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Ovarian Function in Hysterectomized Macaca fascicularis

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ABSTRACT

Seven hysterectomized cynomolgus monkeys (*Macaca fascicularis*) were studied for more than 1 year. Menstrual cycle lengths in hysterectomized monkeys were based on the recurrent pattern of estrogens and progestins and were identical to menstrual cycle lengths in the same animals prior to hysterectomy based on the appearance of menses. Peripheral plasma levels of total estrogens and progestins demonstrated the persistence of a normal follicular phase with a preovulatory estrogen peak, followed by a normal pattern of luteal progestin secretion. Steroid patterns of hysterectomized animals were comparable to those of contemporary intact controls.

INTRODUCTION

Earlier studies in both human and nonhuman primates have indicated that there is no effect of hysterectomy on cyclical ovarian function (see discussion for references), contrary to studies in many nonprimate mammalian species (Anderson et al., 1969). Studies in hysterectomized rhesus monkeys have indicated a normal luteal progesterone secretion (Neill et al., 1969; Marcus, 1973), but these studies did not delineate both follicular and luteal phases of the cycle.

In the present study, therefore, peripheral levels of both estrogen and progestin were used to estimate the time of ovulation and the subsequent length of the follicular and luteal phases. Menstrual cycles in hysterectomized cynomolgus monkeys were recorded for a period of 12–20 months and are still being followed. Intact cycling animals served as controls and were routinely bled for steroid determinations on the same schedule as for hysterectomized animals.

MATERIALS AND METHODS

Adult female cynomolgus monkeys (*Macaca fascicularis*) were individually housed under conditions of natural lighting supplemented with artificial lighting and a regulated temperature (24 ± 1°C). Monkey chow was fed twice daily and augmented with fresh fruit and vitamins. Water was available *ad libitum*. Length of the menstrual cycle was determined by taking daily vaginal swabs with cotton-tipped applicators. The first day of menstrual bleeding was considered to be the first day of a cycle and only those monkeys which had a history of normal menstrual cycles were used in this study.

Six normally cycling cynomolgus monkeys were hysterectomized during the first week of the menstrual cycle and a seventh animal during the late luteal phase. Food was withheld from each animal for 12 h prior to surgery, which was performed under Sernylan (phencylidine hydrochloride, Parke-Davis) anesthesia. The ovarian ligament was transsected to free the ovary from the uterus and the fimbria was carefully dissected away from its ovarian attachment. The ovarian artery and vein were left intact to the ovary, but severed and ligated between the ovary and uterus. The uterus was excised at the level of the cervix and the uterine artery and vein ligated. After transsecting the broad ligament, the uterus and fallopian tubes were removed and the cervix was covered with peritoneum.

Following hysterectomy, animals were sampled with sufficient frequency to obtain a complete pattern of estrogen and progestin levels during the follicular and luteal phases of the cycle. This generally involved sampling every third to fourth day, although more frequent samples were taken at key stages, especially to include the period of the expected preovulatory estrogen peak. A group of 4 intact cycling monkeys was subjected to the same frequency of blood sampling in order to serve as controls for these studies. It was expected from its inception that these hysterectomized monkeys would be followed for several years and consequently daily blood sampling, from the standpoint of the animals' health and the sheer volume of blood sampled which would require assay, was ruled out.

At infrequent intervals (approximately 6 months) blood samples were taken for hematological parameters (hematocrit, CBC) to ascertain that the frequency of blood sampling was not deleterious to the animals' health. Body weight of all animals was recorded at 3 month intervals.

Blood samples (1.5 ml) were collected in heparinized syringes from the femoral vein and plasma was

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stored frozen until assay. In the first year of this study, progestins (ng/ml) were assayed by competitive protein binding (CPB) (Johansson, 1969) and estrogens were assayed by radioimmunoassay using an antiserum with 100% cross reaction for both estrone and estradiol with no attempt at chromatographic separation of these steroids (Shaikh et al., 1976). Estrogen values are therefore expressed as total estrogens (pg/ml). We have recently changed to a specific RIA for progesterone using antiserum (GDN-337) generously supplied by Dr. G. D. Niswender (Colorado State University) (Gibori et al., 1977). Progesterone values in both assays (CPB and RIA) were comparable with a correlation coefficient of 0.95. The within assay coefficient of variation was 9.89% and the between assay coefficient of variation was 19.87%, with a sensitivity of 0.1 ng/ml of plasma. Since the majority of data have been from CPB assays we have retained the term progestins where results from both assays have been combined. We also switched to a specific RIA for estradiol using antiserum (E_2TG-K) kindly provided by Drs. Wright and Collins (Emory University). The pattern of total estrogens and estradiol were entirely comparable, except for the lower basal levels of estradiol. The within assay coefficient of variation of the estradiol assay was 5.61% and between assay coefficient of variation was 11.59% with a sensitivity of less than 10 pg/ml plasma.

