separated fractions derived from tuberculin or tubercle vaccines affords some encouragement. It has been shown by Sapin, Doan, and Forkner that the lipid fractions of tuberculin lead, when injected, to proliferation of epithelioid cells, while Seibert has demonstrated that the protein fraction induces necrosis in a tuberculous animal and not in one free from that infection. Tuberculin and tubercle vaccines are powerful substances. It is certain that they can do harm. What I hope may emerge from our discussion is a clear conception of the conditions under which they can be helpful. I am still hopeful that a real specific treatment will eventually be discovered on bacteriological lines, and I think the biochemists, with the bacteriologists, may eventually provide the solution of this difficult but fascinating problem.

THE COMPARATIVE PHYSIOLOGY OF THE MENSTRUAL CYCLE *

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Research on reproduction chiefly owes its remarkably successful growth in the past fifteen years to the excellence of an organized method that is built on a basis of interlocked histological and experimental observation. By this means the oestrous cycles of many mammals have been elucidated, and various reproductive hormones have been discovered and isolated. Unfortunately for physiological knowledge, it is a method that is not readily applicable to human beings, and the difficulty of obtaining well-documented normal histological material of the human uterus and ovaries, together with the impossibility of conducting experimental research into the human menstrual cycle, has prevented agreement about many essential points that must necessarily be settled before profitable comparison between human and other mammalian reproductive mechanisms can be instituted. Actually, such comparison was being attempted more than thirty years ago, when the question of the homology of the menstrual cycle could not have been of more than academic interest. Many still treat it as a purely academic problem; theirs, however, is an unsound attitude, a reaction to years of seemingly sterile discussion. Today, with preparations like oestrin and "anterior lobe hormones" that are ready to be applied in clinical medicine, the question of the homology of the menstrual cycle is of distinct practical importance. The human placenta and human urine are the common sources of the supplies of reproductive hormones used in laboratory practice. The biological properties of the substances extracted from them are determined by experiment on lower mammals. The attempt to apply these substances in morbid human conditions should, as far as possible, be rational and non-experimental. To attain this ideal, full consideration must be given to the similarities and dissimilarities between the menstrual cycle and the oestrous cycles of lower mammals.

SEXUAL-SKIN ACTIVITY IN PRIMATES

In approaching this question of homology, it must be remembered that not only man but all the Old World primates that have been studied have a menstrual cycle, and that considerable advances in our knowledge of the menstrual cycle have been made through the study of apes and monkeys. This fact raises the question whether or not the cycles of all primates can be regarded as being

the same in type. The common characteristic of all is bleeding from the uterus approximately every four weeks. Although the differences between the cycle of one primate and that of another do not affect this phenomenon, they are nevertheless conspicuous. Thus, in some Old World primates the skin of the external genitalia—and also of neighbouring parts of the body—is specialized, and forms a highly sensitive area which, at regular times in the cycle, swells or becomes highly coloured, or does both. Other Old World primates, including man, do not exhibit such changes, and their only external physical manifestation of the cycle is the menstrual bleeding. These questions have been discussed at length elsewhere,^{29, 30} and it was concluded that the general plan of the cycle is the same in all the primate species that manifest activity of a "sexual skin." Menstruation normally occurs at fairly regular intervals of about thirty days. Immediately after its onset the skin around the external genitalia becomes red in colour and swells, reaching a maximum before the middle of the cycle. Shortly after the mid-point the activity of the sexual skin, as a rule, suddenly decreases, and the skin resumes its quiescent appearance, which continues until the onset of the next bleeding, when it again becomes active.

The main variation in this kind of cycle is in the actual character of the external changes. They are very pronounced in animals like baboons and chimpanzees, the swelling of the sexual skin in the former being sometimes as large as about one-eighth of the normal volume of the trunk of the animal. In others—for instance, some macaques—the changes are very slight, and such catarrhines can hardly be differentiated from the group which includes man, where there are apparently no external changes. Another factor which varies is the time after the mid-point of the cycle taken by the skin to resume its quiescent appearance. Although the initial change seems to be abrupt in all primates, the further absorption may be slow, as, for example, in rhesus monkeys, or very rapid, as in some baboons. Instead of these differences confusing the issue, however, they significantly add to our understanding of the menstrual cycle as a characteristic of Old World primates.

