in response to infection by such an organism would probably be pathological rather than adaptive. Uterine infection by *N. gonorrhoeae*, which can exploit lactoferrin, however, actually causes less intermenstrual bleeding than does infection by *Chlamydia trachomatis* (Cromer and Heald, 1987), which cannot exploit lactoferrin. But this may be because the former is more likely to receive prompt treatment. *N. gonorrhoeae* has an incubation period of only two to five days (Sweet et al., 1986), and infection of the oviducts by this organism usually causes severe symptoms—such as abdominal pain, fever, and sometimes vomiting (Cromer and Heald, 1987)—which are likely to motivate patients to seek medical help immediately. By contrast, the only salient symptom in many cases of oviduct infection by *C. trachomatis* is overt bleeding, which means that the infection may go untreated for months while the patient experiences frequent bouts of heavy bleeding. (This underscores the importance of being alert to sudden changes in uterine bleeding.)

Chronic endometritis, like acute endometritis, is characterized by extensive infiltration by immune cells and by inflammation of the uterus (Brudenell, 1955); however, it can also have nonpathogenic etiologies, such as abnormal tissue growth. In a study by Greenwood and Moran (1981), the primary symptom of

93 of 99 women with chronic endometritis (most of whom had no apparent bacterial contamination of the uterus) was abnormal uterine bleeding. The uteri of all of these patients exhibited significant leukocyte infiltration, and, in most cases, surgical removal of the inflamed parts of the endometrium ended the abnormal bleeding. Greenwood and Moran (1981) note that chronic endometritis is accompanied by hemorrhage of arterioles that have been infiltrated by leukocytes, and they suggest that these leukocytes may cause the arterioles to become fragile and to leak blood. I propose, rather, that the endometrial arteries are designed to break down readily in the presence of inflammatory factors released by leukocytes.

Inflammation of the endometrium should trigger increased uterine bleeding, even in the absence of pathogens. Inflammation is triggered by immune cells in response to infection by pathogens, to injury (which invites infection), or to invasion by abnormal tissue. It may well be the primary signal of infection that triggers increased uterine bleeding. The relationship between uterine inflammation and increased bleeding may explain why the contraceptive intrauterine device (IUD) increases uterine bleeding. For the duration of its presence in the uterus, the IUD causes inflammation of the endometrium (Moyer and Mishell, 1971) and a roughly twofold increase in the volume of menstrual bleeding (Guttorm, 1971; Hefnawi et al., 1974). This inflammation results from the IUD's chronic mechanical injury to uterine tissue and the consequent recruitment of large numbers of immune cells to the uterus (Srivastava et al., 1989). IUD users bleed more profusely, bleed on more days per cycle, and are more likely to experience overt intermenstrual bleeding (Nygren and Johansson, 1973; Bonnar et al., 1976; Barthwal and Srivastava, 1991). In the study by Guttorm (1971), women with the scantiest menstrual flow experienced the greatest increase in bleeding after IUD insertion, both absolutely and proportionately; this reaction may represent adaptive compensation, during periods of infection, for an otherwise low degree of protection. These side effects of the IUD—profuse bleeding and intermenstrual bleeding—have puzzled clinicians and researchers for decades and have spurred substantial research to discover underlying mechanisms (Bonnar et al., 1976; Surico et al., 1988; Z.-I. Zheng and Lo, 1988).

The persistent inflammation caused by the IUD is, in fact, believed to be a major reason for its contraceptive effect. The chemicals released during the inflammatory response appear to be toxic to sperm and implanting blastocysts (Moyer and Mishell, 1971). As summarized by Berkow (The Merck Manual, 1987: 1737), "A sterile tissue reaction in the endometrial cavity is generally accepted as the main cause of the contraceptive effect. There is bacterial contamination for 24 h after insertion of an IUD, and although the endometrial cavity rapidly becomes sterile, inflammation persists after the bacterial infection disappears. Breakdown products of intrauterine neutrophils are toxic to the sperm and blastocyst. The major mechanism of action of IUDs is prevention of fertilization because of this toxic effect on the sperm. The inflammatory foreign body reaction is transitory and ceases when the IUD is removed."

