The Œstrous Cycle in the Common Ferret.

By

Francis H. A. Marshall, D.Sc.

With Plates 19—21.

"Œstrus vocatur hoc malum."—PLINY.

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INTRODUCTORY.

The investigations which form the subject of the present paper were commenced in the summer of 1901, and were carried on at the University of Edinburgh in connection with the Zoological Department. A preliminary account has already been published, being included in the memoir on 'The Œstrous Cycle and the Formation of the Corpus Luteum in the Sheep' (Marshall, 1903).

Through the courtesy of Professor Schäfer I was permitted to make use of the resources of the Physiological Department for keeping the ferrets used in the research. Both "polecat

ferrets" and white ferrets were employed, and were kept under constant observation.

The material for the histological part of the work was generally fixed and preserved in a 10 per cent. solution of formalin, and afterwards treated in the usual way for section cutting. Sometimes corrosive sublimate was used instead of formalin as a fixing agent. The stains ordinarily employed were a combination of hæmatoxylin and eosin.

I wish to record my obligations to Professor Ewart and Professor Schäfer for the encouragement and assistance which they have rendered me in furthering my researches. To Mr. Heape, also, I must express my indebtedness for valuable suggestions on a subject which he has made peculiarly his own. Lastly, I take this further opportunity of thanking Sir Thomas Gibson Carmichael, Bart., for his great generosity in providing an endowment.

The Œstrous Cycle.

The ferret is monœstrous, the female usually coming in season at the end of March or beginning of April. If permitted to become pregnant at this time a second sexual season may be entered upon in July, while occasionally ferrets have been known to breed three times within twelve months (Carnegie and other authorities, 1901).[1]

I do not know whether the female ferret ever experiences a second sexual season after failing to become pregnant during the first œstrus. It is frequently stated by fanciers that for ferrets to live healthily it is necessary for them to breed, and that "a doe ferret will sometimes die the first

[1] The above statements are based upon information given by ferret breeders (cf. Carnegie, etc., 1902). In my paper on the "Œstrous Cycle in the Sheep" (1903) I stated that the ferret was monœstrous and had a single sexual season annually. This conclusion, which is only sometimes correct, I had deduced from my own observations, having never had a ferret which experienced more than one œstrous cycle. As stated in the text, I have kept ferrets from October to the end of March, during which time they showed no signs of coming "on heat." A ferret fancier assures me that only very exceptionally has he known ferrets come in season between August and February.

time she is refused access to the buck" (Carnegie, etc., 1902). Several of my ferrets grew unhealthy and died during the sexual season, and while still "on heat," and I am disposed to believe that the mortality was partly due to their being refused copulation.

The period of œstrus in the absence of the male I have found to be extremely prolonged. In one individual it extended for six weeks, at the end of which time the animal was killed, the uterus being found to be in a condition of advanced recuperation. In another ferret, however, in which œstrus was observed in the beginning of June (at the time when it was procured), the period of "heat" was completely over at the end of the first week of July, coition not having been permitted. Five bitch ferrets which I obtained in the month of October lived perfectly healthily during an anœstrous period which extended until the close of the following March, when they began to show signs of coming "on heat," and were subsequently killed during the sexual season.

It appears then, that the ferret, to some extent, showed a transition between the monœstrous and polyœstrous condition, since in those individuals which experience two breeding seasons these are restricted to the spring and summer; so that it must be a matter of some doubt whether the time between the two "heat" periods should be correctly described as a diœstrous or an anœstrous interval. But, as already indicated, this interval is, as a matter of fact, generally, or perhaps always, occupied partly by gestation.

A number of interesting observations bearing on this subject have been made by Mr. A. H. Cocks, who has kept several members of the family Mustelidæ in activity. A female otter is described (Cocks, 1881) as coming in season nearly every month in the absence of the male. Upon a male being introduced, copulation was observed on July 17th, and a second time on August 12th, or nearly a month later. Young were born on October 12th, so that pregnancy lasted apparently for sixty-one days. From these observations it may be inferred that the female otter is polyœstrous in the

absence of the male, the duration of the diœstrous cycle being about a month, there being also a longer anœstrous period.

Bell (1874) describes the otter as having young in March or April, thus indicating that the wild otter has a single sexual season about the beginning of the year. The same author states that the progeny of the stoat are produced in April or May, while the polecat, of which the ferret is a domesticated variety, is said to give birth to young in May or June. These animals, therefore, are probably monœstrous, or perhaps diœstrous, while the weasel may perhaps be inferred to be polyœstrous from Bell's account (1874).

With the pine-marten, in captivity, it appears from Cocks' description (1900) that the œstrous period may extend to about a fortnight. A female was noticed to deposit here and there in her cage little mouthfuls of straw, an indication of her being in season, this habit having been previously observed in the case of the otter. A male was admitted on January 5th, shut off on the 16th, readmitted on the 17th, and finally separated on the 18th. Copulation is supposed to have occurred probably on the 8th, 10th, and 13th, and possibly also at other times, but was never actually observed. Young were produced on April 22nd. Cocks states that it is hazardous to allow the male and female to run together at other times than the œstrous period, as it is apt to result in the death of the female.

