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THE EVENTS OF THE PRIMATE OVARIAN CYCLE*

BY

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It is a privilege and a responsibility to speak here at Charing Cross Hospital in grateful memory of Thomas Henry Huxley, thus placing among his laurels another wreath from a nation overseas to which he gave notable counsel and inspiration. The promoters of the Huxley Lectureship have three times interrupted their extraordinary succession of eminent British and Continental scholars to bring over someone from America. Each time they have chosen a medical scientist closely associated with Baltimore and the Johns Hopkins University. This cannot be altogether a coincidence, for surely among all the centres of learning in America where Huxley's voice was heard and where his books are read it was that city beside the Chesapeake to which he has given the most. When the Johns Hopkins opened its doors in 1876 he was invited to give its first public lecture. What he said on that occasion about the principles of university education is as provocative now as it was then. He recommended his pupil Newell Martin to be the first professor of biology in the new university, and thus had a direct influence upon the development of a great centre of biological research. A Baltimorean like myself who studied under Jennings and Andrews—who were disciples of Martin, who was a pupil of Huxley, who studied at Charing Cross Hospital—may therefore claim to be himself a kind of great-great-grandson of Alma Mater *juxta crucem*. Professors of Charing Cross Hospital, pray mind your words and actions as you teach your young men of to-day; there may be among them some other who is destined to spread science and the love of truth through four generations on both sides of the sea.

My own first experience of Huxley's genius came from the book *Man's Place in Nature*, in which he wrote so boldly and so well about the natural history of the man-like apes and the relation of man to the lower animals. In recollection of this interest of his I have chosen to discuss with you our present knowledge and concepts of the reproductive cycle of the human female, as a topic of medical interest, in the light of what can be learned from the other primates. In the past few decades enough has been discovered on this subject to warrant a summary review in this series of lectures on the general theme of recent advances in science in their relation to practical medicine.

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Amid all the diversity of reproductive behaviour among the mammals, there are two basic events in the cycle of every mammalian female. These are (1) the maturation and discharge of the ovarian follicle, by which the corpus luteum is formed and the progestational phase of the reproductive cycle initiated, and (2) retrogression of the corpus luteum, which brings that phase to an end.

There is a strange difference in the outward expression of these two events of the cycle between the human species and the other mammals that are commonly observable about us, in the house, barnyard, and laboratory. In these latter it is the ovulation phase that makes itself evident, by oestral excitement and (in many species) by cyclic changes in the external genitals. This is strikingly true of the two mammals which man observes in the greatest numbers—namely, swine and dog, in both of which the recurrent period of "heat" is accompanied by swelling of the vulva, by a mucous or muco-sanguineous discharge, and by sexual behaviour of unmistakable intensity. The signs of oestrus are less evident in some other familiar animals—for example, the mouse, rat, and guinea-pig—and there are no obvious changes in the external genitals. Laboratory investigation has, however, revealed in these animals a cycle of cellular change in the lower reproductive tract, detectable by microscopical study of vaginal scrapings, by which the time of ovulation can be ascertained within an hour or two. Thus in all the mammalian species which have been thoroughly studied, except certain primates, the critical event of ovulation can be detected with reasonable assurance by the appearance or behaviour of the female or by a simple technical procedure. In all these animals, it should be repeated, sexual activity of the female is restricted to a limited period at the time of ovulation.

In the human female a very different pattern exists. The event of ovulation is not marked by any outwardly observable sign, nor by a surge of erotic responsiveness. This great recurrent crisis in the human life-process is silent and occult. Neither self-observation by women nor medical study through all the centuries prior to our own era taught mankind to recognize it.† Even

†After the time of ovulation in the cycle became known it was recognized that certain minor signs and subjective symptoms that occur in a few women about the middle of the interval—for example, intermenstrual bleeding (*Mittelschmerz*)—are associated with the ovulation phase.

at this day, when we have learned to calculate its incidence approximately from the date of subsequent menstruation, or from embryological data, more precise methods of dating ovulation are still in the exploratory state. I shall return later to further consideration of this remarkable suppression of the physical accompaniments of follicular maturation, and the equally remarkable diffusion of sexual receptivity throughout the cycle, in the human female.

Although in the human species the corpus luteum phase begins with no outward sign, its conclusion is marked by a conspicuous event—namely, menstruation. Exactly the opposite condition prevails in those animals in which oestrus and the ovulation phase are physically evident. Here it is the end of the corpus luteum phase which is inconspicuous. The corpus luteum degenerates (in most species) about two weeks after ovulation if in the given cycle there is no mating, or if mating is infertile. In most animals the changes in the uterus which are induced by the corpus luteum hormone quietly lapse and its lining and musculature revert to the state characteristic of the follicular phase. In the human species, in the man-like apes, and in the Old-World monkeys, on the other hand, the breakdown of the corpus luteum and consequent withdrawal of progesterone cause a destructive haemorrhagic disturbance in the endometrium.