Inflammation, as a signal of infection or potential infection, appears to induce a variety of changes that promote or complement defensive uterine bleeding. The presence of the IUD in the uterus, for example, causes significantly reduced hemostatic plug formation and increased vascularity of the endometrium, which promotes increased tissue shedding and blood flow (Barthwal and Srivastava, 1990). In a study of rhesus monkeys by Barthwal and Srivastava (1991), the IUD even perturbed the ovarian cycle, decreasing the length of the menstrual cycle by 2.7 days and thereby significantly increasing the frequency of bleeding. In a study of women by Nygren and Johansson (1973), the IUD did not alter the length of the cycle, but menstrual bleeding was nonetheless triggered more easily, and it generally began before the levels of estrogen and progesterone had declined to the low levels normally required to induce bleeding. Sedlis et al. (1967) showed that the insertion of the IUD led to an increase in uterine acidity, particularly near the time of menstruation; whether this antipathogenic change in pH represents an adaptive response to inflammation or an effect on uterine tissue of the materials composing the IUDs was not clear.

Although the IUD increases the volume of menstrual blood loss, women with IUDs are not less susceptible to uterine infection than are noncontracepting women, because insertion of the IUD through the pathogen-laden vagina and cervix inevitably causes at least short-term bacterial contamination of the uterus. The risk of developing PID increases manyfold for a few weeks following IUD insertion, but it appears to decline considerably thereafter (Farley et al., 1992); however, the tail that is usually attached to the IUD and that protrudes (for easy removal) into the vagina may facilitate the ascension of pathogens to the uterus for the duration of IUD use. Although the multifilament tails that promoted extensive bacterial migration to the uterus (Tatum et al., 1975; Skangalis et al., 1982) have been phased out, many studies suggest that the monofilament tails currently in use also facilitate bacterial ascension to the uterus (Sparks et al., 1981; Wolf and Krieger, 1986; Wilkins et al., 1989; Batár et al., 1991). Methods to decrease the heavy and intermittent bleeding of women wearing IUDs are currently being researched and developed (Surico et al., 1988; Barthwal and Srivastava, 1990), but the achievement of this goal could be detrimental to uterine health if the increased bleeding protects against an IUD-associated increase in uterine pathogen load.

For medical purposes it is extremely important to determine whether uterine bleeding is a defense against or a cause of uterine infection. Dahlberg and Ursing (1979), for example, believe that "spotty bleeding and menorrhagia favour bacterial invasion resulting in endometritis and in turn increased bleeding and pain. IUDs releasing inhibitors of fibrinolysis . . . might be an approach to eliminate the bleeding problem and thereby infection and pain" (p. 74). In their study of women undergoing removal of the IUD, intermenstrual bleeding was strongly associated with positive bacterial cultures in the mucus obtained from the top of the IUD, and bacteria were found in the semen of the partners of many of the infected women. The intermenstrual bleeding had resolved before IUD removal in the four women who had been treated with antibiotics. To assume that infection is caused by bleeding because the two are reliably associated, however, is like assuming that fires are caused by firemen. If, as I believe, the authors of this study confused cause and effect, then the medical procedure that they propose would promote rather than prevent or cure infection (except when infection is caused by bacteria that can readily obtain iron from menstrual blood). Although medicated IUDs that continuously release synthetic progesterone appear to significantly decrease the risk of PID—even though they decrease the volume of menstrual bleeding—their antipathogenic effect probably is caused by a progesterone-induced increase in cervical mucus density, which renders the mucus much less penetrable by sperm and bacteria (see Toivonen et al., 1991).

Uterine bleeding in response to inflammation may account, in part, for the late premenopausal increase in the volume of menstrual blood loss. Women generally experience a significant increase in volume of menstrual blood loss by 50 years of age (Rybo et al., 1985). Benign uterine tumors (leiomyomas) are very common in the endometrial tissues of premenopausal women over the age of 40 and are strongly associated with chronic menorrhagia (Fraser, 1992). They are also associated with a significantly increased density of uterine macrophages (Adany et al., 1990), implying chronic inflammation and endometritis.

Ewald's (1980) evolution-minded guidelines for the treatment of infectious diseases may be of use in deciding whether to mitigate heavy uterine bleeding. This decision should depend upon whether the increased bleeding represents (1) an adaptation to defend against pathogens, (2) a manipulation of the woman's machinery of menstruation by a particular type of pathogen that benefits from increased bleeding, or (3) a maladaptive side-effect response to dysfunctional inflammation (certain inherited or acquired disorders of other organ systems can also lead to maladaptive heavy menstrual bleeding). Uterine hemorrhage that is severe enough to be life-threatening should, of course, be inhibited promptly.