The badger is probably monœstrous, with an annual sexual season, its period of gestation being between four and five months (Meade-Waldo, 1894). (See postscript at end of paper.)

I made no observations on the length of the ferret's gestation, but this period is generally stated to be about six weeks, or approximately the same as that observed for the polecat (Harting, 1891; Cocks, 1891).

External Evidence of the Pro-œstrum and Œstrus.—The pro-œstrum with the female ferret appears to extend for about three weeks, and is characterised by a marked swelling of the vulva and a sanguineo-mucous flow. With

two or three individuals I did not observe any external bleeding, but it may have occurred and escaped my notice, since it was sometimes impracticable to make regular observations upon the animals during their prolonged sexual season. But bleeding into the uterine cavity, as I shall presently show, regularly occurs at the pro-œstrum, and is accompanied by a greater or less removal of uterine mucosa. I am inclined to think, however, that the discharge so formed is usually disposed of very gradually.

During the pro-œstrum, as at all other times during the cycle excepting at the œstrous period, the female will not permit copulation.

The period of œstrus can be recognised by the behaviour of the female ferret towards the male. The vulva remains enlarged, and a slight flow of mucus may continue to be discharged at the external genital aperture. As before remarked, the œstrus may last for several weeks, and is associated throughout with the swelling of the vulva. This extension, in the absence of pregnancy, of the period of desire, is perhaps comparable to what occurs in the case of bears in captivity, for with these animals in the Zoological Society's Gardens œstrus is said to last continuously for two or three months. (Heape, 1900.)

The female ferret, as already described, is monœstrous, coming in season about the end of March, but presents a transition to the polyœstrous condition in sometimes having a second (and occasionally a third) œstrous cycle in the summer months. In showing this tendency towards a concentration of sexual seasons the ferret may be regarded as standing midway between such animals as the dog or cat which are monœstrous, with, as a rule, two fairly regularly recurring œstrous cycles, and the otter, which, in captivity at any rate, is polyœstrous, and has a recurrent diœstrous cycle of a month's duration. (Cocks, 1881.)

So far as I am aware there is no periodicity of the sexual season with the male ferret, which is said to be capable of copulation at any time of the year.

Ovulation.

So far as my observations go, ovulation in the case of the ferret probably takes place at the beginning of the period of œstrus, but only as a result of coition. If the female is not allowed to copulate the mature follicles and contained ova appear to undergo atresia, notwithstanding the continuance of the œstrus. As a consequence the female fails to become pregnant if warded too late in the season. Thus the persistence of the œstrus, which may continue far into the recuperative period of the uterus, or even beyond it, is associated with degenerate follicles in the ovary. These facts may perhaps afford an explanation of the observations made by Robinson (1893), who found that, with the ferrets employed in his investigation, coition very frequently did not result in pregnancy, although the animals might have copulated more than once during œstrus.

The extension of the period of œstrus under conditions such as to preclude the possibility of the occurrence of pregnancy can only be regarded as one of those "disharmonies" in the apparatus of reproduction upon the existence of which in the animal and human organisation Metchnikoff in his recent work (1903) has laid so much stress.

A bitch ferret which I artificially inseminated failed to become pregnant, owing probably to the presence of the spermatozoa in the uterus without the additional stimulus of coition failing to induce ovulation; but it may have been in this case also that the mature Graafian follicles had begun to degenerate, and that the season for ovulation had passed by.

In failing to ovulate during œstrus except as a result of coition the ferret resembles the rabbit in some cases at any rate (Heape, 1897), and the sheep more exceptionally (Marshall, 1903). The majority of the mammalia in which the subject has been investigated have been found to ovulate spontaneously when "on heat."

Fig. 9 represents a section through an atretic follicle from a ferret in which œstrus had lasted for at least three weeks,

and perhaps longer. The animal had copulated on the day on which it was killed, but not previously during that œstrus. The ovum is seen to be much shrunken and obviously degenerate, while it is no longer surrounded by a discus proligerus. The membrana granulosa has almost completely disappeared, but a few cells in an advanced state of degeneration remain scattered in the cavity. There is the beginning of a loose ingrowth of connective tissue, but this, at the stage under consideration, is very slight. The connective-tissue wall of the follicle presents the appearance of being composed of very irregularly arranged strands, the distinction between theca externa and theca interna having become obliterated, while there is no distinct line of separation from the outlying ovarian stroma.

The Formation of the Corpus Luteum.—I made no attempt to obtain a series of stages illustrating the development of the corpus luteum in the ferret. Such few examples as I have examined show the usual ingrowth among the lutein cells of connective tissue from the follicle's wall; and, although, taken by themselves, they do not prove that the lutein cells are derived from the membrana granulosa, they are, in a general way, confirmatory of the description given elsewhere of the origin of the corpus luteum in the mouse, the rabbit, and the sheep, there being distinct evidence of the interepithelial nature of the ingrowth. I have also lately obtained sections through a young corpus luteum of a cat which, at the time of killing, was "on heat," or had been very shortly before; and these sections show the same point.