Menstruation is a well-defined phenomenon only in the higher primates just mentioned, but recent studies on New-World (platyrrhine) monkeys have revealed the occurrence of internal bleeding in the endometrium at a corresponding stage of the cycle. In the elephant shrew, a mammal presumably related to the primates, extensive but local haemorrhage from the endometrium is thought by Van der Horst and Gillman to represent a modified, perhaps early evolutionary, type of menstrual bleeding. The evolution of menstruation is one of the large unsolved joint problems of natural history and physiology. Some day we may have information about it which a later Huxley can use in writing on woman's place in nature.

Time Relation Between Ovulation and Menstruation

Menstruation being a conspicuous and ovulation an inconspicuous event in the human cycle, those who sought to decipher the meaning of the menstrual cycle needed first of all to discover the relative time of ovulation with respect to menstruation. It was more or less generally supposed that menstruation in humans is equivalent to oestrus in animals. Another hypothesis held by certain physicians in the nineteenth century was that ovulation may occur at any time in the menstrual cycle, there being no regular temporal connexion between ovulation and menstruation. After a century of inquiry and conflicting conjecture, however, the true relation was worked out, largely by the German gynaecologists Schroeder, Meyer, and Fraenkel. When they learned, by direct observation of the human ovary at their operating tables and in the laboratories of surgical pathology, that ovulation takes place about midway between two menstrual cycles, thus preceding menstruation by about two weeks, the human cycle was seen to be fundamentally similar to the cycles of the other mammals that were being analysed about the same time—that is, the guinea-pig, rat, swine, and dog.

Walter Heape's pioneering efforts, at Cambridge and in India, to work out the reproductive cycle of Indian monkeys were baffled by the same fact that had made the human cycle a puzzle—namely, the lack of obvious oestrous phenomena and the occurrence of menstruation. When I took up the

same problem, beginning in 1919, I had the advantage of knowing something about the time of ovulation in the human cycle, and therefore was able to guess when to look for it in the monkey. In the second animal I explored we found a freshly ruptured follicle and recovered the ovum from the Fallopian tube, thus promptly securing positive evidence of ovulation at the mid-interval in a second primate species.

Had we only known it, there are two primates whose cycles might have given an earlier clue to the mystery. In the baboons and in the chimpanzee menstruation and the time of ovulation are both accompanied by outstanding physical signs. The cycle is four and a half to five weeks in length. During the first half of the intermenstrual period there is a marked swelling of the genital region, resulting in immense protuberances, and in the baboon there is extreme reddening of the skin of the perineal and adjacent areas. After the middle of the interval the pudendal turgescence, which has reached its maximum, suddenly subsides. Menstruation begins about two weeks later. Although females of both these primate genera will accept mating during the entire cycle, there is an increase of sexual responsiveness at the time of maximum swelling, which in many of them is so definite that it may properly be compared to oestrus.

We do not know yet by direct observation what is going on in the ovary at the time of maximum genital swelling in these particular primates; but there is ample evidence from mating experiments that ovulation occurs in this phase of the cycle. In our Carnegie Embryological Collection there are five early embryos of the chacma baboon, obtained for us at Johannesburg by Gillman and Gilbert, and two eleven-day chimpanzee embryos from the Yerkes Laboratories in Florida, all of them deliberately procured by timed matings based on the external sex cycle.

It is surprising that observation of the baboons and the chimpanzee did not long ago suggest to naturalists that oestrus and menstruation are two distinct affairs, and thus give an earlier clue to the meaning of menstruation in the human cycle. We must remember, however, that the keeping of exotic primates in zoos, in the robust health necessary to maintain reproductive functions, is an achievement of the present century, and also that mere observation of natural phenomena may tell us very little unless the observer asks the right questions. It was not until the late 1920's and the 1930's that Zuckerman, Yerkes, and others who had the opportunity to study baboons and chimpanzees under good conditions, knowing of the recently won information about the human and the rhesus cycle, began to collate with critical judgment available knowledge about the large monkeys and apes, and to make observations of their own.

Sex Activity

It should be added that after the cycle of the rhesus monkey was worked out renewed attention was paid to the sex-skin colour, which in that species had not been very helpful in ascertaining the time of ovulation. It was found (Rossman, 1940) that in many individuals there is a peak of colour intensity associated with the ovulatory phase, regularly enough at least to aid the investigator by notifying him when in a given cycle it is time to begin using the more precise method of daily ovarian palpation.

In spite of the lack of external physical signs of the ovulation phase in the human cycle, and the obvious absence of any oestrus-like wave of sexual responsiveness at that time, nevertheless sex activity is to a certain extent cyclic in the human female; and here we come to one of the most remarkable and seemingly inexplicable features of the natural history of sex in the primates. In all those Old-World monkeys and anthropoid apes in which enough is known about the sex-cycle to warrant a statement observers have reported a peak of sex activity associated with the maximum state of sex-skin colour or of pudendal swelling. In other words, there is a fairly typical oestrous phase, resembling

that of lower mammals in the combination of ripening of the ovarian follicle with a special condition of the external genitals and increased sex activity. Yet in all these animals sexual behaviour is less closely bound to the ovarian cycle than in lower mammals, for female monkeys and apes may and often do accept the male at other times of the cycle.