If increasing the volume of menstrual bleeding generally decreases the risk of uterine infection, it might be expected that decreasing the volume of bleeding generally increases the risk. Oral contraceptives, however, which de-

crease the volume of menstrual bleeding by about half (Hallberg and Rossander-Hultén, 1991), do not necessarily increase the risk of uterine infection, because they dramatically alter the normal hormonal profile of the reproductive tract throughout the menstrual cycle. As Eschenbach et al. (1977) point out, oral contraceptives may even inhibit the ascent of sperm and bacteria to the uterus by increasing cervical mucus density. It is not anomalous, therefore, that oral contraceptives have been found in some studies to be protective against certain types of infection of the reproductive tract (Eschenbach et al., 1977; Rubin et al., 1982; Wølner-Hanssen et al., 1990) and in other studies to be a risk factor for certain types of infection (Washington et al., 1985; Louv et al., 1989; Oh et al., 1989). Sex hormones influence both the recruitment of immune cells to the female reproductive tract and the growth of pathogens. Estrogen directly inhibits the growth of *Paracoccidioides brasiliensis*, for example, but stimulates the growth of *Chlamydia trachomatis* (Styrt and Sugarman, 1991). It can also alter the properties of mucosal surfaces, which are barriers to pathogens (Styrt and Sugarman, 1991). Progesterone inhibits the growth of *Neisseria gonorrhoeae*, and when progesterone levels sharply decrease, inducing menstruation, the number of *N. gonorrhoeae* organisms colonizing the cervix increases markedly (James and Swanson, 1978). The ability of various pathogens to exploit sex hormones is underscored by the existence of binding sites for estrogen on the common vaginal pathogen *Trichomonas vaginalis* and binding sites for progesterone on the common vaginal pathogen *Candida albicans* (Styrt and Sugarman, 1991). Assessing the risk of uterine infection to women using oral contraceptives would entail taking account of the following variables: the specific combination of hormones of the particular contraceptives being used (there is a wide array of oral contraceptives, each with different levels and types of synthetic sex hormones); and the specific pathogens transmitted sexually to the uterus (there is a wide array of pathogens that can be sexually transmitted, each of which is affected differently by the sex hormones).

The development of artificial hormones, such as oral contraceptives, opens up the potential for hormonal manipulation of the degree of menstrual bleeding, which could be tailored to individual circumstances and preferences. Understanding the function of menstruation, however, is essential for making good decisions about whether and when to interfere with menstruation. The optimal degree of bleeding may depend on such variables as level of sexual activity and nutritional status. Many women view menstruation as an unpleasant burden and might welcome the opportunity to suppress it with artificial hormones. Methods for suppressing menstruation are discussed in the literature on oral contraception, including a report of one clinical trial of an oral contraceptive that reduced the frequency of menstruation to once every three months (Loudon et al., 1977).

If menstruation is an adaptation, menstruation-suppressing contraceptive technologies would in some cases promote uterine infection. Women who have never had sexual intercourse probably could suppress menstruation safely, but women with a history of sexual intercourse may want to be cautious about suppressing menstruation, even if they are currently sexually abstinent. Once the uterus has been colonized by bacteria it may benefit from periodic cleansing in order to prevent tenacious strains of pathogens from recolonizing it. Women who opt to suppress menstruation should not only be especially alert to the signs and symptoms of infection, they should also try to prevent infection by using some form of barrier protection. Although condoms (male or female) are generally recommended for the prevention of sexually transmitted diseases, the diaphragm with spermicide is approximately as effective in preventing sperm from reaching the uterus.

The high end of the normal range of menstrual blood loss does not necessarily represent the optimal degree of menstruation. As Beach (1976) points out, women in modern industrialized societies experience many more menstrual cycles than did ancestral hunter-gatherer women, whose multiple pregnancies and prolonged periods of intensive nursing would have suppressed menstruation throughout most of their reproductive lives. The unnaturally frequent menstruation that is the norm in industrialized societies may have some

as yet unknown harmful effects, just as does the unnaturally frequent flux of hormones of continuous cycling, which Henderson et al. (1991) point out is a risk factor for the hormone-dependent cancers (cancers of the breast, uterus, and ovaries). Frequent menstruation may increase a woman's risk of endometriosis (the migration and implantation of endometrial tissue in the peritoneal cavity), for example, because endometriosis is widely believed to result from extensive retrograde menstruation. Endometriosis is a risk factor for infertility (although the causal relationship has not been elucidated) (Liu and Hitchcock, 1986), which means that menstruation, whose apparent function is to help protect against infertility, may sometimes cause it instead.