In the course of these studies, hysterectomized monkeys have been administered several treatments known to be luteolytic in intact monkeys (Shaikh et al., 1978b) in order to test the possibility that the uterus may be a mediator of these treatments. In all cases these treatments were preceded and followed by untreated cycles. These treatments are indicated in the figures by a hatched bar above the graph. These studies are still in progress and the results will be the subject of a future report.

Determination of Menstrual Cycle Length in Hysterectomized Monkeys

In intact animals, cycles were followed by daily vaginal swabbing and the first day of bleeding was designated Day 1 of the cycle. In hysterectomized animals, since they did not have menstrual bleeding, cycle length was determined from the pattern of estrogen and progestins in peripheral plasma. Three different criteria were used for the measurement of cycle length in hysterectomized animals: 1) when the preovulatory estrogen peak was clearly discernible in successive cycles, the time between these two peaks was one indication of cycle length. The criteria for the preovulatory estrogen peak were not only a sharp increase in estrogen, but also a subsequent increase in luteal progesterone production. 2) The initiation of luteal progesterone production (≥1 ng/ml) in 1 cycle to the initiation of luteal progesterone increase in the subsequent cycle was a second criterion and measure of menstrual cycle length. 3) The third method used was the time between the termination of luteal progesterone secretion (<1 ng/ml) in 1 cycle to the termination of luteal progesterone secretion in a subsequent cycle. Figure 1 is a diagrammatic representation of the estrogen and progestin pattern through several menstrual cycles and indicates methods used in the determination of menstrual cycle lengths.

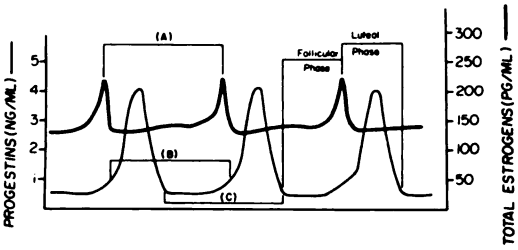


FIG. 1. A diagrammatic representation of the estrogen and progestin pattern through several menstrual cycles, which delineates the methods used for the determination of menstrual cycle lengths: A) from 1 preovulatory estrogen peak to the next: B) from the initiation of luteal progestin production (>1 ng/ml) in 1 cycle to the same event in the subsequent cycle and C) from the termination of luteal progestin production (≤1 ng/ml) to the same decline in the following luteal phase. Using the same endocrine landmarks, the limitations of follicular and luteal phases are also indicated.

Determination of Follicular and Luteal Phase Components of the Menstrual Cycle in Hysterectomized Monkeys

In the intact cyclic monkey, the duration of the follicular phase of the cycle is measured from the first day of menses to the day of the preovulatory estrogen peak or of the LH surge (these two events are usually coincident and never more than 1 day apart). In hysterectomized monkeys, we have taken the termination of luteal progestin secretion (specifically, when progesterone levels decline to less than 1 ng/ml), to the day of the preovulatory estrogen peak as the hormonal limitations of the follicular phase. In intact animals, menses generally follow within 1–4 days after this decline in progesterone (Shaikh, unpublished results; Stabenfeldt and Hendrickx, 1973) and consequently this estimate is correspondingly longer than in intact animals.

The luteal phase in intact cyclic monkeys is measured from the preovulatory estrogen peak to the appearance of menses. In hysterectomized monkeys, we have measured the time from the estrogen peak to the decline in luteal progesterone secretion (when peripheral progesterone levels fall below 1 ng/ml) as the luteal phase. In intact monkeys, the determination of the luteal phase as judged by the appearance of menses, occurs 1–4 days following the decline in progesterone (Shaikh, unpublished results; Stabenfeldt and Hendrickx, 1973) and consequently this estimate is correspondingly shorter than in intact animals. Figure 1 delineates the endocrine landmarks to determine both follicular and luteal phases.

Statistical analyses of data were made using Student's t test.