This statement is perhaps most fully definable in the case of the rhesus monkey, in which the time of ovulation can be ascertained, as Hartman showed, by palpating the ovaries. Ball and Hartman rated the intensity of sexual response in female rhesus macaques and correlated it with the time of ovulation. They found that the peak of sexual responsiveness occurs shortly before ovulation, although under special conditions the female may receive the male at any time, regardless of the phase of her cycle. Similar reports about macaques of other species, mangabeys, and baboons have been given by Zuckerman. At the Yerkes Laboratories of Primate Biology the sex behaviour of the chimpanzee has been very carefully studied by Yerkes, Tinklepaugh, Carpenter, Elder, Young, and others, who find that a well-defined phase of heightened sexual responsiveness occurs coincidentally with the period of maximum genital swelling, and therefore at the time when we must suppose ovulation takes place. In this animal, however, sex activity is bound to the physical events of the cycle even less than in monkeys. Varying conditions in the daily life of the consorts, individual preferences and dislikes, and all sorts of conditioning circumstances outweigh the hormonal influences which rigidly confine mating, in such animals as the sow, bitch, and rat, to a limited oestrous period, and thus mating occurs in the chimpanzee throughout the cycle. Individual episodes of mating behaviour described by Yerkes reveal a weakening of purely physical rhythmicity, and dominance of emotional and temperamental factors to a degree sometimes amusingly suggestive of human pride and prejudice.

Cyclic Sex Rhythmicity

It is superfluous to point out that in our own species, as observed in our kind of society, sex behaviour is so largely controlled by psychological factors that any remainder of cyclic sex rhythmicity in the human female is to say the least inconspicuous. Yet there is such a remainder, for all investigators who have secured information about the fluctuations of erotic response in women by direct interviewing report the occurrence of maximal responsiveness during a few days before the onset of menstruation or shortly after the flow has ceased. The height of the peak—that is, the difference between the amount of sex activity at this phase of the cycle and that in the interval—is not great as compared with the all-or-none pattern of the oestruating animals. The rhythmic increase, moreover, does not occur in every individual; and fluctuations in sex responsiveness due to transient stimuli and distractions may often be greater than the cyclic variation. The stated existence of a rhythm is thus a statistical generalization, but it is true of a majority of women much of the time. Professor Alfred C. Kinsey, of Indiana University, informs me that this picture has been amply confirmed by the extensive and authoritative investigations of his Institute for Sex Research and will be discussed in his forthcoming book on sex behaviour in the female.

The concept is, however, contrary to the general theory that has been built up by observation and experiment on oestruating animals. The physical signs of oestrus, such as swelling of the vulva, vaginal discharge, oedema, and intensified colour of the sex skin, etc., can be reproduced in castrate animals by injections of oestrogenic hormones. In some species the full pattern of oestrus can be reproduced in this way, even to copulation. In others oestrogen alone will not complete the picture, but, as W. C. Young discovered in the guinea-pig, the addition of a little progesterone elicits copulatory behaviour. Upon such observations as these, made it is true upon only a few species, we have based the perhaps too-facile assumption that sexual

behaviour in oestruating female mammals is fully controlled by hormonal factors. It is easy to assume, for example, that the unruptured follicle can provide the progesterone which is required for oestrus by some species at least. It is also easy to explain hypothetically some of the variant patterns—for example, the persistence of responsiveness in rabbit does for many days at a stretch, or the presence in monkeys and chimpanzees of a certain degree of willingness to mate through the whole cycle—by assuming that a small amount of progesterone may be present in the blood stream even when there is no corpus luteum. There is direct evidence for the first of these assumptions and indirect evidence for the second.

In the case of the human female, however, the peak of sex response occurs at the very time when both oestrogen and progesterone are at or approaching their lowest levels in the cycle. We must therefore assume either that the rhythm of endocrine control differs from what we know in other animals, in the face of all the similarities in the cyclic histology of ovaries and uterus between the human and other species, or (what is more probable) that in women endocrine control of sex arousal has become subordinate to other factors, presumably neuropsychological, which culminate not at the time of ovulation but shortly before menstruation.

However this may be, it thus appears that in our own species a biologically inefficient condition exists, for, if the rhythm of mating is controlled to any appreciable extent by the seemingly ill-timed peak of female responsiveness, to that extent insemination will occur most frequently at the very time in the cycle when fertilization is least probable. At this point the cautious biologist had better desist from further conjecture until more is known about the whole subject to which this lecture is devoted; but there is room for less responsible queries. How does this situation, for example, affect the thinking of those puritanical sects which would allow coitus for reproduction only? And are there pessimists who will consider this seeming dissociation of insemination from ovulation one of those evolutionary dis-integrations which may ultimately make the human race as extinct as the dinosaurs? At any rate, the present excessive human birth rate shows that the danger of extinction (from this cause) is still negligible. As for the moralists, they may be surprised to find science, less mechanistic than usual, declaring that at present this phase of human conduct seems more accessible to control through the mind than by the endocrines.