An understanding of the function of menstruation could guide patients and physicians in choosing optimal solutions for dealing with menstrual pathologies. Pathological retrograde menstruation or chronic menorrhagia unassociated with infection or the IUD might be treated by oral contraceptives that significantly decrease the volume of menstrual bleeding without suppressing menstruation entirely. Painful menstruation (dysmenorrhea), however, is not always mitigated by altering the cyclic hormonal flux with standard oral contraceptives. [Painful menstruation is thought to result from unusually strong uterine contractions; uterine contractions in macaques, for example, become much stronger and better synchronized during menstruation (Germain et al., 1986), presumably to help shed blood and tissue.] Women with severe pain may opt to suppress menstruation in most or in alternate cycles by taking oral contraceptives continuously (i.e., without a monthly break to allow menstruation to occur). Since they would face greater risks of uterine infection, however, they should use barrier protection. Lack of observable menstruation (amenorrhea) is common in female athletes and other women who are exceptionally lean (Frisch, 1988). (It is assumed that amenorrheic women are not menstruating, but some may be menstruating covertly.) Although there do not appear to be data on whether amenorrhea increases the risk of uterine infection, amenorrheic women may want to take precautions against infection and infertility by using barrier protection.

Understanding the function of menstruation can also guide women in maintaining uterine health through different reproductive stages. Among nonhuman mammals, females typically copulate only when they are capable of becoming pregnant, hence they subsequently either menstruate or have implantation bleeding. Modern humans, by contrast, often copulate during stages of reproductive life in which uterine bleeding does not occur: during middle and late pregnancy, during lactation, and after menopause. Whether ancestral hunter-gatherers generally abstained from sexual intercourse during these stages is not known. It is important to determine whether the seemingly anomalous sexual behavior of modern humans has adverse, but preventable, consequences.

Following implantation bleeding, menstruation is suppressed during pregnancy, since it would abort the embryo or fetus. This means that sexual intercourse without barrier protection during pregnancy may pose a threat to the uterus, oviducts, or fetus. During early pregnancy, implantation bleeding most likely helps to combat pathogens transported by sperm. In addition, very early in pregnancy a dense meshwork of mucoid filaments—the cervical mucous plug—forms at the base of the cervix, providing a barrier to sperm and large bacteria (Chrétien, 1978). This mucous plug becomes highly acidic by the eighth week of pregnancy (Shettles and Guttmacher, 1940), and it becomes progressively denser throughout the first seven months of pregnancy; in some women, however, the plug becomes significantly thinner during the last two months (see Chrétien, 1978). Evidence strongly suggests that during these last two months the cervical mucous plug is not always an effective barrier against sperm and sperm-borne pathogens.

Sexual intercourse without barrier protection during the last two months of pregnancy is associated with infections of the extraplacental membranes and the amniotic fluid (chorioamnionitis) (Naeye and Ross, 1982), which often leads to spontaneous rupture of the fetal membranes and premature delivery (Naeye and Ross, 1982; McGregor et al., 1988). In their study of 541 pregnancies, Naeye and Ross (1982) found that condom use protects

against placental infection and preterm delivery, although they caution that this finding should be considered preliminary, since condom use was not randomly assigned among couples. They specifically note that some infectious agents may be transported through the cervical mucous plug by sperm.

Following the period of postpartum uterine bleeding, intensive lactation normally suppresses further overt uterine bleeding (Howie and McNeilly, 1982; Brown et al., 1985). Even though periodic postpartum bleeding would help to combat uterine pathogens that survived the hemorrhage of parturition, overt uterine bleeding during lactation probably would inflict significant nutritional costs during a period of greatly increased nutritional needs. The possibility that women with lactational amenorrhea bleed covertly has not been investigated. The extent of uterine exposure to sperm-borne pathogens among sexually active women with lactational amenorrhea is not known. Although the postpartum cervical mucus of women with lactational amenorrhea is significantly less receptive to sperm than is periovulatory cervical mucus, it nevertheless does not appear to be a reliable barrier to sperm. In an in vitro study by Vigil et al. (1991), 39 percent of the 54 postpartum cervical mucus samples allowed sperm migration. If lactating amenorrheic women lack highly effective adaptations to counter sperm-borne pathogens, they may risk uterine infection if they do not use barrier protection.

Postmenopausal women may also be at higher risk for uterine infection if they have sexual intercourse without barrier protection. Selection pressures for antipathogen protection of the postmenopausal uterus would have been extremely weak, since ancestral hunter-gatherer women rarely lived long past menopause (which is why various degenerative processes tend to accompany it). Since the cervical mucus in postmenopausal women tends to be dense, it is usually (although not necessarily always) impenetrable by sperm (Chrétien, 1978). But estrogen therapy can alter this characteristic. Shettles and Guttmacher (1940) report that, above a certain dose, the estrogenic compound stilbestrol converts the normally scant, viscous cervical mucus of menopausal women into a profuse, watery secretion that is penetrable by sperm. Uterine infections in postmenopausal women sometimes disseminate, and in some cases have been fatal (Horan et al., 1983). Horan et al. (1983) even remark in their clinical case study of gynecologic sepsis in old age that the endometrium appears to be more susceptible to infections after menopause because it lacks cyclical shedding.