Thus, since the time relations of sexual-skin activity and menstrual bleeding are approximately the same throughout Old World primates, it may be inferred that the physiological mechanism of the skin is the same in all. Actually it has been shown that it is the oestrous hormone, oestrin, which activates the sexual skin in such widely different genera as *Macaca* (macaques),¹ *Papio* (baboons),²³ and *Cercocebus* (mangabeys).²⁷ The physiological evidence thus indicates that sexual-skin activity is an oestrous phenomenon, in the sense that vaginal cornification is in the mouse. The facts of behaviour point to the same conclusion. Observations recorded elsewhere³⁰ show that those subhuman primates which experience pronounced external cyclical changes are more sexually active in captivity than those that do not. They also show that sexual activity in normal conditions varies directly with the degree of activity of the sexual skin. For example, female baboons are more receptive during the period of swelling than at other times.

Catarrhine primates could therefore be arranged in a series showing all degrees of externally visible oestrous changes. The period of functioning of the oestrous hormone, so far as can be judged, is much the same in all, irrespective of the actual character of the sexual-skin changes. In the absence of conflicting data, it thus seems legitimate to infer that in catarrhine primates which do not show external changes in a sexual skin, the period of homologous oestrous hormone activity is also the same. Accordingly, although knowledge of normal changes occasioned by the oestrous hormone during the human

* Read in opening a discussion in the Section of Comparative Medicine at the Centenary Meeting of the British Medical Association, London, 1932.

menstrual cycle is lacking, comparative study of other types of catarrhine menstrual cycles suggests that, if there are any such changes, they occur mainly in the first two weeks following the onset of menstrual bleeding. This period can be called the follicular or oestrous phase of the menstrual cycle.

OVULATION

In the non-primate mammal the follicular phase of the oestrous cycle ends with ovulation. The corresponding phase of the menstrual cycle is no exception, for it is generally believed that ovulation occurs normally about two weeks before the onset of menstruation, at the time when the abrupt decrease in sexual-skin activity indicates that the phase is coming to an end. This belief, however, has recently been questioned by Evans and Swezy,^{6,7} who have attempted to prove "that primate ovulation occurs at all periods of the cycle." In view of its important implications and already far-reaching reverberations, their strong statement* of this radical view demands close examination. But before their main arguments are reviewed, it is advisable to consider briefly the cyclical endometrial changes that occur in mammals.

CYCLICAL CHANGES IN ENDOMETRIUM

Evans and Swezy's own remarks about endometrial changes provide an introduction to this topic. These authors consider the oestrous cycle (by which they apparently mean the vaginal cell cycle, as well as the cycle in behaviour) and the utero-ovarian cycle separately. They very briefly describe the latter cycle as consisting of "growth of the endometrium in the pre-ovulation stage, the period of maturity of the endometrium, and its regression in the later post-ovulatory stages. The changes proceed *pari passu* with the growth and rupture or degeneration of the ovarian follicles." Thus, the endometrium of the dog grows under the influence of the follicular hormone, oestrin, during the period of growth of ovarian follicles. When the follicles rupture and corpora lutea form, "there is further glandular growth but more especially glandular hypertrophy." On the other hand if, as may happen in the cat, the maturing follicles become atretic, the uterine mucosa that has grown up under the influence of oestrin regresses.

Their account is a very fair description of the biphasic oestrous cycle, a cycle in which ovulation sharply demarcates the first or follicular phase (in which the endometrium is growing under the influence of oestrin) from the second or luteal phase (in which the endometrium is being subjected to the action of luteal hormones). It does not sufficiently emphasize, however, the stage of endometrial degeneration which occurs, especially in the dog, at oestrus (that is, at ovulation) and which is distinct from the "regression in the later post-ovulatory (luteal) stages." Evans himself,⁵ however, appears to have confirmed this important finding of several earlier workers. Oestrous uterine degeneration is not an event confined to the dog. Its existence has been established in the rat, mouse, guinea-pig, and pig, and it is generally attributed to the removal of the influence of oestrin at the time of ovulation.⁴ It is a much more abrupt change than the slow "regression" which, according to Evans and Cole,⁵ ends the pseudo-pregnant period in the bitch—although Marshall and Halnan's¹⁸ descriptions suggest a somewhat abrupt end to this phase as well. The important point to recognize about a typical biphasic oestrous cycle is, therefore, that it consists of two phases of uterine growth separated by two phases of uterine degeneration.