Maturation of the Follicle

Nevertheless, let us return to consideration of events in the ovary. There is one aspect of the histological cycle about which we know almost nothing—namely, the rate of growth of the follicle which is to ovulate in a given cycle, and the time when it begins to enlarge beyond the average size of the follicles waiting in the ovary. This question has been fairly well answered for the sow, rat, and guinea-pig, in all of which the fortunate combination of clearly definable oestrous cycles and unlimited material has favoured research. In the sow and the guinea-pig the follicles which are to rupture begin to be evident a very few days before ovulation; in the rat it is a matter of hours. Study of this question in human and other primate ovaries by direct observation has been balked by various difficulties. The problem is essentially a statistical one. We need a timed series of ovaries containing ripening follicles from individuals examined during the pre-ovulatory phase of the cycle. There is never a guarantee that a given follicle will go on to rupture; atresia may set in at any stage. Therefore the assumption that an enlarging follicle will ovulate is less safe in animals which normally ripen only one follicle in each cycle, and in which at best only a few specimens can be studied, than in swine and guinea-pigs. In the case of the human species, uncertainty is increased by the fact that specimens come almost wholly from persons with disorders of the reproductive system.

In the rhesus monkey the menstrual cycle is irregular enough to make the dating of a specimen with respect to the next ovulation precarious; nor have we been able to divert a significant number of specimens from the more urgent study of the later phases—that is, progestation and menstruation. Maturing follicles dated with reasonable assurance are, therefore, almost unknown. In more than 30 years of attention to this problem, in the course of which, combining the material of Hartman, Bartelmez, and Van Dyke with my own, I have been able to study the ovaries of about 300 rhesus females of reproductive age, I have seen no more than three rhesus ovaries and one human ovary containing maturing follicles subject to plausible dating with respect to impending rupture. These specimens, in accord with what has been found in better-known animals, indicate that the final growth and maturation of the follicle is a rapid process occupying only a few days.

Indirect evidence on this question is available. In the rhesus monkey, enlargement of the ovary by the growing follicle can be detected by palpation about two to four days before ovulation. Mr. Arthur G. Rever, of the Carnegie Laboratory, who learned the method from Hartman and has practised it longer than anyone else, agrees with me that palpable enlargement of the ovary means that a follicle has grown from the resting stage of about 1 mm. diameter to about 2.5 mm. or more. In the next two to four days it reaches the full diameter of 6 to 7 mm. This again indicates that the maturation process is rapid. Both the Farris test and the vaginal smear studies of De Allende and Orías, which I shall discuss later, tell us that changes in pituitary and ovarian hormone levels associated with the maturing follicle are first detectable in the last few days preceding ovulation. Thus it appears that if we could obtain a microscopical x-ray view of the human ovaries and microassays of the blood-borne hormones we should see that about day 9 of the typical 28-day cycle, counting from onset of the last menstrual flow, one of the waiting follicles in the ovary begins to enlarge under hormone stimulation and grows from 2 to 3 mm. diameter to the full size of 15 mm. in three to four days, finally rupturing and discharging its ovum.

Tests for Ovulation in Non-oestrating Animals

How are we to recognize the occurrence and the precise time of ovulation in the cycle of the non-oestrating animals? For the study and treatment of sterility this is a practical question of the utmost importance; for the scientific analysis of the cycle it is equally important. In the case of both the human and the rhesus monkey the basic fact that ovulation is intermenstrual had to be worked out by direct observation of removed ovaries, obtained from women at the operating-table and from monkeys by timed post-mortem examinations or surgical explorations. With Bartelmez and Hartman, I learned to recognize the age of the corpus luteum from microscopical sections, chiefly from Hartman's series of pregnancies dated by palpation of the ovaries or by single coitus. A good deal of similar though more empirical information, not yet fully published, has been assembled by gynaecological pathologists, notably Hertig and Brewer, by piecing together observations from the occasional specimens that are more or less datable from the operative history. I may add from my own limited experience with human material the observation that the progress of histological differentiation of the corpus luteum is so nearly alike in the two species that human corpora lutea may be dated fairly closely by comparison with rhesus.

Under the microscope we can estimate the age of a corpus luteum in days and thus calculate back to the day of ovulation with respect to the menstrual history. A recent excellent calculation of this sort has been made by Brewer and Jones (1947) on human ovaries removed at operation. Another way of getting at the time of ovulation is by compiling cases in which conception resulted from a single insemination on a known day of the cycle. The date of

effective insemination cannot in the present state of our knowledge be assumed to be the day of ovulation, but they must be practically the same, for neither ova nor sperm cells are long viable. Experience with the Carnegie rhesus colony shows that a mating to be effective must take place within a day before rupture of the follicle. Farris has recently presented a graph of the distribution of ovulation as indicated by 50 human cases in which conception occurred when either coitus or artificial insemination was practised on a specific day of the cycle.