RESULTS

Mean (±SEM) menstrual cycle length in

monkeys prior to hysterectomy (30.4 ± 1.0 days) was not significantly different from cycle lengths of the same animals following hysterectomy (29.7 ± 0.9 days) (Table 1). The mean of individual cycle lengths indicated a difference in cycle length between intact (31.2 ± 0.6 days) and hysterectomized (29.6 ± 0.4 days) monkeys; however, these data in the hysterectomized animals were heavily weighted in favor of the animals with shorter menstrual cycles. The individual data are presented in Table 1; however, the mean of the group, for the above reasons, is calculated from the mean cycle lengths of individual monkeys. Although cycle lengths were determined by two different methods (i.e., vaginal swabbing in intact animals and the pattern of estrogen and progestion secretion in the hysterectomized animals), values determined by either of these two methods indicated a remarkable similarity before and after hysterectomy (Table 1). In addition, the duration of the follicular and luteal phases has been determined by similar methods (Fig. 1). The mean duration of the follicular phase in hysterectomized animals is 14.1 ± 0.5 days and is, of necessity, 1–4 days longer than would be measured in intact monkeys and is related to the time required for menses to occur after the decline of progesterone. Similarly, our determination of luteal phase length (15.3 ± 0.4 days) in hysterectomized monkeys is shorter than would be measured in intact animals by this same 1–4 day period (Table 1). The total duration of mean follicular and luteal phases is equal to the mean cycle length in hysterectomized monkeys and is a further indication of the validity of the methods used.

A comparison of the three methods used to determine menstrual cycle length in hysterectomized monkeys is presented in Table 1. Measures of individual cycle lengths for each of the three methods are presented and means of the same values for all 7 monkeys were identical. The resulting mean of cycle lengths from a combination of these methods is therefore considered to be a valid method for determination of cycle length. A limited evaluation of the same parameters for determination of menstrual cycle lengths in intact monkeys yields the same type of corroborative results (in 3 monkeys, mean cycle lengths based on menses are 29.7, 28.6 and 33.0 days while the mean cycle lengths determined from steroid parameters in the same animals are 31.5, 28.4 and 32 days, respectively).

Figure 2 depicts the pattern of total estrogen and progestin levels normalized around the day of the preovulatory estrogen peak in both hysterectomized and intact monkeys. The pattern of estrogen secretion was identical in both cases, with no significant fluctuations through the luteal phase. The duration of progestin secretion was similar in both groups and, even though the luteal phase appeared to be a day shorter in the hysterectomized group (Fig. 2), these results were not significantly different, nor were the apparently higher progestin levels of intact monkeys. The normal pattern of estrogens and progestins in peripheral plasma in individual animals is shown in Fig. 3. Three hysterectomized monkeys are presented as well as 2 normally cycling intact animals with a similar schedule of blood sampling. The normal pattern of estrogen rising to a preovulatory peak followed by the increase in luteal progestin secretion is evident in both intact and hysterectomized monkeys.

Of the 7 monkeys, 4 clearly demonstrated ovarian cyclicity for a full year or more after hysterectomy, in spite of the repeated blood samples which were necessary to estimate the time of ovulation and the length of the luteal phase. Only 1 of these animals (X60) developed what seemed to be an insufficient luteal phase 16 months after hysterectomy; it was characterized by minimal increases in progestin for short periods of time. After a rest period of 5 weeks, typical ovarian cycles had resumed. Three other animals (X62, X65 and X41) maintained cycles through 16 months of monitoring after hysterectomy. A fifth animal (X17) has had 2 or 3 anovulatory cycles in the course of 12 months. The remaining 2 animals (X25 and X29) demonstrated atypical cycles soon after hysterectomy (Fig. 4). These animals were not bled for almost 2 months and, when bleeding was reinitiated, showed normal ovarian cyclicity. In all cases, hysterectomized monkeys which demonstrated atypical cycles resumed normal cyclicity after a rest period of one to two months. Figure 5 presents 1 normal menstrual cycle from each of the 7 monkeys from 10–20 months after hysterectomy.

Four intact normally cycling animals were selected as controls on the basis of previous regular menses. Although we have menstrual cycle control values from other experiments (Shaikh et al., 1978a), they represent a composite picture of estrogen and progesterone

TABLE 1. Effect of hysterectomy on menstrual cycle parameters in *Macaca fascicularis*.

Monkey No.	Mean cycle length before hysterectomy[a]	Mean cycle length after hysterectomy[b]	Individual cycle lengths based on:[c] Preovulatory estrogen peak	Increase in luteal progesterone	Decrease in luteal progesterone	Mean follicular phase[d]	Mean luteal phase[e]
X60	28.0 ± 1.0 (2)	27.4 ± 0.7 (12)	25, 25, 30, 26, 31	26, 25, 27, 27	33, 27, 27	11.5 ± 1.3 (4)	14.4 ± 1.3 (5)
X62	32.8 ± 1.9 (8)	29.8 ± 0.8 (12)	26, 31, 36, 30	29, 32, 28, 32, 29, 28	28, 28	13.9 ± 0.5 (7)	15.8 ± 0.6 (5)
X65	26.3 ± 0.5 (4)	27.3 ± 0.6 (13)	25, 29, 31, 28, 26, 27	30, 24, 29, 26	27, 24, 29	12.5 ± 0.6 (6)	15.3 ± 0.5 (8)
X41	32.0 ± 0.6 (9)	32.6 ± 0.6 (11)	29, 33, 31, 34	34, 31, 31, 36, 32	33, 35	18.0 ± 1.1 (6)	13.8 ± 0.5 (4)
X17	31.5 ± 1.1 (8)	32.4 ± 0.8 (8)	34, 28	33, 34, 32	35, 30, 33	15.8 ± 1.3 (4)	16.2 ± 1.1 (5)
X29	33.2 ± 1.3 (10)	31.3 ± 0.6 (6)	32, 31	34, 31, 30	30	13.7 ± 1.5 (3)	18.0 ± 1.0 (2)
X25	29.3 ± 1.3 (8)	27.2 ± 0.4 (6)	26, 28, 26	28, 28	27	11.7 ± 0.3 (3)	14.6 ± 0.8 (5)
Group mean[f]	30.4 ± 1.0 (7)	29.7 ± 0.9 (7)	29.2 ± 0.6 (26)	29.9 ± 0.6 (27)	29.7 ± 0.9 (15)	14.1 ± 0.5 (33)	15.3 ± 0.4 (29)

