

Process of Ovulation

Experiments basis of facts in study of ovulation

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IT IS in response to the invitation of Ye Editor that this paper has been prepared. Its object is, in brief compass, to point out some hiatuses in our knowledge of the ovulation process in vertebrates.

Ovulation or the discharge of the ovum from the Graafian follicle is a slow, orderly process, not explosive or cataclysmic. "Rupture" of the follicle is not quite the correct term. Of this fact a person may best be convinced by direct observation as has been done with the frog, hen, rabbit, and sheep. Bartelmez (1912) was the first eye-witness to the emergence of the pigeon's egg from the ovary and B. G. Smith observed that of the egg of the amphibian *Cryptobranchus*. Anyone interested in this subject who has not already done so should see the motion picture, in color, of ovulation in the hen, as produced by Warren and Scott of Kansas State College. The film of ovulation in the rabbit by the late Edgar Allen and co-workers and that by Everett of the U. S. Bureau of Dairy Industry are also most instructive. While it is true that the rabbit or sheep follicle, upon opening, may at times show a little spurt of thin follicular fluid (McKenzie, et al), the motion pictures show that about 7 seconds are required for the process, a period certainly undeserving of the term "explosive." In the body, of course, where the viscera are in immediate contact, such a "spurt" can be ruled out in any event.

A histological study of ovaries of rat, guinea pig, and monkey has demonstrated some of the visible changes in the tissues of the follicle leading to ovulation. We

need, however, some more precise cytological analysis of the finer changes in the follicle wall just preceding (a matter of minutes) its attenuation and breakdown at the "stigma." This can best be done on the rat, rabbit, guinea pig, hen, or frog where the hour of ovulation can be predicted. It would be interesting to have comparable stages for farm animals, and, of course, for man also.

Turgidity Indispensable

This view of the mechanism of ovulation does not eliminate the function of intra-follicular pressure. A certain turgidity of the organ is indispensable, just as accurate vision demands an optimal intraocular pressure; or in the case of the uterus, as an edema of that organ, at least in some mammals, is a physiological concomitant of implantation and the continuation of pregnancy. The internal pressure in these cases is a secretion pressure of certain membranes of the Graafian follicles, for example the granulosa membrane and the theca interna. The activity of these tunics is, in turn, dependent on hormonal influences, interaction of products of the anterior pituitary and of the tunics themselves. Some progress has been made in the study of the physico-chemical processes involved in the secretion of liquor folliculi, but less than can, for example, be quoted for the physiology of kidney secretion. Such studies should be much simpler for the Graafian follicle, an enormous organ compared with the parts of a nephron. Besides, the ovary may readily be transplanted into the anterior chamber of the eye or even exteriorized and made available for precise studies.

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Nor are we ready to dump the old theory that smooth muscle fibers of the theca externa have to do with ovulation. Quite the contrary. A mammalian follicle suspended in saline solution and attached to a light heart lever can, upon the addition of adrenalin to the bath, be made to write a record of its contraction. Ripe follicles removed singly from a frog's ovary can be seen to "ovulate" in a saline bath. It will be noted that the follicle is "skinned" off, as it were, or in other words that the egg emerges from a "rip" smaller than the diameter of the ovum, which is literally squeezed out. The same may be seen in the hen, as e.g. in the Warren-Scott film.

Smooth Muscle Demonstrated

Smooth muscle fibers have been demonstrated in the theca interna of the rat. There are scattered references in the older literature to casual observations on such cells in other mammals and birds. But no one seems to have subjected the matter to intensive study. It should also be quite easy to get actual tracings of the contraction of the hen follicle during ovulation by means of a tube inserted into the follicle and connected with a delicate tambour just before ovulation. It may indeed be possible to remove the follicle from the bird for this purpose, for the egg will emerge even though being thus severed from the ovary at such a time.

The time element in the foregoing experiment of removing the nearly ripe follicle at its stalk is important because, as we now know, maturation of the follicle and ovulation require anterior pituitary hormone and possibly also estrogens and progesterone.

One can easily demonstrate this in a suitable frog, say during the winter months, when the frog has large eggs but does not normally ovulate. Implant a bit of fresh frog pituitary (or extract of it or suspension of pituitary previously "saved up" by drying from acetone or absolute alcohol) and 20, 40, or 60 minutes later remove the ovary and suspend it in frog saline. Eggs will drop off like berries from a bunch of grapes, the number being roughly proportionate to the length

of exposure to the hormone while the follicles are still in contact with the circulating blood. This can also be demonstrated by the following experiment of Robinson and Hill. Suspend the ovary and add extract of minced frog pituitary to the bath—the same thing will happen, ovulations will occur, the number being roughly proportionate to the fraction of a pituitary added.

In both hen and frog there is splendid opportunity of studying the changes in the follicle wall which lead to ovulation. They are more than vascular. Results attained in frog and bird are certain to prove very suggestive for the mammal.

Failure to ovulate is the cause of much sterility. The ovaries are extremely sensitive to non-specific influence deleterious to the health of the body in general. Any of the avitaminoses interfere with cyclic changes in the ovaries. If a female of a wild species, having ripe follicles in the ovaries, is caught in a steel trap the follicles are likely to degenerate without ovulation. Captivity itself is deleterious to the gonads. Even the domestic hen brought into close confinement from the free range while in the process of laying a clutch of eggs immediately stops laying and absorbs the remaining large oöcysts and ovulation ceases until adjustment to the close quarters has been attained.

Cystic Ovaries

In cows, the cystic condition of the ovaries is a source of greatest worry to the veterinary obstetrician. No "cure" has yet been found for this. In Everett's (Duke University) "constant estrus" strain of rats the condition is temporarily corrected by injection of 0.5 mg. of progesterone; ovulation occurs and the following cycle is "normal," after which the original condition recurs. Progesterone is as yet too expensive to use in cows, although doubtless any manufacturer of the synthetic hormone would be glad to have it tried, if this has not already been done.

Other female mammals, including the farm animals, are sterile because of ovarian inactivity. Their anterior pituitaries are either less active than normal or the

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OVULATION

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ovaries are too refractive. Both conditions probably occur, for (1) it is easy to overstimulate the ovaries of some individuals with low dosages and (2) it is impossible to "budge" the ovaries of others even with enormous doses.

In general, the ovary must have follicles with antra before it will respond to gonadotrophic stimulation. Thus, the juvenile rat is unresponsive until about 15 or 16 days of age. For the growth of follicles up to the attainment of small antra no gonadotroph is required, for such occur in hypophysectomized females. Hence replacement therapy is effective in most hypophysectomized individuals, for the ovary proceeds to a certain stage of follicular development by virtue of its own inherent growth impulses.

It appears, therefore, that the ovaries of some individuals of any colony or flock of animals fail to attain this favorable stage. With some individuals the condition is temporary, the animal recovering spontaneously—at least that has been the writer's experience with the monkey.

There is no doubt but that in any species ovulation may be precipitated in the cycle or brought about during hibernation or in the anestrus or non-breeding season; also, that fertility may be increased in some otherwise normal individuals. To date it has not been shown that the total annual fertility of a herd or even a colony of rats has been increased by administration of gonadotrophic hormones. The reasons are two: (1) the ideal combination of good follicle-stimulating and ovulating hormones has not yet been produced and (2) although ovulation and even hyper-ovulation may be produced, the concomitant prerequisites to fertilization (mating behavior) and pregnancy (ovarian hormones as well as prolactin in right amounts) are not forthcoming. Nevertheless, it is desirable to keep on trying—first on laboratory and farm animals. Promising results in this field will then be a boon to the gynecologist, one of whose important clinical problems is sterility.