In the rhesus monkey, as I have mentioned, the enlargement and rupture of the ovarian follicle can be detected by palpation with a high degree of accuracy. Hartman thus plotted the time of ovulation in the cycle in a large series. In citing these studies I have not separated the findings in human females from those in monkeys, for they are the same. With respect to the cycle length of 28 days, which in both species is the modal—that is, most commonly occurring—length, ovulation may occur on any day from day 6 to day 20, with high frequencies from day 12 to day 15, and the peak about day 13. It is indeed remarkable that the distribution curves drawn by Brewer and Jones and others, from women who were subjected to operation for pelvic disorders, match so closely that of Hartman from healthy and relatively young females of another species.

These methods of securing scientific data on ovulation involve disturbing the cycle by ablation of the ovary or by pregnancy. For clinical use, and for investigations on animals in which the events initiated by ovulation are to be studied, we need a precise test that does not interrupt the cycle. Direct diagnosis of ovulation by daily palpation of the ovaries, so useful in the rhesus monkey, in which it reveals a distribution curve corresponding to that mentioned above, is not practicable in women except when the abdominal wall is exceptionally thin, and would not in any case be clinically convenient. Direct observation by culdoscopy is beginning to be practised clinically, but cannot of course be used lightly, nor can it give day-to-day readings of the human cycle. Another method that reads a signal coming direct from the ovary, the electrical test of Burr, depends upon the occurrence of a sudden, brief increase of electrical potential across the body from vagina to abdominal wall when a follicle ruptures. It seems to work well in the rabbit, but is scarcely practicable with the restless rhesus female, and has not been found reliable for women.

Indirect Methods of Test

The other tests that have been tried do not depend upon ovulation itself. They merely tell us of the presence of one or another physiological state or activity that is usually concomitant with the ovulatory phase of the cycle. These include such recondite matters as the onset of excretion of pregnanediol glycuronide derived from the corpus luteum, and cyclic changes in the mucus of the cervix uteri. More fundamental is the use of fluctuations in the basal body temperature, which is in a general way related to the cycle. In spite, however, of occasional striking successes in individual cases and a degree of statistical validity, the consensus is that the basal body temperature cannot be depended upon for precise indication of ovulation.

The study of vaginal smears provides still another means of determining the time of ovulation. De Allende and Orías, who have acquired great proficiency in the study of the cycle by this method, have published a tabular summary of 61 cycles in 28 women. The earliest ovulation occurred on day 11, the latest on day 20, and the modal day was day 13. This method gives a semi-quantitative measure of hormone activity at all stages of the reproductive cycle. As we shall see later, it promises to be very useful in analysing aberrations of the human cycle; and, in spite of the laborious technique of counting the cells, deserves the serious attention of gynaecologists.

Farris has introduced a test for ovulation based on the cyclic excretion of a gonadotrophic hormone, presumably

from the pituitary gland, which is present in the urine during about four days preceding ovulation. Urine containing this substance, when injected into immature rats, produces hyperaemia of the ovaries. Having collaborated with Dr. Farris in checking his test against direct observations of the ovaries, obtained at operation, from women upon whom the test had been made pre-operatively, I believe that it indicates the time of ovulation in a high proportion of cases with sufficient accuracy for clinical use. For such tests to be practicable on an extensive scale requires at present a large rat colony; but if, as we may hope, the tell-tale substance, which must be of protein nature, proves to be detectable by chromatography or an immune reaction or some other laboratory trick, the test will come into general use. This urinary rat test, like the vaginal smears, places the time of ovulation in the same range as that indicated by the direct methods, again with a peak of most frequent ovulation around day 13 of the cycle.

Every once in a while somebody, usually the proprietor of a new test for ovulation, puts forward the idea that in women ovulation may occur more than once in each cycle, or that it may be induced by strong stimuli like that of coitus, as in the rabbit, cat, and ferret. There is no sound evidence at present for such assumptions. No one has seen in either human or rhesus ovaries two corpora lutea of different age within the span of a single cycle. It would be reckless, however, in the present limited state of our knowledge, to deny the possibility of either induced ovulation or of spontaneous extra-ovulation as an atypical variation. In the rat, which normally ovulates spontaneously on a fairly rigid schedule, experimenters (Dempsey and Searles; Everett) have shown that a ripe follicle can for a time be restrained from rupturing by changing the rhythm of daylight and darkness, or by treatment of the animal with a barbiturate; but while the follicle is in this condition coitus will cause it to ovulate. Who can say that such aberrations may not occur in the human cycle, in view of all the instabilities of daily existence and the hints we have that in mankind the nervous system tends to override the endocrines? When we get a simple convenient daily test for ovulation all such questions can be attacked.

Passage of Ovum to Uterus

After ovulation the next event of the cycle is transportation of the ovum to the uterus. We have very little information about this journey in primates. A few observations on rhesus monkeys suggest that the ovum reaches the uterus about the fourth day, as in most known mammals; and the still fewer relevant human cases agree with these. The Hertig-Rock two-cell embryo in the Carnegie Collection was still in the tube; 10-cell and 30-cell morulas and a blastocyst, all $3\frac{1}{2}$ days or more old, were in the uterus. I have long supposed that the chief function of the Fallopian tube is to delay the journey of the ovum until the corpus luteum has had time to prepare the uterus for its reception.