Although postmenopausal women do not necessarily bleed in response to uterine infection, various pathological conditions can lead to episodes of postmenopausal bleeding, including atrophic endometrium (in which the endometrium recedes excessively), nonspecific inflammation (chronic endometritis), polyps, and carcinoma (Choo et al., 1985). Postmenopausal women appropriately tend to view uterine bleeding as a possibe warning sign of a serious condition (Choo et al., 1985), but the absence of bleeding should not necessarily be regarded as a sign of uterine health. In summary, sexually active women who are not menstruating should consider guarding against sperm-transported pathogens by using barrier protection.

CONCLUSIONS

Defenses against pathogens have shaped much of mammalian physiology. Internal fertilization creates special problems of defense because it necessarily entails allowing pathogen vectors (sperm) passage into internal reproductive organs. Periodic bleeding of the reproductive tract occurs asymmetrically between the sexes because these vectors are transmitted unidirectionally.

The timing of menstruation indicates that it is designed to occur in response to sperm-borne pathogens. Menstruation tracks sexual activity. The augmentation of defenses against sexually transmitted pathogens would be expected to be triggered by sexual maturity, which generally marks the onset of sexual activity and the potential for infection of the reproductive tract. Menarche (first menstruation), accordingly, occurs at sexual maturity. Throughout the reproductive life of menstruating mammals, sexual cycles culminate in menstruation unless pregnancy ensues and induces other forms of uterine bleeding. Since copulation in mammals is usually tied to ovarian cyclicity, and since copulation entails the

transmission of some pathogens to the uterus, ovarian cyclicity and menstruation should be inextricably linked. The medical literature presented above regarding infection-induced uterine bleeding implies the existence of a significant facultative component to the degree and frequency of uterine bleeding.

Additional mechanisms may have evolved in mammals specifically to defend against pathogens transported by sperm. Female mammals that store sperm in their uteri or oviducts may possess adaptations to cleanse the sperm of pathogens, particularly if their breeding systems expose them to a large number and diversity of sexually transmitted pathogens. Females of some bat species with multimale (i.e., highly promiscuous) breeding systems store sperm in their uteri or oviducts for periods of from 16 to 200 days (Fenton, 1984); whether they menstruate during the period of sperm storage or have mechanisms to selectively eliminate pathogen-bearing sperm is not known. Nonmammalian animals with internal fertilization would also be expected to have adaptations to defend specifically against sperm-transported pathogens. Such adaptations may include extensive cyclic shedding of the epithelia of reproductive organs or mechanisms that have no homologs among mammals.

The myths surrounding menstruation are many. In various nonindustrialized societies menstruation is perceived as the body's way of ridding itself of some form of pollution (see Snowden and Christian, 1983 and Delaney et al., 1988). Such explanations are rooted, of course, primarily in superstition rather than in science and fail to specify the source and form of the pollution, but they are not totally incorrect. "Pollution," in the form of pathogens, is an unavoidable concomitant of insemination and, I have tried to demonstrate, the main selection pressure that shaped the machinery of menstruation.