[a]Menstrual cycle length based on menstrual bleeding in cycles prior to hysterectomy.

[b]Menstrual cycle lengths in hysterectomized monkeys based on the pattern of total estrogens and progestin secretion. Three different methods have been used and are described under footnote (c). Since more than one of these methods may be utilized in any cycle, the number of determinations (n) may be greater than the actual number of cycles involved.

[c]Individual methods for cycle length determination include: 1) days from 1 preovulatory estrogen peak to the next; 2) days from the initiation of luteal progesterone production (when values are ≥1 ng/ml) in one cycle to the same point in the subsequent cycle and 3) the time between the termination of luteal progesterone (<1 ng/ml) in 1 cycle to the same event in the subsequent cycle.

[d]Follicular phase length measured from the termination of luteal progestin secretion to the preovulatory estrogen peak.

[e]Luteal phase length is measured from the preovulatory estrogen peak to the termination of luteal progestin production.

[f]Group means are derived from either the individual means of each animal or the mean of all individual observations and can be distinguished by the value for n in each case.

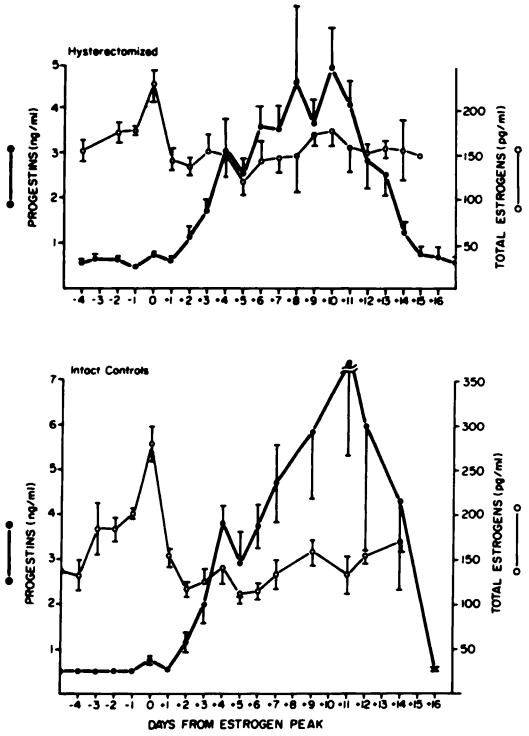


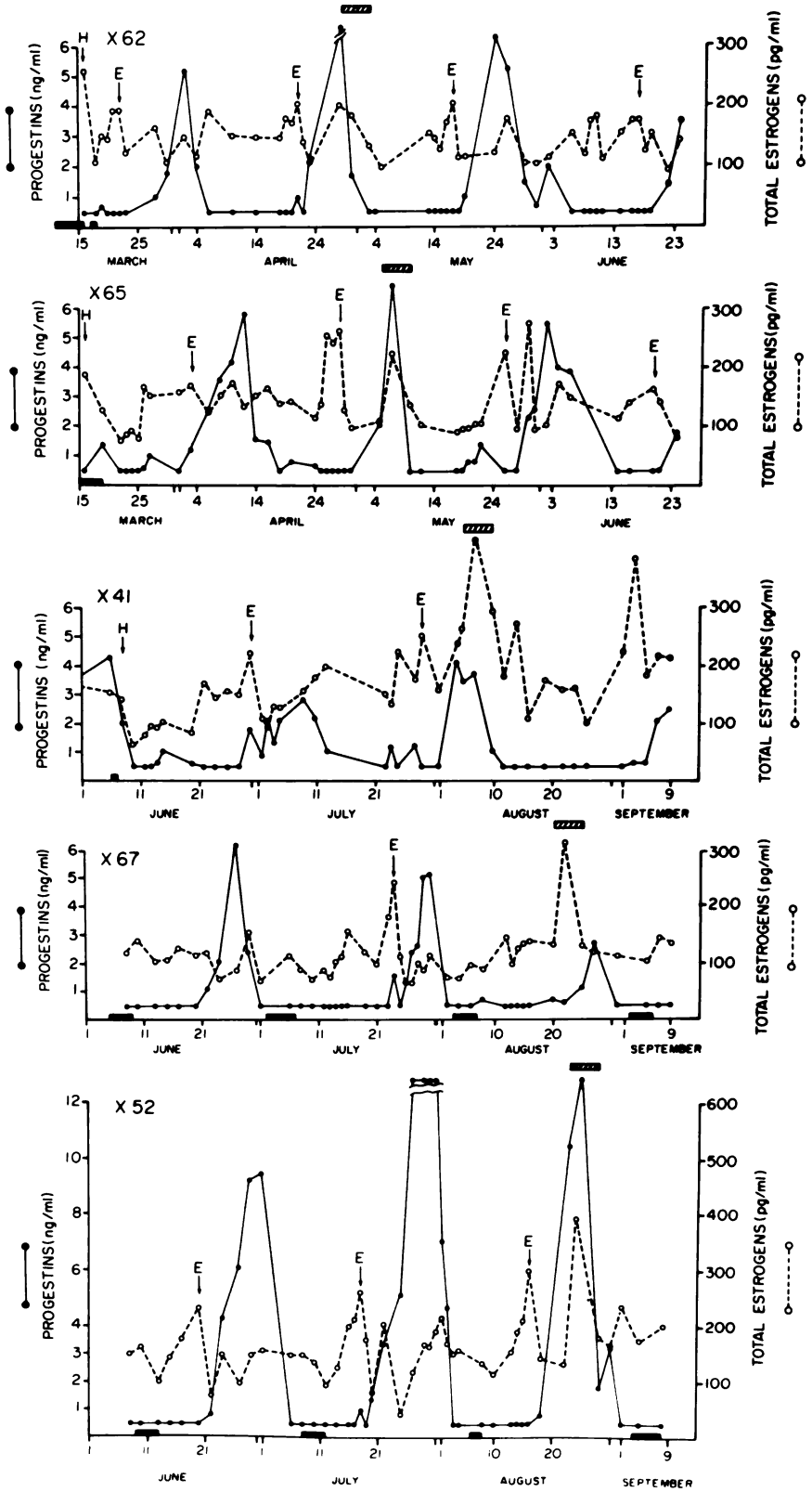
FIG. 2. Peripheral plasma levels of total estrogens and progestins normalized around the day of the preovulatory estrogen peak (Day 0) in hysterectomized monkeys in the upper panel and intact controls in the lower panel. Values are presented as means ± SEM. Data have been collected from 17 cycles in intact control monkeys and 34 cycles in hysterectomized monkeys.

throughout the cycle derived from infrequent and isolated bleedings. Therefore, these control animals were subjected to the same type of bleeding schedule as were the hysterectomized animals. Two of these animals demonstrated normal recurring cycles with estrogen and progestin patterns comparable to those in the hysterectomized animals (Fig. 3). Two other animals exhibited 1 or 2 apparently normal cycles and then entered what seemed to be an anovulatory period. Even menses, which occur in anovulatory cycles, were delayed in these 2 animals (Fig. 4).