It is in its apparent lack of phasic variation that the menstrual cycle, and particularly the human cycle, differs so conspicuously from the oestrous cycle. The generally accepted view of the cyclical changes in the human uterus may be summarized as follows: spontaneously occurring ovulation divides the cycle into pre-ovulation and post-

ovulation (follicular and luteal) phases: The endometrium, destroyed at menstruation, is regenerated in the first few days of the cycle, and the end of the pre-ovulation phase—the "interval"—is a resting period in which the mucosa is shallow and the glands are straight. The luteal growth phase of the endometrium begins when the corpus luteum is formed after ovulation, and ends at the next menstruation. During this luteal phase the endometrium increases in depth and its glands become sinuous and distended with secretion. It is now also believed that sometimes ovulation may not take place, and that menstruation then occurs from an interval endometrium at the expected period.

This brief description of the human cycle applies equally to the internal changes of the cycle of catarrhine monkeys. It should be noted that menstruation from an interval endometrium in the absence of ovulation has been found to occur commonly in *Entellus* langurs, rhesus monkeys, and common macaques, but that it has not been seen in baboons, in which spontaneous ovulation seems to take place regularly in each cycle.³¹ It is also important to recognize that in both the human and sub-human menstrual cycle the period of menstruation is the only time when the endometrium normally shows signs of degeneration. None occurs during the interval period, when ovulation takes place.

RELATION OF OVARIAN TO UTERINE CYCLE

Evans and Swezy base their argument that ovulation may occur at any time in the menstrual cycle chiefly on the fact of the existence of some correlation between the endometrial and ovarian phases, and they advance criteria for inferring the condition of the ovaries from that of the endometrium. In the light of these they examine the data about monkeys given by Corner and the data about man provided by Schroeder. They state that "the presence of active growth in the endometrium without evidences of secretion or enlargement of the cells or great complexity in the glands" is "indicative of the ovulation or pre-ovulation period," while "a regressing endometrium normally occurs only after an ovulation period has passed." These generalizations, however, are open to criticism. In the descriptions on which they are based the terms regression, degeneration, and secretion are used as more or less interchangeable. For example, the "secretion phase of the endometrium" is said to occur in the cycle of the unmated rat after ovulation (that is, late oestrus) and to consist in "the so-called 'vacuolar degeneration' (Long and Evans, 1922)." Allen,⁴ on the other hand—and here he confirms earlier observations which Evans himself made¹⁶—states that the secretory phase in the uterine cycle of the rat occurs in pro-oestrus. He writes that "extensive vacuolar degeneration and leucocytic invasion of the epithelium" occur during oestrus, the time of ovulation. This change seems to be true degeneration as the term is used in pathology, degeneration in which, as Allen points out, the basement membrane of the epithelium may be completely destroyed. Accordingly, there seems to be little justification for referring, as Evans and Swezy do, to this uterine change as secretion, in the same sense that they later use this term for the post-ovulation phase of the human endometrium—the stage in which the glands are numerous, complex, and distended with secretion.

A more serious criticism can be made against Evans and Swezy's criteria of ovulation. They do not apply to the rat, one of the types on whose endometrial changes they are said to be based. According to Allen, the pro-oestrous or pre-ovulation phase of uterine secretion in the rat "is unaccompanied by any evidence of growth of the surface epithelium or of the glands," whereas on the criteria advanced by Evans and Swezy there should be signs of cellular growth without any secretion during this pre-ovulation phase of the cycle. Since their criteria do not apply here, it is difficult to trust the conclusions that have been drawn by applying them to the descriptions given by Corner of the macaque uterus and by Schroeder of the human uterus. The fact that a "pre-ovulation" or "interval" endometrium has been observed at all times

* Since its publication, both Allen² and Hartman¹¹ in America have reviewed the evidence on which they based their own conclusions about the time of ovulation, while an account of Evans and Swezy's papers in the columns of the *British Medical Journal* resulted in a strong restatement by Shaw²⁵ of the generally accepted view that ovulation normally occurs about the middle of the cycle.

of the human and monkey menstrual cycle is evidence of no more than that the uteri concerned had not been subjected to the activity of the corpus luteum previous to their examination. The persistence of an interval endometrium throughout the cycle is what one expects to find in cycles in which ovulation does not occur. By itself it cannot be taken to suggest that ovulation may occur at any time. Evans and Swezy, however, claim further support—but very questionable support—for this view in the occurrence of desquamation (menstruation) from endometria in any stages of growth, maturity, or regression (Schroeder's data). This would be valid evidence for their view, provided that all the possible conditions of the non-pregnant endometrium were in a fixed temporal relation with one another, and if ovulation was associated with only one of them.