Since the publication of my account a paper by Cohn (1903) describing an experimental investigation on the mode of formation of the corpus luteum in the rabbit has appeared, and the result of this investigation has been to further confirm the view that the lutein cells are formed from the follicular epithelium. Cohn obtained a series of stages, the animals being killed at stated intervals after coition.

A similar conclusion has been arrived at by Sandes, who describes the process of formation of the corpus luteum of

Dasyurus in a paper read before the Linnean Society of New South Wales and abstracted in 'Nature' (1903). This author states further that the corpus luteum atreticum is formed in the same way as the corpus luteum verum, a result which, so far as I am aware, differs from those of all other investigators. (See postscript at end of paper.)

Papers bearing on this subject have also lately appeared by Bühler (1902) and Wallace (1903), who describe the changes undergone by newly-discharged follicles in various fishes. Bühler's descriptions, which refer to Cyclostomes and to certain Teleosteans, indicate that there is nothing of the nature of a corpus luteum formed in the cases investigated, while Wallace shows that with the Teleostean Zoarces and the Elasmobranch Spinax there is a very distinct hypertrophy of the follicular epithelium after rupture, thus confirming Giacomini's account (1896) of the recently discharged follicles of certain Elasmobranchs.

Note on the Anatomy of the Internal Genital Organs.

The uterus of the ferret is typically bicornuate, each of the uterine horns passing forward into a slender Fallopian tube, which is very much coiled at its anterior end, passing several times round one side of the ovary. The mouth of the Fallopian tube encloses the ovary, so that the ova on being discharged pass into a sac, and consequently are not shed into the body-cavity. Fig. 8, Pl. 20, represents a transverse section through the ovary, and shows its attachment to the wall of the body-cavity, as well as the sac into which the eggs are shed and the coiled Fallopian tube. The latter appears no less than six times in the section.

The Histology of the Uterus during the Œstrous Cycle.

The changes through which the non-pregnant uterus of the ferret passes during the œstrous cycle may be conveniently arranged according to the same method of grouping as that

employed in describing the similar phenomena occurring in the monkey (Heape, 1894) and the sheep (Marshall, 1903), as follows:

1. Period of rest.
2. Period of growth.
3. Period of degeneration.
4. Period of recuperation.

The changes taking place during each of these periods occur almost simultaneously throughout the whole uterus. Period 1 represents the anœstrum, while the pro-œstrum occurs during Periods 2 and 3. Œstrus, or the period of desire, commences at the close of the period of degeneration, and, as already mentioned, may extend until the end of the recuperation stage, or perhaps even beyond it. Consequently there may be no metœstrum with the ferret, since the period during which copulation can occur is liable to persist until the uterus has reached the resting stage.

1. Period of Rest.—The stroma, of which the greater part of the uterus is formed, is bounded internally by an epithelium consisting of a single row of cubical cells. There is no very clear line of demarcation between the protoplasm of the epithelial cells and the protoplasm of the stroma, neither are there distinct boundaries between the individual cells of the stroma. The latter tissue is fairly uniform in character throughout both the body of the uterus and the two cornua. It contains numerous glands, bounded by epithelia similar to that lining the cavity. Blood-vessels of small size are also present, but are not nearly so abundant as in the succeeding growth stage. Some of these are shown in the figure (Pl. 19, fig. 1), where the general nature of the uterine stroma during the resting stage is indicated.

In comparison with the other stages of the cycle, the uterus at this period may be described as being negatively characterised.

The general shape of the uterine cavity, as it appears in transverse section, is shown in fig. 5 (Pl. 20), which, however, represents a section through an early stage of the growth

period. The same shape and the same general relations between the various layers of tissue are maintained both for the two horns and for the body of the uterus, transverse sections of the latter having a diameter only slightly longer than that of sections cut through one of the horns.

2. Period of Growth.—The beginning of the pro-œstrum is marked by the growth of the uterine stroma, which goes on until the cavity is reduced to about half its normal size. The growth takes place through multiplication of the stroma nuclei, the increase in number occurring for the most part regularly throughout the whole tissue, and not being confined to any particular part. As a result of this process the size of the uterus, as indicated by the length of the diameter of a transverse section through the body or one of the horns, is slightly enlarged, the increased thickness of the walls being not entirely compensated for by the reduction in the size of the cavity.

The multiplication of the stroma nuclei occurs, apparently, by direct division, no mitoses being visible. This appearance is scarcely due to the method of fixation, since evidence of mitotic division can be detected among the cells of the epithelium.

The first indications of growth are followed by an increase in the size of the blood-vessels. At a slightly later stage these also multiply in number, apparently by division of one vessel into two. The increase of the vessels, like that of the nuclei, occurs fairly equally throughout the stroma. The blood-vessels in the surrounding muscular tissue also tend to become enlarged and congested.

Before the close of this period the blood-vessels of the stroma become still further enlarged and packed with corpuscles, while their walls appear stretched, as if preparatory to the breaking-down process which characterises the commencement of the next period.