DISCUSSION

Previous studies on nonhuman primates, indicating that hysterectomy was without effect on the menstrual cycle, utilized such parameters as perineal sex skin (Hartman, 1932; Burford and Diddle, 1936; Gillman and Gilbert, 1944), vaginal cytology and desquamation (Hartman, 1932; van Wagenen and Catchpole, 1941; Burford and Diddle, 1936) and peripheral plasma progesterone levels (Neill et al., 1969; Marcus, 1973). This study confirms and extends those original observations and demonstrates that, in the cynomolgus monkey, hysterectomy was without effect on ovarian function, as judged by normal estrogen and progestin secretory patterns. Although peak luteal progestin values seemed higher in intact animals, this was not a statistically significant difference (Fig. 2). The methods used to determine follicular and luteal phase lengths in hysterectomized monkeys, in the absence of menses, rely on the decline in progesterone (to values less than 1 ng/ml), as the indication of the termination of luteal function. Studies from this laboratory (unpublished observations) and others (Stabenfeldt and Hendrickx, 1973) have indicated that progesterone levels decline 1–4 days prior to menses and a corresponding correction in our estimates of these two menstrual components is required. In a thorough study of estradiol and progesterone levels and of the component phases of the menstrual cycle in this species (Shaikh et al., 1978a), the follicular phase was found to be relatively constant at 11–12 days. A similar duration of the follicular phase in this species has been reported by others (Goodman et al., 1977). The luteal phase was variable and related to the duration of the menstrual cycle, with a mean luteal phase length of 13.1 days in the shortest cycles (22–26 days) to 24.2 days in the longest cycles (32–37 days), with the predominant normal cycles (27–31 days) having a mean luteal phase of 15.9 days (Shaikh et al., 1978a). Goodman et al. (1977), in a more limited study in this species, have determined the luteal phase to be 15.7 ± 1.2 days. Both our follicular