The human embryo implants itself in the uterus as early, perhaps, as the seventh day after ovulation. Implantation of the rhesus monkey embryo takes place about day 9. Nothing is known about the timing of this important event in any other primate. The one normal chimpanzee embryo in the Carnegie Collection, 11 days old, is so extraordinarily like human embryos of corresponding age that we may plausibly assume that implantation occurs at the same time as in the human species.

Before concluding this lecture I shall have something to say about the irregularities and uncertainties of the primate cycle, but first it should be said that the period of 9 to 10 days after ovulation is a time of relatively regular progress. Histological differentiation of the corpus luteum seems to constitute a kind of escapement which keeps the clockwork of progestational development of the endometrium on time. When all is going well, ovary, uterus, and the embryo, if one is present, march together in such agreement that an expert histologist looking at any one of the three under the microscope can date it almost to the exact day within this 10-day span.

It has long been evident that this must be so if all the physical and chemical processes of embryonic development are to be successfully integrated. An experimenter (Chang), who has been putting this thought to the test by studying the development of rabbit embryos transplanted to foster mothers, has recently re-emphasized the necessity for physiological co-ordination in early development, when, as he says, a series of activities is set up "in a definite sequence which is essential to the survival, development, and implantation of eggs. Any disturbance of the physiological conditions in the ovary, the tube, and the uterus, or even a disturbance of the magnitude of these physiological activities, will lead to the degeneration of the eggs before or even after implantation."

Variability of the Cycle

Other phases of the cycle are less predictable. The whole cycle, in both human and rhesus, may be as short as 15 days, or prolonged to an indefinite extent, depending on when one chooses to stop speaking of a cycle and begins to call it amenorrhoea. The standard 28-day cycle length is only a statistical mode, and in healthy regular women recurrence of the flow will vary by two or three days over or under this length more often than not. Rhesus monkeys as we know them in captivity are somewhat less regular. Within the cycle it has been something of a surprise to find that the second phase—that is, the span from ovulation to the onset of the subsequent menstruation—is as irregular as the first phase. Inasmuch as we do not clearly understand the pituitary-ovarian activities which control the preparatory growth and the subsequent cyclic maturation of follicles, it has been easy to accept, without much thought, the fact of variation in the length of the follicular phase of the cycle. Menstruation is, however, a direct sequel of progesterone withdrawal, and might be expected to depend upon degeneration of the corpus luteum at a rather precisely determined time after ovulation. When, however, Hartman compared a large series of rhesus cycles in which ovulation had been timed by palpation, it was clear that the post-ovulatory phase varied in length by about two weeks—that is, from 7 to 22 days. Siegler and Siegler (1951), compiling human cycles in which ovulation was dated by basal temperature, found a similar variation. G. W. Bartelmez discussed this whole question of the variability of the cycle in his presidential address before the American Association of Anatomists in 1950, which it is hoped will be published shortly. Analysing 126 human cycles from a series in which Farris determined ovulation by his urinary rat test, Bartelmez found the post-ovulatory interval to range from 8 to 20 days.

Evidently there are significant variations in the rate of biological and physiological retrogression of the corpus luteum, causing a variation in the time of effective progesterone withdrawal, or in the rate at which the endometrium responds to the hormonal deprivation by menstrual breakdown. Probably both these processes are variable. Bartelmez reminds us of Markee's observations on menstruation in bits of endometrium grafted in the anterior chamber of the eye (in monkeys) in which the premenstrual ischaemic phase varied from one to six days. In his own descriptive account of menstruation in the monkey he showed that great differences exist in the degree of degeneration of the endometrium on the same day of the menstrual flow. These variations in rate of the breakdown processes may in some cases result from different degrees of upbuilding in the antecedent premenstrual phase. At any rate we are dealing with a biological activity of extremely complex nature; it is no wonder that it does not run like a machine.

In our eagerness to discern and analyse the events of the human cycle we have naturally focused attention upon the modal pattern. It is, of course, useful to have a working diagram, and a picture of the standard condition of the follicle, corpus luteum, and endometrium on each successive day. Such theoretical norms are necessary as a basis for practical dating of embryological and pathological specimens; but as Bartelmez has emphasized, they have at best only statistical validity, and any statement about

the cyclic date of a human specimen must include, explicitly or tacitly, a plus or minus quantity of the order of one to two or more days according to the phase of the cycle. This limitation on the precision of our data becomes important if cyclic dates are to be used for artificial insemination or for contraception as in the Knaus-Ogino "safe period" method, or in the laboratory for estimating the age of an early embryo. Clearer knowledge, moreover, of the reasons for variation in the cycle-length of healthy women will help us to understand better the causes of menstrual pathology.

Anovulatory Cycles

As we have seen, the study of the human cycle and that of the other primates has proceeded simultaneously, each helping to explain the other. Generally speaking, the main outlines have been gained from human subjects, whereas much of the precise histology has been learned in the laboratory from the rhesus monkey, and the endocrinology from rhesus and baboon. There is one major feature of the primate cycle about which the rhesus monkey gave us the first clue. I refer to the occurrence of menstrual cycles without ovulation. The pioneer students of reproductive cycles of monkeys, Heape and Van Herwerden, were much at a loss to understand their frequent failure to find recent corpora lutea in the ovaries they obtained from animals known to be menstruating.