The epithelium lining the cavity undergoes no material change, though cell-division is perhaps somewhat more frequent. The same may be said of the epithelium of the

glands, which at the beginning of this period undergo a marked swelling, accompanied by greater secretory activity.

3. Period of Degeneration.—Fig. 2 (Pl. 19) represents a portion of a transverse section through the uterus, showing the commencement of the breaking-down process which characterises the period of degeneration. Many of the blood-vessels have their walls still intact, but these are for the most part much congested. Others have apparently just given way, and red corpuscles are already scattered in considerable quantities in the mucosa. Leucocytes are also seen in the tissue outside the vessels, and these probably were extravasated at the same time as the red corpuscles.

The breaking-down process, so far as I have observed, occurs throughout practically the whole of the stoma, and is not confined to the more superficial portion, as in the case of the pro-œstrum of the sheep. The walls of the vessels in the muscular layers, however, do not give way, neither is there any evidence elsewhere of a breaking-down of vessels.

The single layer of lining epithelium during the earlier stages of this period undergoes no change. Subsequently, when nearly all the vessels in the underlying stroma have ruptured, and corpuscles are lying free in most parts of the tissue, indications of degeneration are seen both in the epithelial cells (including those of the glands) and also in the cells of the stroma.

The degeneration of some of the stroma nuclei is accompanied by a tendency on the part of the blood-corpuscles to become aggregated in the more superficial part of the mucosa, where the tissue has become looser, the nuclei being much less densely packed. The process results in the denudation of some portion of the mucosa, and the pouring of little streams of corpuscles into the cavity of the uterus. Meanwhile the glands in the deeper part of the mucosa show an increased secretory activity.

Fig. 6 (Pl. 20) represents a transverse section through one horn of a uterus in which denudation has recently occurred. Most of the blood-corpuscles have already been

got rid of, or at any rate have passed into the lower part of the uterine cavity. Pieces of mucosa, accompanied by corpuscles and mucus, can, however, still be seen lying free in the cavity. A portion of the same section, more highly magnified, is shown in fig. 11 (Pl. 21), where isolated epithelial cells, in a more or less degenerate condition, can be detected among the denuded fragments. In the mucosa forming the uterine wall it is seen that considerable tracts of tissue have been stripped of the lining epithelium, while in some places portions of the underlying stroma also appear to have been removed. Extravasated corpuscles are still seen in the mucosa, but not in any considerable quantity. In some parts of the section there are already indications of recuperation having set in.

I am disposed to believe that there is a not inconsiderable amount of variation in the severity of the pro-œstrous phenomena of the ferret, and that in the case above described the denudation of tissue was exceptional. This was the only example of a ferret killed during the period of degeneration which showed indications of a definite removal of stroma, although a comparison between the thickness of the uterine wall (and, conversely, the size of the uterine cavity) in animals at the beginning of the recuperation stage and during the period of rest also points to the conclusion that destruction is not always confined to the epithelium. In the case of the sheep I found evidence that the severity of the process tended to diminish with each successive diœstrous cycle in the breeding season, so that it is not unlikely that the ferret is subject to some similar variation, depending possibly upon age or upon physical condition.

The chief characteristics of the period of degeneration in the ferret occur in a regular succession almost simultaneously throughout the whole of the uterus, so that this period is capable of subdivision into two or more stages, the first of which is marked by the rupture of the vessels and the extravasation of blood in the stroma. Then further degeneration sets in, and the corpuscles tend to become aggregated

in the proximity of the surface epithelium; and finally, bleeding into the cavity takes place. The whole process, therefore, is very closely comparable to what occurs with monkeys during the degeneration period of menstruation (Heape, 1894, 1897). There is, however, no pro-œstrous clot formed in the ferret's uterus, the discharge seeming to be disposed of very gradually.

4. Period of recuperation.—Fig. 7 (Pl. 20) is a drawing of a part of transverse section under a low magnification, showing the relatively large cavity and correspondingly slight thickness of the mucosa during an early stage of the recuperation period. The epithelium is almost entirely re-formed, but is somewhat attenuated, the individual cells being less columnar in shape than they are normally. Another section through one of the horns of the same uterus is represented in fig. 3 (Pl. 19), which is more highly magnified. This shows that the nuclei of the epithelium are more irregularly arranged than during the other stages of the cycle, while the line of demarcation between epithelium and stroma is even less evident.

The new epithelium is formed, for the most part at any rate, either from that covering certain particular tracts which escaped denudation, or from the epithelium of the glands. I am not quite certain, however, whether the whole of the new epithelium arises in this way, for the absence of a separating line between this layer and the underlying stroma, and the irregular arrangement of the nuclei, upon which I have commented above, suggest that parts of the epithelium may be re-formed from the tissue of the stroma. This is the view adopted by Mr. Heape (1894, 1897) regarding the manner of formation of the new epithelium with monkeys during the recuperative stage of menstruation.