FIG. 3. Continuous record of peripheral plasma levels of total estrogens and progestins in hysterectomized monkeys in the 3 upper panels (Monkeys X62, X65 and X41) and intact monkeys in the 2 lower panels (X67 and X52). The day of hysterectomy is indicated by the letter H and an arrow above the graph. The letter E with an arrow indicates a clearly definable preovulatory estrogen peak. Solid black bars on the abscissa represent menstrual bleeding. The hatched bars above the graph are days of treatment with different hormonal regimens, generally containing estrogen, accounting for the increases in peripheral estrogen levels during these periods.



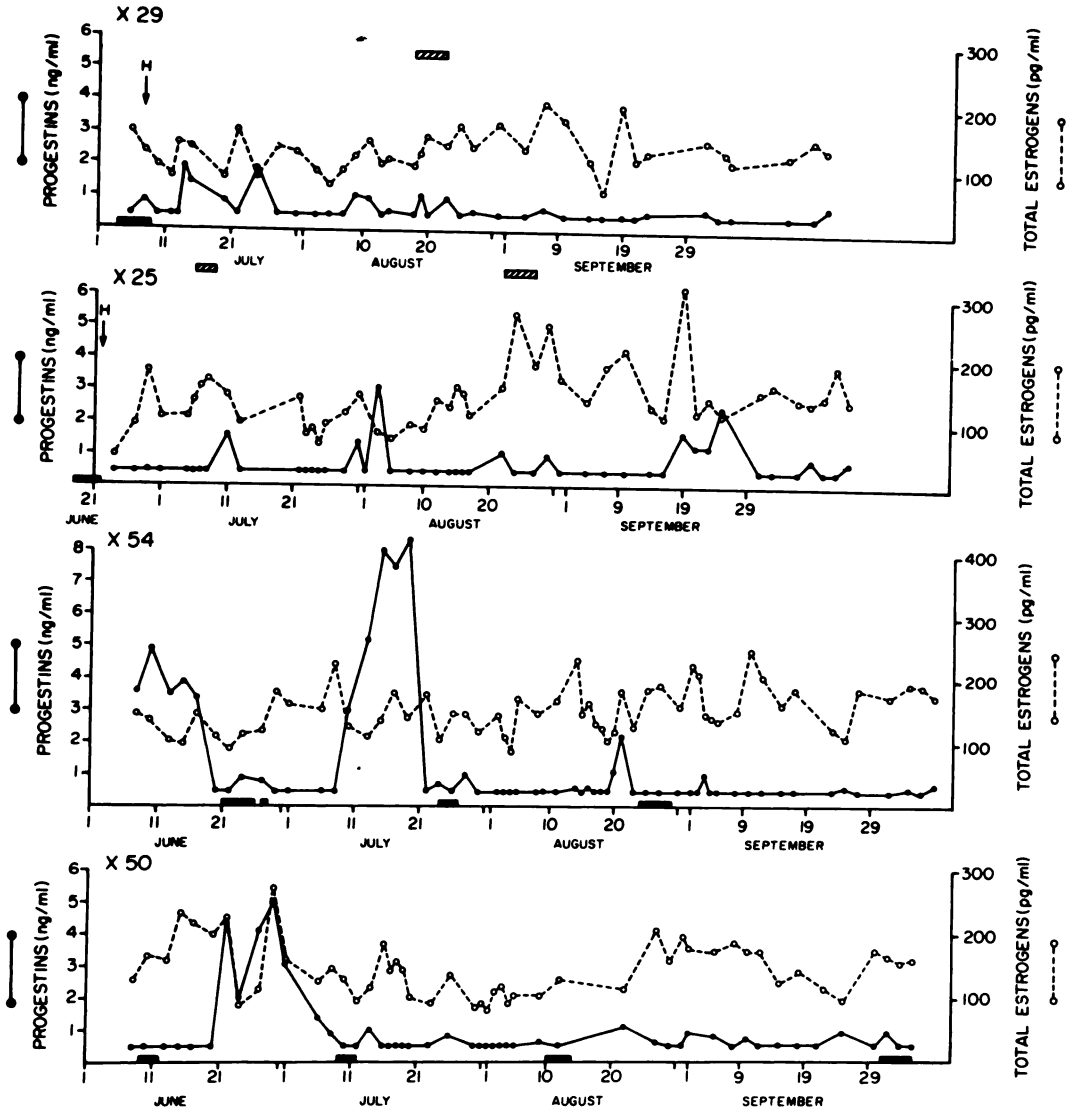


FIG. 4. Continuous record of peripheral plasma levels of total estrogens and progestins in poorly cycling hysterectomized (X29 and X25) and intact (X54 and X50) animals. Both X29 and X25 had a normal luteal progestin pattern in the cycle prior to hysterectomy. The apparent anovulatory condition develops after more than one cycle of frequent bleeding. Symbols in this Figure are the same as in Fig. 2.