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APPENDIX

Uterine bleeding in mammals

Species	Type of uterine bleeding	Duration and amount of flow	Weight of female (grams)	Breeding system	Notes and references
Marsupialia					
Dasyurus viverrinus (Marsupial cat or Eastern quoll)	menstrual	covert?			Menstruation occurs at the end of pseudopregnancy (J. P. Hill and O'Donoghue, 1913) It is marked by tissue desquamation, extravasation of blood in the uterine cavity, and invasion of leukocytes.
Carnivora					
Canis latrans (Northern coyote)	proestrous	several weeks overt			This information was based on a single captive female (Whiteman, 1940).
Chiroptera					
Carollia perspicillata (Leaf-nosed bat or Seba's short-tailed bat)	menstrual		<50	unimale?	Menstruation occurs shortly after copulation, at or shortly after ovulation, and most endometrial regeneration is deferred until after ovulation. The ovum is retained in the oviduct during this period (Bonilla and Rasweiler, 1974; Quintero and Rasweiler, 1974)
Desmodus rotundus (Common vampire bat)	menstrual		<50	multimale	Menstruation occurs shortly after copulation, at or shortly after ovulation, and most endometrial regeneration is deferred until after ovulation. The ovum is retained in the oviduct during this period (Quintero and Rasweiler, 1973, 1974).
Glossophaga soricina (Palla's long-tongued bat)	menstrual		<50		Menstruation occurs shortly after copulation, at or shortly after ovulation, and most endometrial regeneration is deferred until after ovulation. The ovum is retained in the oviduct during this period (Rasweiler, 1972; Quintero and Rasweiler, 1974). See also Hamlett (1934).
Molossus ater (Black mastiff bat)	menstrual	covert			Endometrial necrosis, sloughing, and extravasation of blood can be substantial, but most of this debris does not pass into the vagina (Rasweiler, 1991).
Dermoptera					
Cynocephalus variegatus (Malayan flying lemur)	menstrual?				Van Herwerden (1906) found uterine specimens with extravasated blood and hematomas in the subepithelial tissue, suggestive of menstruation.
Insectivora					
Elephantulus myurus (Transvaal elephant shrew)	menstrual	overt			Menstruation is vigorous but localized to the small area of the uterus (the polyp) where implantation takes place (van der Horst, 1941, 1955).
Erinaceus europaeus (West European hedgehog)	periovulatory				Shortly after fertilization, before implantation, but prior to the proliferation of uterine tissues, the uterus becomes edematous. In some regions the epithelium is destroyed and blood pours into the uterine cavity. This also happens in the cervix (Deanesly, 1934).

APPENDIX *continuation*

Species	Type of uterine bleeding	Duration and amount of flow	Weight of female (grams)	Breeding system	Notes and references
Tana tana (Large tree shrew)	menstrual periovulatory	overt			Menstruation occurs at the end of pseudopregnancy, following the postpseudopregnancy ovulation, and it is represented by degenerating masses of tissue and much extravasated blood. Hematomas can be large. In some cases, bloody vaginal discharge can be seen. Uterine bleeding also occurs postpartum and during resorption of fetuses (Conaway and Sorenson, 1966).
Tupaia belangeri (Northern tree shrew)	menstrual?				Uterine bleeding takes place, possibly postpartum or postpseudopregnancy (Martin, 1967) (Postpseudopregnancy bleeding is menstruation, even though Martin doesn't regard its occurrence in tree shrews as genuine menstruation.)
Tupaia chinesis (Tree shrew)	menstrual periovulatory	overt			Menstruation occurs at the end of pseudopregnancy, following the postpseudopregnancy ovulation, and it is represented by degenerating masses of tissue and much extravasated blood. Hematomas can be large. In some cases, bloody vaginal discharge can be seen. Uterine bleeding also occurs postpartum and during resorption of fetuses (Conaway and Sorenson, 1966).
Tupaia glis (Common tree shrew)	menstrual?				There are cases of intrauterine bleeding suggestive of menstruation (Hendrickson, 1954).
Tupaia gracilis (Slender tree shrew)	menstrual periovulatory	overt			Menstruation occurs at the end of pseudopregnancy, following the postpseudopregnancy ovulation, and it is represented by degenerating masses of tissue and much extravasated blood. Hematomas can be large. In some cases, bloody vaginal discharge can be seen. Uterine bleeding also occurs postpartum and during resorption of fetuses (Conaway and Sorenson, 1966).
Tupaia javanica (Javan tree shrew)	menstrual?				The uterus contains blood, and epithelial tissue is extravasated (van Herwerden, 1906).
Tupaia longipes (Tree shrew)	menstrual periovulatory	overt			Menstruation occurs at the end of pseudopregnancy, following the postpseudopregnancy ovulation, and it is represented by degenerating masses of tissue and much extravasated blood. Hematomas can be large. In some cases, bloody vaginal discharge can be seen. Uterine bleeding also occurs postpartum and during resorption of fetuses (Conaway and Sorenson, 1966).
Tupaia minor (Pygmy tree shrew)	menstrual periovulatory	overt			Menstruation occurs at the end of pseudopregnancy, following the postpseudopregnancy ovulation, and it is represented by degenerating masses of tissue and much extravasated blood. Hematomas can be large. In some cases, bloody vaginal discharge can be seen. Uterine bleeding also occurs postpartum and during resorption of fetuses (Conaway and Sorenson, 1966).