During the earlier stages of recuperation a variable and frequently a large number of red corpuscles, accompanied by wandering cells, remain scattered free in the stroma. These are very numerous in the sections represented in fig. 3 (Pl. 19) and fig. 10 (Pl. 21). At a subsequent stage of re-

cuperation these extravasated corpuscles are no longer seen in any quantity, while numerous small blood-vessels appear to have been formed. In the case of the sheep, it has been shown that the blood which is extravasated during the pro-œstrum, and which is not discharged into the cavity of the uterus, forms pigment in the mucosa. On the other hand, I have never found any trace of pigment formation in the uterine mucosa of the ferret, while sections of this tissue from animals with which recuperation had lately commenced support the view that the corpuscles are gathered up afresh into the circulatory system by becoming enclosed within the walls of newly formed blood-vessels. It is a matter of difficulty in a case of this sort to make quite sure of the correctness of one's interpretation of a series of sections, but unless this explanation, which is in agreement with Mr. Heape's description of what occurs with monkeys, is adopted, I am unable to account for the disappearance of the extravasated corpuscles during the later stages of recuperation.

At a subsequent stage of this period the stroma tissue tends to become more and more dense, and also to increase in thickness, until the mucosa once more acquires its normal condition. This process is effected by the multiplication of the stroma nuclei.

Conclusions.—It is evident, from the foregoing account, that the pro-œstrous process in the ferret is homologous with that of the bitch (Retterer, 1892), the sheep (Marshall, 1902), and the monkey (Heape, 1894, 1897). In severity it is intermediate between the pro-œstrum of the sheep and that of the monkey, while it differs from the same process in the bitch in the somewhat greater denudation of mucosa, at any rate in particular individuals. The "heat" period with the ferret, however, is of considerably longer duration than is the case with the other animals mentioned. Another point of difference from the sheep exists in the absence of pigment formation during the ferret's metœstrum.

The study of the œstrous cycle in the ferret shows very clearly the erroneousness of the view that the degenerative

stage of the pro-œstrum occurs as a consequence of the absence of a fertilised ovum, for which the uterus was preparing, in the preceding growth stage. For, since copulation and ovulation can only take place during œstrus, the uterine denudation occurs prior to the period when fertilisation becomes possible. This is a point to which I have already alluded.

The view that the pro-œstrum is an act of preparation, followed, where this happens to be useless, by a destruction of the preparation, being untenable, I am led to the conclusion that this process is the result of a "wave of disturbance," as Mr. Heape expresses it, which ushers in the period of desire, and is of the nature of a consequence rather than a purpose. On the other hand it appears to me not altogether improbable that the renewal of the mucosa tissue which is consequent upon the degenerative changes may, in some way, help to prepare the uterus for the attachment of the ovum. This view seems to have been entertained by Milnes Marshall (1893).

There is evidence, however, that the pro-œstrous discharge may become not only functionless but even injurious, as in the more severe cases of menstruation in women. This is in accord with the view of Metchnikoff (1903) that the condition of the menstrual flow in the human subject at the present time is essentially a "disharmony" of organisation, and is probably the result of modifications acquired recently in the history of the race. Metchnikoff refers also to the existence of similar disharmonies in the reproductive apparatus of animals, and especially of animals kept in captivity, and probably the severity and long duration of the ferret's "heat" period would be regarded by this author as a further example of the occurrence of such disharmonies.

Summary and Concluding Remarks.

The female ferret is monœstrous, and may have one, two, or three sexual seasons within a year; but although the

œstrous cycle may recur the "heat" periods are usually restricted to the spring and summer months, the autumn and winter being occupied by a prolonged anœstrum. In showing this tendency towards a concentration of sexual seasons the ferret approaches the polyœstrous condition, being in fact, in this respect, intermediate between the dog or cat, which have two, or occasionally three, fairly regularly recurrent œstrous cycles, and the otter, which, in captivity at any rate, has been shown to be polyœstrous with a series of diœstrous cycles, each of a month's duration, occasionally interrupted by a longer anœstrous period.

The pro-œstrum with the ferret may extend for three weeks, while the œstrus, in the absence of the male, may last for another six weeks, or even longer.

The changes which occur in the non-pregnant uterus during the œstrous cycle may be divided according to four periods as follows:

(1) Period of rest.
(2) Period of growth.
(3) Period of degeneration.
(4) Period of recuperation.

The first period corresponds to the anœstrum during which the uterus is in the normal state. This is followed by the growth period during which the uterine cavity becomes reduced to about half its usual size, while the mucosa is correspondingly thickened. Meanwhile the blood-vessels become much congested and subsequently break down, thus marking the commencement of the period of degeneration. The blood-corpuscles become scattered in considerable numbers in the stroma, and eventually in the uterine cavity also, owing to the removal in many places of the lining epithelium. In one specimen I found evidence also of a pro-œstrous denudation of the underlying stroma tissue. Œstrus probably commences towards the close of the period of degeneration, and continues throughout the recuperation stage, or perhaps even beyond it. During the latter period the uterus recovers its normal condition, though the cavity is

at first larger in size than at any other time throughout the cycle.