But the danger of deducing the condition of the ovaries from preconceived ideas of the corresponding picture of the uterus was clearly shown by the instance of the rat. The condition of the endometrium is at any moment determined both by its own sensitivity to the hormones to which it is subjected, and by their concentration in the blood stream. There are no data to show that these factors are constant for given stages of the cycle: our entire knowledge of the normal primate endometrial changes rests on qualitative differences. It is known that to some extent the condition of the uterine mucosa is always correlated with the ovarian cycle, and that there are three clearly recognized endometrial stages—disintegration, the follicular phase of repair and rest, and the luteal phase of progesterational proliferation. It is also known that these phases may be subdivided further, again qualitatively. But there are no data to show any specific relation between a given ovarian stage (for example, ovulation, or beginning of luteinization, or solidification of the corpus luteum) and a particular condition of the endometrium (for example, a definite height, a definite number of glands to a given area, a definite number of mitoses in an oil-immersion field). It is very unlikely that there is such exact correlation, and it is therefore somewhat unreasonable to suppose that menstruation may be associated with any phase of the ovaries just because it may occur when the endometrium is in a condition of growth (that is, in an interval phase), or when it is in a condition of secretion (that is, from a luteal endometrium). The most that may be inferred from such premisses is that in the former case no ruptured follicle is present in the ovaries, and that in the latter the ovaries contain a functioning corpus luteum.

TIME OF OVULATION

Evans and Swezy refer for support of their view that ovulation may occur at almost any point in the menstrual cycle to testimonial evidence that conception may follow intercourse at any time. As numerous workers have pointed out,¹⁹ such testimony is inherently unreliable, and particularly so is that of the German women of the war period to which Evans and Swezy refer. Moreover, evidence of the same kind detailed by Ogino²¹ is contradictory, and supports a view that the period of conception is only from the nineteenth to the twelfth days before menstruation (that is, ninth to sixteenth days of a twenty-eight days' cycle). The cases he describes are fewer than those mentioned in the German reports, but his investigation was more scientific.

There are only a few reliable ways of establishing the period of conception and the time of ovulation in relation to periods of menstrual bleeding; the main ones are (a) controlled matings of monkeys, (b) direct observation of the ovaries, and (c) observation of some readily measurable event that has been shown to be immediately related to some normal phase of the ovarian cycle.

Evidence of the first kind has been provided by Hartman.¹¹ Fifty-eight pregnancies have occurred in his colony of rhesus monkeys, conception in all cases taking place between the

ninth and eighteenth days of the cycle. Evidence of the second kind has been collected by many workers^{11, 20}, and it also goes to show that ovulation is confined to a small number of days in the middle of the cycle. Evidence of the third kind is also available. Knaus,¹⁷ having established the fact that pituitrin has no contractile effect on the rabbit uterus when corpora lutea are present in the ovaries, has shown that a corpus luteum is almost certainly present in the human ovaries in the second half of a normal twenty-eight-day cycle, since injections of pituitrin have no effect on the uterus during that period, although they cause uterine contractions in the two weeks following menstruation.

But there is a more obvious and a readier sign of ovulation in the primate menstrual cycle to which Evans and Swezy do not refer—namely, the subsidence of sexual-skin swelling. Man and the rhesus macaque, the two types on which students have concentrated almost all their attention in attempts to elucidate the menstrual cycle, are only two of about 300 recognized species of Old World primates. Man has no sexual skin, and in the rhesus macaque it is comparatively little developed. When notice is taken of some of the more available of the remaining catarrhine primates (for example, baboons, mangabeys, other macaques), the sexual-skin phenomenon is the most conspicuous event of the menstrual cycle—far more conspicuous and dramatic in its cyclical occurrence than menstruation itself. As was explained above, it is an oestrous phenomenon, which varies little in its time relations amongst the many genera and species that exhibit it. In the baboon (genus *Papio*) the sudden decrease of the swelling about the mid-point of the cycle has been shown to synchronize, apparently closely, with ovulation.²² The decrease in coloration which usually occurs in the rhesus monkey shortly after the middle of the cycle is also clearly correlated with the time of ovulation, determined by direct methods. There can be little doubt that the same relation applies in other species.