When I began work on rhesus monkeys, with the lessons of modern zoo practice to aid me and a plan of research based on the knowledge of the human cycle recently acquired by the German gynaecologists, my first two monkeys placed the problem before me in clear terms. The two animals had been kept together in the same corral; they had menstruated regularly for several months, and their cycles could not be distinguished from one another by any external sign. Each was killed at the middle of an intermenstrual interval in the hope of finding a ripe or recently ruptured follicle. In one this hope was fulfilled and I had the satisfaction (as mentioned above) of recovering the ovum from the Fallopian tube. The ovaries of the other monkey were quite blank so far as ovulation was concerned; they contained no sign of a maturing follicle or of a corpus luteum, not even one from a previous cycle. Menstruation had evidently been going on for two to three months, at least, without ovulation.

Study of still other animals gave the key to the puzzle. Contrary to the previous conjectures that ovulation has no constant relation to the menstrual cycle, the fact is that when it occurs it takes its place in the regular sequence of events; but it may not occur at all, and in that case we have an anovulatory cycle, without a corpus luteum and thus without a progestational phase of the endometrium. In the monkeys I have studied, which have mostly been relatively young, anovulatory cycles are almost as frequent as the more complete ovulatory kind. In 1927 I called this finding to the attention of the medical profession in a brief article in the *Journal of the American Medical Association* in which a few human cases were also cited. To prove anovulatory menstruation in women requires the same sort of evidence as in monkeys—namely, examination of both entire ovaries of an individual with a history of regular menstruation and known dates of the cycles just previous to operation or necropsy. Such specimens are rare. Citing only one from personal observation and three on the authority of competent nineteenth-century physicians, I made bold to suggest that anovulatory menstruation occurs in women as well as monkeys. This idea drew heavy fire from Germany and Britain, but other American workers (Hartman, Edgar Allen, Bartelmez, Markee, Hisaw) who had begun to study rhesus monkeys agreed with me, and before long the gynaecologists accepted anovulatory menstruation as a not infrequent occurrence.

In the rhesus monkey the usual history of the anovulatory cycle is simply that a follicle does not mature at the usual time. The hormonal mechanism by which the pituitary gland cyclically stimulates the ovary evidently does not go

far enough to bring about ripening of a follicle. Palpation of the ovaries reveals no cyclical enlargement, and if we remove and section them at the end of such a cycle, on the first day of menstruation, they are found to contain nothing in the way of a large atretic follicle to show that ovulation had even been adumbrated.

What goes on in the human ovary in anovulatory cycles is not altogether clear. Study of excised ovaries from well-documented cases has not been done often enough, nor with sufficiently expert knowledge of cyclic histology, to yield much useful information. The evidence most generally accepted that ovulation has not occurred is the absence of signs of corpus luteum secretion in the latter half of the cycle. If a biopsy reveals that a progestational ("premenstrual") reaction has not occurred, or if pregnanediol, the excretory derivative of progesterone, does not appear in the urine, then presumably there has been no ovulation, or at least no formation of a corpus luteum in that cycle. A more complete picture of events in the cycle is obtainable by the study of vaginal smears as conducted by de Allende. Her day-to-day vaginal-cell counts reveal some cycles in which the pattern indicating ovulation does not appear at all; there is no evidence of a peak of oestrogen secretion at mid-interval or of progesterone in the latter half. In other cases the vaginal smears show a mid-interval rise of epithelial cornification, which means that a follicle is maturing, but the picture then reverts to the pre-ovulatory type, presumably because of regressive breakdown of the follicle. In still other cases a high cornification level continues throughout the rest of the cycle, suggesting the persistence of a mature or cystic follicle. In a few cases surgical exploration has afforded an opportunity to confirm such diagnoses from the vaginal smears.

Evidence of a more direct sort also indicates that some of the anovulatory cycles involve last-minute atresia of a maturing follicle. E. G. Farris, G. W. Corner, jun., and I studied the ovaries and endometria of 33 women in whom the Farris urinary rat test had been positive before operation. In six of these cases a large unruptured follicle was found in acute retrogression, usually with haemorrhagic walls. In such cases we may suppose that pituitary stimulation goes far enough to cause enlargement, but not rupture and luteinization of the follicle. The vaginal smear pattern would be of the type called by de Allende and Orfias "cyclic hypotrophic cornification curve."

It remains an endocrinological puzzle why menstrual bleeding comes on at all when no corpus luteum is formed, as I pointed out in the Addison Lecture for 1950 at Guy's Hospital, in which I ventured a rather nebulous conjectural explanation. Nor do we know the fundamental clinical causes of anovulatory cycles. Dr. Erle Henriksen, of Los Angeles, has permitted me to see a remarkable series of unpublished records of patients whom he has followed through many successive cycles, with frequent endometrial biopsies and other tests. These cases clearly show that anovulatory, or at least non-luteal, cycles often occur in ostensibly healthy women without demonstrable cause; but in other cases transitory illnesses and even emotional disturbances seem possibly related to the incomplete cycles.