The character of the changes described affords further proof of the homology between the menstrual cycle of the primates and the œstrous cycle of the lower mammalia, the processes which occur in the uterus of the ferret during the cycle being essentially similar to those which take place in the monkey (Heape, 1894, 1897), the bitch (Retterer, 1892), and the sheep (Marshall, 1903).

Ovulation occurs probably at the commencement of the œstrous period, but only as a result of sexual intercourse. An attempt to induce pregnancy by artificial insemination was a failure, the mere presence of the sperms in the uterus being apparently insufficient to produce the stimulus necessary for ovulation. But while ovulation does not appear to take place in the absence of coition, the œstrus continues for a considerable period after that the time for ovulation has passed by, so that the persistence of the œstrus is associated with the presence of atretic follicles in the ovary.

Since coition and ovulation take place after the pro-œstrum, it is clear that the degeneration stages of the pro-œstrum cannot be of the nature of an undoing, in consequence of the absence of a fertilised ovum, of preparations made during the earlier growth stages.

Fraenkel, however, in a recent paper (1903) adopts the view that the phenomena of menstruation, which has been shown to be homologous with the pro-œstrum, are brought about by the secretory activity of the corpus luteum.[1] This hypothesis, in the light of the facts stated above, appears to

[1] According to Fraenkel the corpus luteum is the organ of internal secretion in the ovary, and controls the nutrition of the uterus, not only during pregnancy, but throughout the whole cycle, there being, properly speaking, but one corpus luteum, which renews itself in slightly different positions, in the case of the human subject at monthly intervals. According to this somewhat extended view of the nature of the corpus luteum, it would seem that the secretions of that organ must be regarded as varying from time to time both in character and quantity, to account for the changes which take place during the uterine cycle.

me to be untenable, while the absence in the ferret's ovaries of corpora lutea (or, at any rate, of newly-formed corpora lutea[1]) during the period of desire, an absence resulting from failure to ovulate, precludes the possibility that œstrus in some way results from an internal secretion of the corpus luteum.

It is important to note in this connection that Mr. Heape found (1897) that not one out of forty-two menstruating females of Semnopithecus entellus had a recently-discharged follicle in either ovary, while one only among seventeen individuals of Macacus rhesus, which were menstruating, had a newly-discharged follicle in one ovary. In this case the monkey was passing through a late stage of menstruation (the stage of the formation of the menstrual clot), while the follicle appears to have been one that had very recently ruptured.

There is, however, a considerable amount of evidence supporting the view that the pro-œstrum is brought about by some kind of ovarian secretion. Thus, it is generally stated that if ovariotomy be performed menstruation ceases, the small percentage of cases where it has been known to continue being accounted for on the supposition that some portion of one of the ovaries was not removed. Moreover, Glass (Halban, 1901) has shown that in the case of a woman with whom menstruation had ceased in consequence of ovariotomy, it was again induced by the grafting of a new ovary. Knauer (Halban, 1901) has performed similar operations on dogs, and similar results were obtained. Halban (1901) also found that after removing the ovaries of monkeys menstruation ceased, while it continued after a grafting of the ovary. Halban's experiments show further that the recurrence of menstruation after the latter operation was not a purely nervous phenomenon, since it took place when the ovary was grafted in a position different from the normal. These and similar observations seem to dispose of the view

[1] In any case, on Fraenkel's hypothesis, the occurrence of the pro-œstrum seems to be entirely dependent upon a previous ovulation.

that the pro-œstrum occurs as a result of ovulation, or is brought about by the pressure of the growing Graafian follicles on the nerve-endings, as supposed by Strassmann (1896).

There are other considerations pointing to the conclusion that the pro-œstrum and œstrus are produced by substances circulating in the blood, though not necessarily secreted by the ovary. Kehrer states that the milk from a suckling sow is affected at the "brunst" period, the young, as a consequence, developing unhealthy symptoms; while similar phenomena have been noted in the case of suckling women during menstruation (Halban, 1901). Youatt (1835) says œstrus can be induced in cows by giving them milk obtained from other cows which are "on heat."

The statements of Ferré and Bestion (Dixon, 1901) that injections of ovarian extract may produce genital excitement have perhaps more direct bearing on this question, but these observations have not so far been confirmed.

Although I am unable, for the reasons stated above, to agree with Fraenkel that menstruation is induced by the secretory activity of the corpus luteum, his experiments, carried on in collaboration with Cohn (1901, 1903), appear to me to go a long way towards establishing the view of these investigators regarding the nature of the connection between the existence of the corpus luteum and the changes taking place in the uterus during gestation. The late Gustav Born had suggested that the corpus luteum was an organ, the function of which was to secrete into the blood substances which prepared the uterus for the attachment and growth of the embryo; and the investigations of Fraenkel and Cohn were undertaken to test this view, to which they lend support. The corpora lutea of rabbits were destroyed by a galvano-caustic needle, when it was found that pregnancy did not continue unless at least one corpus luteum was allowed to remain. Thus the occurrence of pregnancy was shown to depend upon the existence of one or more corpora lutea in the ovary.