There is thus in the sexual-skin phenomenon a ready indication of the time of ovulation, which has yielded abundant evidence to support the conclusion, arrived at from many other lines of investigation, that ovulation both in man and in subhuman catarrhine primates normally occurs about the middle of the cycle.

TWO MAIN PROBLEMS FOR SOLUTION

In the interpretation of the menstrual cycle, two separate but overlapping problems can be distinguished. The first concerns the physiological events which determine menstruation, and the second the relation between the rhythmical phases of the menstrual cycle and those of the oestrous cycles of lower mammals.

PHYSIOLOGY OF MENSTRUATION

Menstruation has, at different times, been ascribed in turn to the action of each of the hormones that operate on the reproductive tract. What became known as the clinical view is that it is due to the cyclical cessation of action of the hormones of the corpus luteum. This theory has been generally rejected because it implies that the development and retrogression of a corpus luteum and the growth of a luteal or premenstrual endometrium are essential preliminaries to the destructive process, whereas in fact menstruation sometimes occurs without previous ovulation and the consequent formation of a corpus luteum and "premenstrual" endometrium.

A second theory of menstruation, associated with the name of Allen,¹ is focused on the effects of oestrin. It is well established that oestrin is mainly anabolic in function, and many workers hold that the degenerative uterine phase in the lower mammal at oestrus is due to the withdrawal of oestrin following rupture of the follicles.⁴ Allen's view is that menstruation, too, is an effect of the removal of the follicular hormone, and he suggests that

in the primate the stimulus of oestrin is not removed at ovulation, as it is in the lower mammal, but that it normally continues until the next menstruation a fortnight later.

There is enough evidence in the occasional persistence in some primate species of a certain amount of sexual-skin activity through the greater part of the cycle to support his belief in the continued activity of oestrin after ovulation, but he ascribes its continued secretion to the corpus luteum,³ a view which some workers²² regard as untenable.

The main grounds upon which this explanation of menstruation is based is the uterine bleeding which follows double ovariectomy or cessation of injection of oestrin into ovariectomized monkeys. Hartman's recent experiments¹² suggest, however, that this is not primarily an effect of the ovarian secretion, but of the secretions of the anterior lobe of the pituitary. He found that uterine bleeding did not follow the cessation of oestrin injections into a monkey whose pituitary gland had been removed. Hartman and his co-workers also discovered that administration of extracts of the anterior lobe to a monkey results in bleeding "whether the animal be normal, sick and amenorrhoeic, castrated or hypophysectomized, old or young." The bleeding thus produced is unaccompanied by growth or congestion of the uterus and ovaries, and it was therefore tentatively concluded that menstruation "is due to a hormone elaborated by the anterior lobe, separate and distinct from that of growth, follicle stimulating (Smith and Engle), luteinizing (Evans and Simpson), or thyroid activating (Smith; Crew and Wiesner)." Although these experiments, as Hartman hopes, help to raise the menstruation problem from the realm of theory, they are unfortunately an insufficient basis for this conclusion, and in a somewhat similar series of experiments another observer, Saiki,²⁴ did not obtain confirmatory results. For example, injection of hypophyseal extract into several spayed, immature rhesus monkeys failed to stimulate uterine bleeding, while one of the animals used in this experiment subsequently bled after the cessation of a course of injections of oestrin. It was also found that the bleeding which would normally follow injection of hypophyseal extract could be postponed by administering oestrin immediately after the injections of anterior lobe were stopped. As a result of his experiments Saiki concluded that it is unnecessary to postulate the existence of a separate anterior lobe hormone as the direct cause of menstruation, but that "bleeding is dependent upon the presence of the ovary, and the uterine changes follow the induction by the hypophyseal extract of some alteration in the ovary."

Hartman began his investigation of the pituitary-uterus relation impressed with "the inadequacy of the theory which sets up the absence of something as the causative factor" in menstruation, and as a result of his observations he concluded that "the cause of menstruation is an *active* one"—namely, the special hormone of the anterior lobe. Saiki's experiments, however, and indeed those also of Hartman and his co-workers on intact monkeys, clearly indicate that it is the withdrawal of the stimulus of the anterior lobe that results in uterine bleeding. Haemorrhage does not occur at the time the pituitary substance is administered, but follows after an interval of about a week.