APPENDIX *continuation*

Species	Type of uterine bleeding	Duration and amount of flow	Weight of female (grams)	Breeding system	Notes and references
Proboscidea					
Loxodonta africana (African elephant)	menstrual?				Smears taken from the urogenital canal by the keeper of a captive elephant sometimes contained considerable amounts of blood. The occurrence was not regular but suggested a possible cycle of about 6 weeks (Perry, 1952).
Primates			*	**	
Prosimians					
Loris tardigradus lydekkerianus (Slender loris)	menstrual proestrous	covert	260	solitary?	Rao (1932) analysed slender loris uteri at many phases of the menstrual cycle and observed both proestrous bleeding and menstruation. The period of proestrum is marked by slight sanguinous discharge. Menstruation is characterized by tissue degeneration, extravasation of blood, infiltration of leukocytes, and leukocyte ingestion of debris and red corpuscles.
Tarsius syrichta (Philippine tarsier)	menstrual?		120		In some cycles external bleeding occurred and was recovered between the labia and in vaginal washings (W. C. O. Hill et al., 1952).
Tarsius spectrum (Spectral tarsier)	menstrual	covert	200	monogamous?	Van Herwerden (1925) examined nonpregnant uteri of many tarsiers and found menstruating ones with extravasation of blood but no substantial destruction of tissue.
New World Monkeys					
Alouatta palliata (Mantled howler)	menstrual	slight	5,700	multimale	Menstruation occurs regularly, but bleeding is not copious (Dempsey, 1939; Kaiser, 1947).
Aotus trivirgatus (Owl monkey)	menstrual?	covert	1,000	monogamous	Dixson (1983) never found appreciable numbers of erythrocytes in vaginal smears, but Hertig et al. (1976) saw evidence of prior menstruation in dissected uteri.
Ateles geoffroyi (Black-handed spider monkey)	menstrual	3-4 days slight	5,800	multimale	Menstruation occurs regularly, but bleeding is not copious (Goodman and Wislocki, 1935; Dempsey, 1939; Kaiser, 1947).
Callithrix jacchus (Common marmoset)	menstrual?	covert	290	polyandrous?	1 of 4 marmosets exhibited vaginal bleeding coincident with the decline in progesterone level (Torri et al., 1987).
Cebus albifrons (Humboldt capuchin)	menstrual	slight	2,600	multimale	Menstrual bleeding can be detected if cotton swabs are inserted in the vagina; on rare occasion external bleeding is apparent (Castellanos and McCombs, 1968).
Cebus apella (Tufted capuchin)	menstrual	1-8 days slight	2,100	multimale	Menstrual flow is regular, with 1-2 days of bleeding externally visible (E. M. Wright and Bush, 1977; Nagle and Denari, 1982, 1983).
Lagothrix lagotricha (Woolly monkey)	menstrual	3 days slight	5,800	multimale	Menstrual bleeding can be detected if cotton swabs are inserted in the vagina; although on rare occasion external bleeding is apparent (Castellanos and McCombs, 1968; L. Williams, 1967).
Saguinus oedipus (Cottontop tamarin)	menstrual? periovulatory ?	covert	510	polyandrous?	In 3 of 6 females blood could be chemically detected in the urine during the trough and middle part of the cycle (Brand, 1981).