It seems possible that the formation of the corpus luteum marks a change in the character of the ovarian secretion, which, in the presence of that structure, may have regard especially to the preparation of the uterus for pregnancy and the attachment of the ovum, and perhaps even the suppression, so to speak, of a pro-œstrous or œstrous secretion during gestation. When, as is sometimes the case with the ferret, ovulation does not take place during the "heat" period, the persistence of the œstrus may possibly be directly correlated with the absence of the corpora lutea.

But whereas such suggestions in the present state of our knowledge are of course highly speculative, the results of recent experiments seem to me to point to the conclusion that the solutions of some of the problems concerning the œstrous cycle and the ripening and final rupture of the Graafian follicles, will be found in the study of the ovary as an organ of internal secretion.

Postscript.

Since concluding the present paper I have read Sandes' account of the formation of the corpus luteum in Dasyurus, of which I had previously only seen an abstract (see p. 330). It is to be noted that this author, although stating in his summary of conclusions that "the corpus luteum atreticum is formed in the same way as the corpus luteum verum," says also that "other atresic follicles are reduced to fibrous tissue or remain cystic." In the body of the paper he describes the former process as occurring only in atretic follicles which had become ripe, or nearly so, but in which the ovum had not been discharged. In the case of the smaller follicles Sandes describes the follicular epithelium as frequently degenerating but never hypertrophying.

Two new articles on the gestation of the badger by Mr. A. H. Cocks have lately been published in the 'Zoologist.' In the last article Mr. Cocks arrives at the remarkable conclusion "that the pairing may take place at any time during

a range of some ten months, and yet that the young are always born within a season limited to about six weeks;" in other words, the gestation period of the badger may be anything between under five and over fifteen months. (See above, page 326, where Meade-Waldo's paper is referred to.)

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EXPLANATION OF PLATES 19—21,

Illustrating Mr. Francis H. A. Marshall's paper on "The Œstrous Cycle in the Common Ferret." The figures were drawn by Mr. J. Taylor, of Edinburgh.

Reference Letters.

b. v. Blood-vessel. *b. v. rup.* Recently ruptured blood-vessel. *cav.* Cavity of uterus (in Fig. 8 cavity of Fallopian tube). *c. t.* Connective tissue of stroma. *ep.* Epithelium. *ep. c.* Isolated epithelial cell. *ep. gl.* Epithelium of gland. *ex. b.* Extravasated blood corpuscles. *gl.* Uterine gland. *leu.* Leucocyte. *musc.* Muscular layers of uterine wall. *ov.* Ovary.

PLATE 19.

FIG. 1.—Transverse section showing portion of uterine mucosa. (Period I.) × ca. 300.

FIG. 2.—Transverse section showing portion of uterine mucosa. (Period III, very early stage.) × ca. 300.

FIG. 3.—Transverse section showing portion of uterine mucosa. (Period IV.) × ca. 300.

FIG. 4.—Transverse section showing portion of uterine mucosa. (Period IV, advanced stage.) × ca. 300.

PLATE 20.

FIG. 5.—Transverse section of horn of uterus. (Period II, early stage.) × ca. 50.

FIG. 6.—Transverse section of horn of uterus. (Period III, advanced stage.) × ca. 50.

FIG. 7.—Transverse section of body of uterus. (Period IV. The entire section is not shown.) × ca. 50.

FIG. 8.—Transverse section of ovary, showing its attachment to the wall of the body cavity, and its enclosure by a sac into which the ova are discharged. × ca. 14. The section passes six times across the coiled Fallopian tube.

PLATE 21.

FIG. 9.—Section through atretic follicle. × ca. 300. The membrana granulosa has almost completely disappeared, while the ovum is much shrunken and in a very degenerate condition. Ingrowth from the connective tissue wall of the follicle has commenced, but has not advanced very far.

FIG. 10.—Transverse section showing portion of uterine mucosa. (Period IV.) × ca. 300. Large numbers of blood corpuscles are seen extravasated in the stroma, while at the same time new (?) blood-vessels are apparently in process of being formed.

FIG. 11.—Transverse section showing portions of uterine mucosa, as well as products of denudation, in the uterine cavity. (Period III, advanced stage.) × ca. 300.

Fig 1.

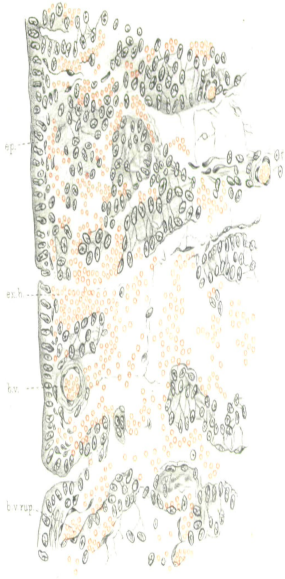

Fig 3.