It has been suggested that sterile cycles may also result from ovulation without subsequent luteinization of the ruptured follicle, and, contrariwise, by luteinization of a follicle that does not rupture. Clinical recognition of such variations of the cycle would be very difficult. Anatomical proof demands painstaking study of every available ovary, excised at operation, that is accompanied by a menstrual history.

Conclusion

Clearly there is much to learn about the events of the ovarian cycle, including those which do not eventuate. In this brief review, in which I have tried to summarize the very considerable progress that has been made towards understanding these complex events, I have aimed also at reminding the young gynaecologists and obstetri-

cians of the opportunities they will have to help solve the problems of ovarian function. The basic outline of the human cycle has been worked out, and it can be understood in relation to the general pattern of mammalian reproduction. Its time-schedule is fairly well known statistically. Much has been learned about the endocrine factors that control cyclic events. Because we have gone so far it is becoming possible to study some of the major variations and abnormalities of the cycle in individuals, with the hope of relieving the distress and suffering that so often attend them. More and more this investigation will have to be carried on in the consulting-room, the operating theatre, and the hospital laboratory, but it calls for workers who know the biology of the cycle.

This word to the clinicians is the first half of my peroration. Let me finish it in the spirit of Thomas Henry Huxley's broad curiosity about mankind's place in nature. Comparing the human cycle with that of other primates, we find that human ovarian functions operate through similar anatomical structures and follow the general primate pattern. In this respect our race is simply another simian species; and yet, passing upward through the primate line we find an increasing domination of nervous and mental processes in the control of reproductive behaviour. This trend reaches its height in mankind. Possessing a generalized animal body with a highly specialized brain, our species has grown into a realm beyond the merely animal in which we not only undergo the cycles and fluctuations of animal life but also seek to understand and to direct them; a realm where sex and reproduction are at their best bound up with reason, and a sense of beauty, and human affection.

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According to a report in the *New York Times* (August 14) all packages of chloramphenicol distributed in the United States must now bear a special warning label. The label will read: "Warning: blood dyscrasias may be associated with intermittent or prolonged use. It is essential that adequate blood studies be made." This ruling by the Food and Drug Administration, Washington, follows a nationwide survey of blood-disorder cases. Out of 410 cases reviewed by a committee of the National Research Council, 177 were found to have been associated with the use of chloramphenicol. About half of these cases were fatal. Death was attributed to failure of haemopoiesis in the bone marrow. The committee, headed by Dr. John Holmes Dingle, professor of preventive medicine at Western Reserve University, Cleveland, has recommended the Administration to promote further study of the toxic reactions to chloramphenicol.

THE END-RESULTS IN PRIMARY STERILITY

BY

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In the field of infertility so many diverse factors are involved that a sense of perspective is a prime necessity, for if one is particularly interested in any single factor it becomes easy to exaggerate its importance. From that the next step is to evaluate the result of correcting the particular factor, and indeed the literature contains many reports of excellent results obtained purely by tubal insufflation, or hysterosalpingography, or thyroid medication, or irradiation of the ovaries, or encouraging a clear cervical mucus, or even by having a long waiting-list. There are fewer reports of successful treatment of male infertility.

Consequently it is difficult on the basis of published reports to assess the value of any particular form of treatment, or even to be convinced that subsequent conceptions were in fact therapeutic successes and not due at least in part to the effects of chance and time.

The present investigation has aimed at a wide view of the problem. First, it was thought desirable to ascertain what percentage of all couples seen by the gynaecologist on account of primary sterility achieved a pregnancy; and, more particularly, in what proportion of these the medical treatment of either or both partners could reasonably be held to have effected the desired result. Further, the outcome of these pregnancies was inquired into to see whether it differed appreciably from that of the population in general, especially in regard to the abortion and foetal malformation rates.

Material

The material on which this investigation was based consisted of 700 consecutive traced cases seen by certain members of our departmental staff between 1934 and February, 1949. All the traced couples have been included, whether investigated and treated or not, and whatever the findings and treatment. The youngest woman in this series was 19 and the oldest 43. The longest any couple had been married before seeking specialist advice was 17 years. In this connexion it should be borne in mind that the fertility of the partners when first seen is no index to their fertility when first married. Sterility may be due to some factor or factors acquired after marriage. Because a man examined after 15 years of marriage has oligospermia, it does not follow that his fertility has always been below average.

Standard for Primary Sterility

The prerequisites for inclusion in the series were that the woman had never been pregnant prior to the first consultation, and that there had been the opportunity for normal married life for at least two years, during which time contraception had not been practised. Emphasis is laid on "opportunity," because infrequency of coitus, impotence, and failure of penetration are not unimportant causes of infertility.

The generally accepted standard of two years' married life before considering infertility a legitimate complaint probably errs on the cautious side. It may have originated with Matthews Duncan (1866), but in fact his figures showed the calculated percentage of women in various age groups delivered of their first living child within two years of marriage, the overall figure being 71.33%. Russell (1946)