(14.1 ± 0.5 days) and luteal phase (15.3 ± 0.4 days) estimates in hysterectomized monkeys, when corrected, are in good agreement with the earlier data (Shaikh et al., 1978a) in intact cynomolgus monkeys. Since several of the hysterectomized monkeys had longer menstrual cycles (>32 days), the mean luteal phase would be expected to be between 15.9 and 24.2 days.

In the human, clinical observations over many years have indicated normal ovarian function following hysterectomy (Bancroft-Livingston, 1954; Whitelaw, 1958; Dördelmann and Wölker, 1968; Beavis et al., 1969; Beling et al., 1970; Doyle et al., 1973) or in the congenital absence of the uterus (MacRae and Mohamedally, 1969; Fraser et al., 1973; Coyotupa et al., 1973; Karam et al., 1973). These studies in humans have been based on similar experimental parameters as used in nonhuman primates: biphasic basal body temperature curves (Whitelaw, 1958; Dördelmann and Wölker, 1968); vaginal cytology (Bancroft-

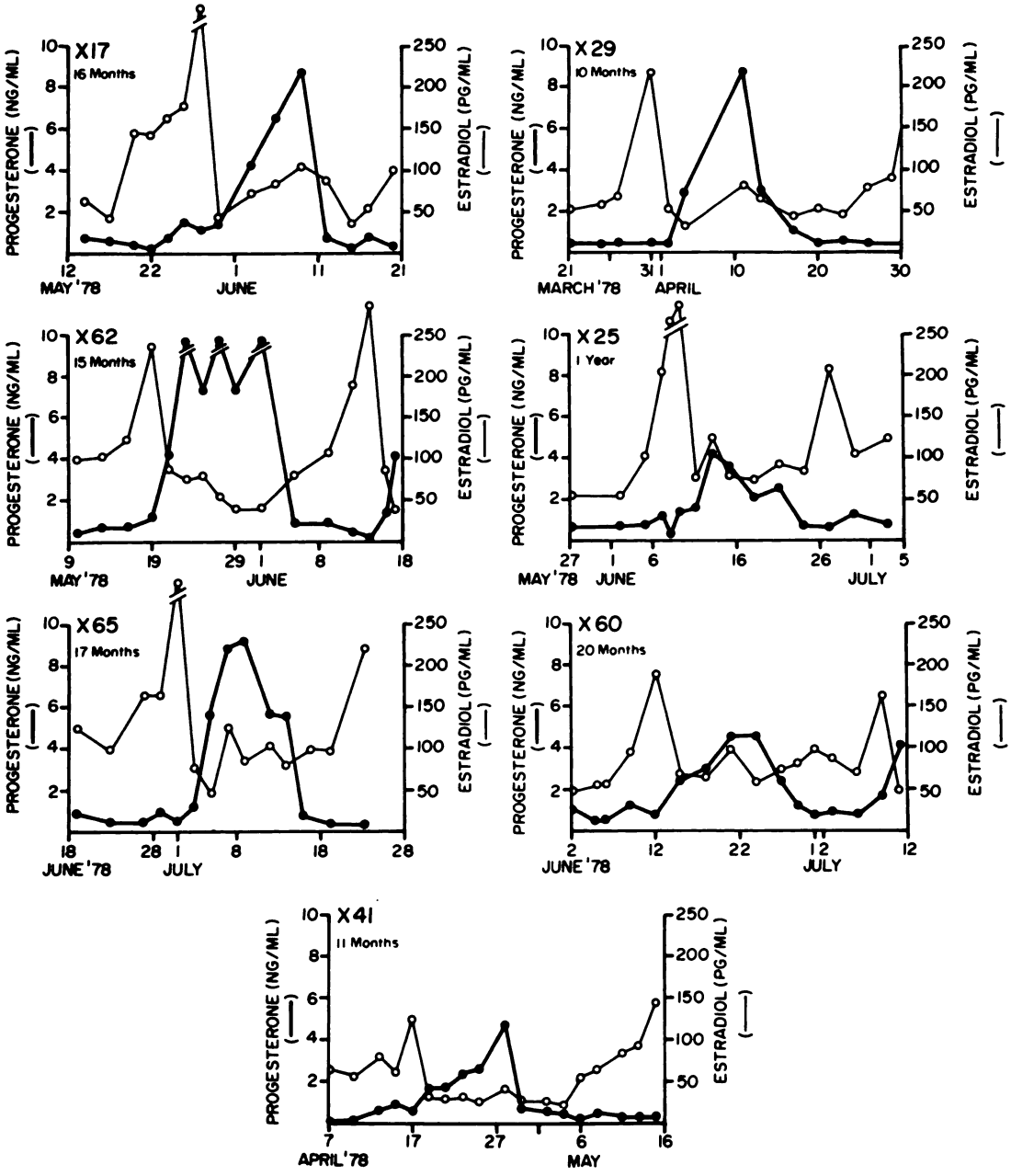


FIG. 5. Estradiol and progesterone levels through a recent cycle for each of the 7 monkeys, ranging from 10–20 months after hysterectomy.

Livingston, 1954; Whitelaw, 1958); urinary hormone excretion, chiefly pregnanediol and estrogen, but also gonadotropins (Beling et al., 1970; MacRae and Mohamedally, 1969; Whitelaw, 1958) and, most recently, gonadotropin and ovarian steroid levels in peripheral plasma (Doyle et al., 1971; Coyotupa et al., 1977). The limited study of Andreoli (1965) indicated that hysterectomy early in the luteal phase (d17–18) shortened luteal function in 5 of 6 women, but not in 4 of 4 women when done later in the cycle (24–25 days). Studies from other laboratories have failed to confirm these results (Beling et al., 1970; Doyle et al., 1971; Marcus, 1973).

A case report of hysterectomy in the baboon

indicates that normal ovarian cyclicity, on the basis of perineal sex skin changes, persists for the first 2 years, after which it becomes "difficult to recognize any obvious cyclical variations in the perineum" (Gillman and Gilbert, 1944). It was, however, impossible to confirm any altered ovarian function on the basis of ovarian examination. That individual case was offered in support of the then prevalent opinion that hysterectomy in women accelerated the onset of menopause. Many clinical studies since then have discounted this notion. The hysterectomized monkeys in this study will be followed as long as possible to determine any effect on ovarian function with increasing time following hysterectomy.