APPENDIX *continuation*

Species	Type of uterine bleeding	Duration and amount of flow	Weight of female (grams)	Breeding system	Notes and references
Saimiri sciureus (Squirrel monkey)	menstrual?	covert	580	multimale	In histologic examinations, the uteri sometimes showed hemorrhagic foci (Castellanos and McCombs, 1968). These authors do not offer an explanation for this menstruationlike effect; they believe the squirrel monkey does not menstruate because vaginal swabs did not show blood. Rosenblum (1968), however, detected red blood cells in some monkeys at modal intervals of 6 or 7 days, during the part of the cycle out of phase with estrus, which he notes may signify menstruation.
Old World Monkeys					
Cercocebus albigena (Gray-cheeked mangabey)	menstrual	slight	6,400	multimale	Rowell and Chalmers, 1970
Cercocebus aterrimus (Black mangabey)	menstrual	4 days slight/overt	5,500		Calle et al., 1990
Cercocebus torquatus atys (Sooty mangabey)	menstrual	4 days	5,500	multimale?	Gordon et al., 1991
Cercopithecus aethiops (Vervet monkey)	menstrual periovulatory	5 days slight/covert	3,560	multimale	Rowell, 1970; Eley et al., 1989
Cercopithecus mitis (Sykes and blue monkey)	menstrual periovulatory	5 days slight/covert	4,400	unimale	Rowell, 1970; Else et al., 1985
Erythrocebus patas (Patas monkey)	menstrual	slight	5,600	unimale	Rowell and Hartwell, 1978; Sly et al., 1983
Macaca arctoides (Stumptail macaque)	menstrual implantation	3 days slight	8,000	multimale	Brüggemann and Dukelow, 1980; Murray et al., 1985
Macaca assamensis (Assamese monkey)	menstrual	slight	5,800	multimale?	Wehrenberg et al., 1980
Macaca cyclopes (Formosan monkey)	menstrual	4 days overt			Peng et al., 1973
Macaca fascicularis (Crab-eating macaque)	menstrual	3 days overt	4,100	multimale	Dukelow, 1975
Macaca fuscata Japanese macaque	menstrual	overt	9,100	multimale	Aso et al., 1977
Macaca mulatta (Rhesus macaque)	menstrual	4 days overt	5,210	multimale	Markee, 1940
Macaca nemestrina (Pigtailed macaque)	menstrual		7,800	multimale or unimale	Blakley et al., 1981; Short et al., 1989
Macaca nigra (Sulawesi crested black macaque)	menstrual		6,600	multimale?	Cross and Martin, 1981; Thomson et al., 1991
Macaca radiata (Bonnet monkey)	menstrual	2-7 days	3,700	multimale	Kholkute et al., 1981
Macaca silenus (Lion-tail macaque)	menstrual	2-2.5 days overt	5,000	multimale	Ramaswami et al., 1982
Macaca sylvanus (Barbary macaque)	menstrual implantation		10,000	multimale	Küster and Paul, 1984
Mandrillus leucophaeus (Drill)	menstrual		10,000	unimale	Böer, 1987
Mandrillus sphinx (Mandrill)	menstrual	1-6 days	11,500	unimale	Linke, 1990
Miopithecus talapoin (Talapoin)	menstrual		1,100	multimale	Rowell, 1977
Papio cynocephalus (Yellow baboon)	menstrual		15,000	multimale	Kling and Westfahl, 1978

APPENDIX *continuation*

Species	Type of uterine bleeding	Duration and amount of flow	Weight of female (grams)	Breeding system	Notes and references
Papio hamadryas (Hamadryas baboon)	menstrual		9,400	unimale	Goncharov et al., 1979
Papio papio (Guinea baboon)	menstrual	2-7 days	13,000	multimale	MacLennan and Wynn, 1971
Papio ursinus (Chacma baboon)	menstrual	1-7 days	16,800	multimale	Bielert, 1986
Presbytis entellus (Hanuman langur)	menstrual	1-3 days slight/overt	11,400	unimale	Hrdy, 1977; Lohiya et al., 1988
Presbytis obscura (Dusky leaf monkey)	menstrual	2-3 days	6,500	unimale	Burton, 1981
Rhinopithecus roxellana (Golden snub-nosed monkey)	menstrual	slight?	6,500-10,000	unimale	Yang et al., 1990
Theropithecus gelada (Gelada baboon)	menstrual	slight	13,600	unimale	Matthews, 1956; Alvarez, 1973
Hominoidea					
Gorilla gorilla (Gorilla)	menstrual	3-5 days slight/overt	93,000	unimale	Noback, 1939; Quiatt et al., 1986; K. D. Dahl et al., 1987
Homo sapiens (Human)	menstrual periovulatory implantation	1-7 days overt (profuse)	55,000	unimale	Shaw and Roche, 1985
Hylobates concolor (Black gibbon or Crested gibbon)	menstrual	1-3 days overt (profuse?)	5,800	unimale? (Haimoff, 1986;1987)	Pocock, 1905; R.-q. Zheng, 1989
Hylobates hoolock (Hoolock gibbon)	menstrual	2-4 days slight/overt	6,500	monogamous	Matthews, 1946-7
Hylobates lar (White-handed gibbon)	menstrual	1-3 days slight/overt	5,300	monogamous	Carpenter,1941; Breznock et al., 1977
Pan paniscus (Bonobo)	menstrual		33,200	monogamous	J. F. Dahl, 1986
Pan troglodytes (Common chimpanzee)	menstrual implantation	1-7 days overt (profuse)	31,100	multimale	Elder and Yerkes, 1936; Graham, 1973, 1981; D. Collins, pers. commun.
Pongo pygmaeus (Orangutan)	menstrual	slight	37,000	solitary	Collins et al., 1975; Nadler, 1981

Blank cells indicate lack of data.
* From Harvey et al. (1986) and Fleagle (1988).
** From Smuts et al. (1986), Harcourt et al. (1981), and A. P. Møller (1988).