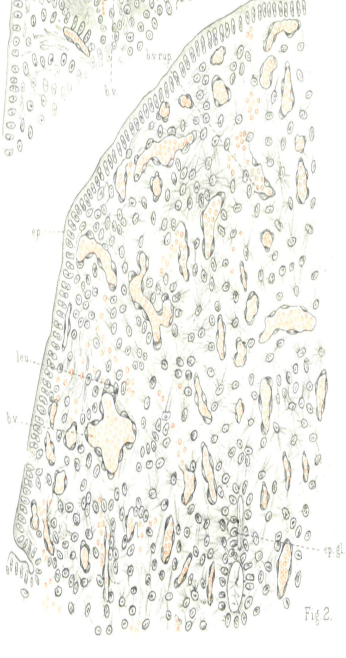

Fig 2.

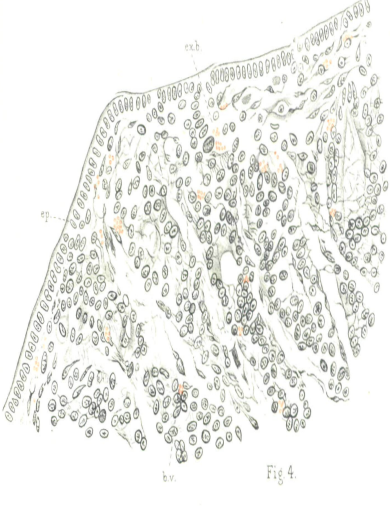

Fig 4.

Heath Lith. London.

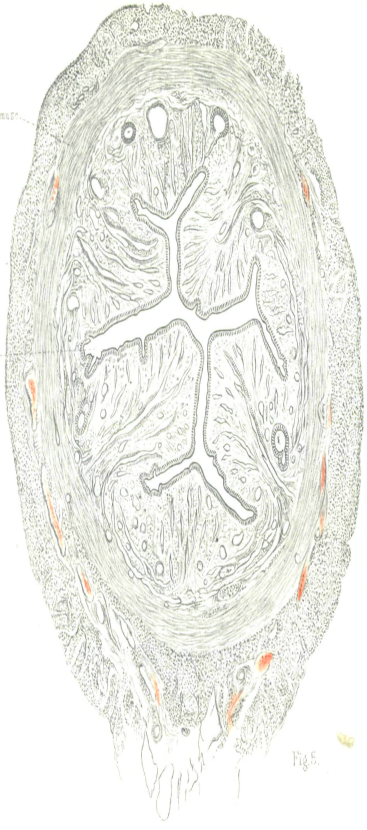

Fig. 5.

Fig. 6.

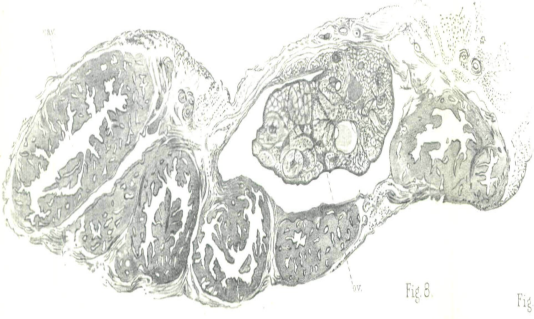

Fig. 8.

Fig. 7.

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Fig. 9.

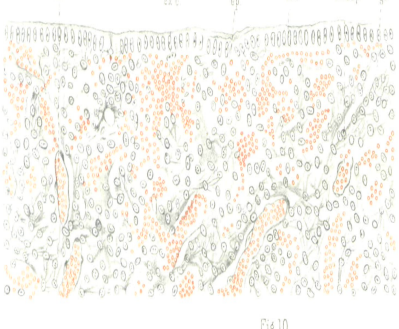

Fig. 10.

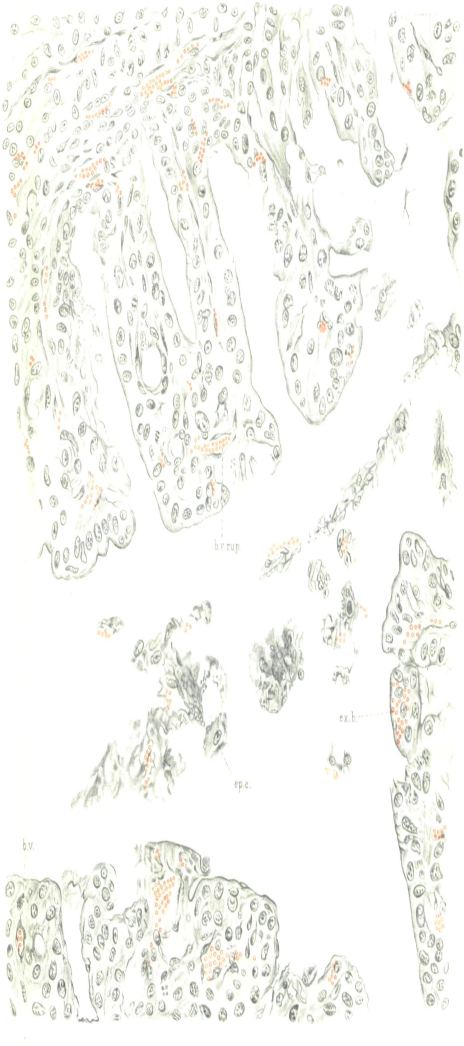

Fig. 11.

Huth Lith. London.