The results of this study have indicated that some animals may develop irregular or anovulatory cycles (Fig. 3) as a result of frequent blood sampling over a prolonged period. Cynomolgus monkeys are well known for their regular cycles and lack a summer anestrous interval (Goodman et al., 1977; Dukelow, 1975). We have seen very few anovulatory cycles in our *M. fascicularis* colony (unpublished observations) and Dukelow (1975) reports only 10% anovulatory cycles in this species. Stress is generally reported to upset ovarian cyclicity (Andrews, 1977; Preston et al., 1974) and it is known that nonhuman primates do not exhibit normal menstrual cycles for several months after capture and delivery to new quarters (Hendrickx and Kriewaldt, 1967). Severe surgical stress has been reported to hasten the termination of the luteal phase (Knobil, 1973). The fact that 2 intact and 2 hysterectomized monkeys developed abnormal ovarian function indicates that the frequent stress of blood sampling may have an effect on, presumably, pituitary gonadotropin release. Hematological parameters and normal body weight gain indicate that the bleeding schedule was not deleterious and the resumption of normal cyclicity following a short rest period suggests that stress had interfered with the normal menstrual rhythm. We have also noted that an increased frequency of blood sampling in the baboon may be associated with an increased frequency of anovulatory cycles (unpublished observations). In Fig. 5, we have presented the estradiol and progesterone levels during a complete menstrual cycle from each monkey ranging from 10–20 months after hysterectomy. Four of these animals have had brief periods of atypical menstrual cycles, but all have resumed and maintained typical patterns of estradiol and progesterone, following a short rest period of 1–2 months.

Contrary to results in primates, experiments in subprimate mammalian species indicate that the uterus often exerts a luteolytic action and consequently, hysterectomy can be associated with prolonged luteal function (Anderson et al., 1969). Prostaglandins may be luteolytic in monkeys (Kirton et al., 1972; Russell, 1975; Wilks, 1977), although these results are equivocal (Shaikh, 1972). Even though the uterus is a site of active prostaglandin synthesis (Castracane and Jordan, 1975; Barcikowski et al., 1974; Demers et al., 1974), there is no indication that prostaglandins of uterine origin are involved in primate luteal regulation. There are, however, studies which indicate that prostaglandins, presumably of ovarian origin, may be involved in such regulation (Auletta et al., 1976a and 1976b). These same hysterectomized monkeys are being treated with several luteolytic regimens and would seem to be useful models to study any uterine involvement in luteolysis. Further studies on the estrogen luteolytic effect could be done to great advantage in this animal model.

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