Although in the light of these two series of experiments it is difficult to draw strong conclusions as to the nature of the physiological events which determine menstruation, the most reasonable point of view to adopt at present seems to be as follows. The anterior lobe of the pituitary controls the ovarian cycle and stimulates the production of ovarian hormones. Its effect is cyclically interrupted or decreased at intervals of somewhat less than four weeks. The ovarian secretions produce changes in the endometrium, and when their action is interrupted or decreased, subsequent to the withdrawal of the stimulus of the anterior lobe, the endometrium degenerates and menstruation ensues. Menstruation itself seems, therefore, to be immediately due, in cycles without ovulation, to the withdrawal of the stimulus of oestrin alone, and, in cycles with ovulation, to the withdrawal of both oestrin and luteal secretions. It is necessary to postulate that the withdrawal of luteal secretions is one of the factors

responsible for endometrial degeneration, because of the existence of such degeneration at the end of the luteal phase of obviously biphasic cycles—for example, the oestrous cycle of the dog. It is very unlikely that the latter degeneration is due to the withdrawal of oestrin, and unless it is due to some unknown factor it is probably an effect that follows the degeneration of the corpus luteum. Unfortunately this hypothesis cannot be readily tested experimentally, for up to now it has only been possible to induce luteal effects in the endometrium by previously sensitizing it with oestrin.^{14 15} Bleeding that may follow such procedure cannot logically be ascribed to the withdrawal of either hormone separately.

RELATION BETWEEN OESTROUS AND MENSTRUAL CYCLES

This inquiry into the physiological events which underlie menstruation has constantly touched on the problem of the relation between the rhythmical phases of the menstrual cycle and those of the oestrous cycle. Granted that there is some connexion between the two (and no one, in fact, doubts this), the relations that are possible seem to be as follows. The first is that the menstrual cycle is practically identical with the oestrous cycle in the distribution of its two phases. According to this view, which has been advanced by Hartman,⁹ the end of the pre-ovulation (follicular) phase is marked in the primate, as in the dog, by uterine bleeding, and, in fact, Hartman has recovered microscopic amounts of blood, which he believes to be uterine in origin, in vaginal smears from the rhesus monkey between the seventh and eighteenth days of the cycle. There is no proof, however, that this blood is uterine, while on the other hand different workers have shown that a few erythrocytes occur in vaginal smears of subhuman primates almost at any time in the cycle.^{24 26} There are two other serious objections to Hartman's hypothesis—the first that histological studies have failed to show endometrial degeneration in catarrhine primates during the interval phase, and the second that his view implies that follicular effects are confined entirely to the pre-ovulation phase of the cycle, whereas they are not.

A second possible relation is that the menstrual cycle represents only one of the two phases of the oestrous cycle.* Thus the "clinical" view of menstruation emphasizes only the luteal phase. As shown above, the fact that menstruation may occur without previous ovulation and the formation of a corpus luteum is strong evidence against this view. Even more striking evidence is the fact that a very pronounced follicular phase exists in primates with sexual skins. The view that the menstrual cycle consists only of the follicular phase is implied by the hypothesis that menstruation is equivalent to pro-oestrous degeneration, a view held by Heape.¹³ This explanation was generally rejected some twenty years ago, when the biphasic nature of the oestrous cycle was revealed, but recently it has also been disproved experimentally by Meyer and Saiki.¹⁹ Nevertheless it is possible to find some truth in this particular hypothesis, since cycles in which ovulation does not occur may be regarded, from the point of view of homology, as consisting only of a prolonged follicular phase, while the menstruation which ends them might be considered to represent pro-oestrous degeneration.

The third possible relation between the menstrual and oestrous cycles is that both consist of two phases, but in different combination. This view was originally put forward by Marshall,¹⁸ but his statement

* It may be noted that Wiesner²⁸ refers to the menstrual cycle as monophasic to signify that a period of destruction does not intervene between the pre- and post-ovulation phases of endometrial growth. Here, however, "one phase" is used in the sense that the endometrium is subjected either to the follicular hormone alone, or, to the luteal hormones alone.

of it implies that menstruation represents the breakdown of the pro-oestrous uterine growth which heralds the succeeding ovulation, combined with (in his own words "tele-scoped into") the breakdown of the pseudo-pregnant endometrial growth which followed the preceding ovulation. This, however, means that the follicular phase, or pro-oestrus, comes to an end at the very beginning of a menstrual cycle, and that an interval of at least ten days elapses between the end of the pro-oestrous destruction and the ovulation which follows. Actually the follicular phase, or pro-oestrus, continues at least throughout the earlier half of the menstrual cycle, as the changes in the sexual skin show.

In spite of the objections to Marshall's hypothesis, the view that the menstrual and oestrous cycles both consist of two phases, but in different combination, seems to my mind the most reasonable explanation of the menstrual cycle, and in the light of facts revealed in the past few years it is possible to state it in a way not open to the criticisms to which Marshall's interpretation is exposed. As I see it,²⁹ the main difference between the menstrual cycle of the primate and the oestrous cycle of the lower mammal lies in the distribution of their respective follicular phases.* In an animal like the bitch, the follicular phase ends with oestrous degeneration, which separates it from the ensuing luteal phase, and the endometrium of pseudo-pregnancy is built up, under the influence of the luteal hormones, from an endometrium that has degenerated at the time of ovulation. In the primate, on the other hand, though the main effects of the oestrous phase occur in the earlier half, they are prolonged over the entire cycle, and in cycles with ovulation, pseudo-pregnant growth is superimposed upon a persisting pro-oestrous endometrium maintained apparently by the follicular hormone. The menstruation which ends such cycles may be taken to represent both pro-oestrous and pseudo-pregnant degeneration.

As I have stated elsewhere,²⁹ if this interpretation is correct, the differences in sexual behaviour between primates and lower mammals largely reflect their different sexual physiological mechanisms. The mating or oestrous phase of the lower mammal is generally brief, whereas that of the primate is diffused over the entire cycle, coinciding with the continuous action of the follicular hormone, but varying in frequency according to the varying degrees of activity of that hormone. In their sexual behaviour, as in many other features, primates thus fail to exhibit an apparent specialization which characterizes all other orders of mammals.

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* Using the term to mean the period in which the follicular hormone (oestrin) functions.

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HEADACHE PRODUCED BY HISTAMINE AND ITS MECHANISM*

BY

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A factor that has always hindered the understanding of headache has been the difficulty of studying it under well-defined circumstances. It seemed to us that a step forward could be made if, by simple means, we could produce headache at will. From its use in other investigations we knew histamine to be suitable for the purpose, and the following is a brief preliminary account of observations made with this substance. We have worked as far as possible on normal subjects, and have always injected the histamine intravenously, thus ensuring the quantity entering the circulation in a given time.

The effects of histamine may be divided into those that are objective, largely vascular, and those that are subjective, of which headache is the most striking, and the only one which concerns us here; these two effects are not simultaneous, the objective changes preceding the subjective. Following an intravenous injection of 0.1 mg. histamine acid phosphate (the dose usually employed by us) nothing happens for an interval during which the substance is travelling to the systemic capillaries. At about the twentieth second a metallic taste is felt in the mouth, and simultaneously the face flushes and systolic and diastolic blood pressures begin to fall. If lumbar puncture has been performed, the cerebro-spinal fluid pressure is found at this time suddenly to rise. This rise in cerebro-spinal fluid pressure has been recently observed by Weiss, Lennox, and Robb,¹ who find it to be accompanied by cerebral vaso-dilatation; for after injecting histamine they observed flushing, bulging, and increased pulsation of a human brain exposed at operation. The changes in facial colour, in arterial blood pressure, and in cerebro-spinal fluid pressure progress for a further period of ten to twenty seconds, and then begin to pass away. The total duration of the facial flush is about three minutes, of the rise in lumbar pressure about one and a half minutes, and of the fall of arterial pressure about thirty seconds.

Headache begins about forty seconds after the onset of vaso-dilatation, when the facial flush is just beginning to fade, when arterial pressure is at its resting level or above, and when lumbar pressure is falling from its peak value. It reaches a maximum about half a minute after its onset, begins to lessen about a minute later, and finally disappears after it has been present for six to ten minutes. The headache is at first conspicuously throbbing in character, waxing and waning with the pulse beat; as time passes, it tends to become continuous, and is not

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