6920

Anterior Pituitary Hormones Acting on the Ovary and Differences in the Reactions in Different Species.*

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There has been much discussion in recent literature as to whether the anterior pituitary gland produces one or 2 kinds of hormones which act on the mammalian ovary, and through the ovary on the uterus, vagina and mammary gland, or also directly on the last named organ. Zondek[1] and others hold that there are 2 types of anterior pituitary hormones acting on the ovary, (1) the follicular growth hormone, responsible for the growth of follicles and (2) the luteinizing hormone causing the production of corpora lutea and of lutein tissue in general.

As previously indicated, the facts which we have established as well as other facts only partly published can be explained most satisfactorily if we assume that there are at least 2 types of anterior pituitary hormones which act on the ovary, one of which affects also the thyroid gland. These 2 hormones are as follows: (1) A hormone (1) which is responsible for the increase in size of the ovarian follicles and for the maturation processes which take place in the granulosa of follicles. This hormone counteracts the tendency of the granulosa to undergo degeneration, leads to the maturation of the granulosa primarily of the large sized follicles, but may also cause beginning or further advanced maturation of the granulosa of medium-sized and even smaller follicles. If no inhibiting mechanisms are at work, the production of large mature follicles leads in due time to ovulation and to the formation of true corpora lutea with the consequences which follow from the functioning of these organs. However, in many other cases, the large-sized mature follicles do not give rise to ovulation, but an ingrowth of capillaries and of connective tissue cells from the theca interna into the granulosa of such follicles; this is followed by the transformation of the granulosa cells into lutein cells and is usually also accompanied by an increase in the size of the theca interna cells. Especially in the rat these processes can be well recognized.

* These investigations were carried out with the aid of a grant for research in science made to Washington University by the Rockefeller Foundation.

[1] Zondek, B., *D. Hormone d. Ovariums u. d. Hypophysen Vorderlappens.* Berlin, 1931.

Whether this hormone actually induces an accelerated cell multiplication in the granulosa of the growing follicle or whether it allows merely the production of many large follicles by inhibiting the premature degeneration of the granulosa and by increasing the size of the granulosa cells and the amount of liquor folliculi remains to be determined. These various possibilities have not been distinguished by various authors. As I have observed,[2] the maturation process as such, which takes place in the granulosa cells, tends to diminish and suppress the proliferative activity of the follicular granulosa.

(2) A second hormone (II), either preformed in the anterior pituitary or originating after removal of the gland from the animal, acts in the opposite manner on the granulosa of the follicles, inhibits its growth or accelerates the degeneration of the granulosa cells in species in which the granulosa cells are of a more labile character. It allows the transformation of theca interna into interstitial gland or pseudolutein tissue and of certain connective tissue cells into lutein-like cells during or following the process of atresia of follicles. Thus structures can be produced which show various kinds of intermediate conditions between atretic follicles and corpora lutea.

These two effects, (1) the inhibition of growth of follicles and of the tendency of the granulosa to undergo maturation, and (2) production of a hypertrophic type of atresia of follicles, leading to the formation of structures which if they reach a relatively large size may resemble corpora lutea, and the production of an often only rudimentary interstitial gland, due to the activity of the theca interna and possibly also of certain connective tissue cells, are combined and may therefore probably be attributed to the same pituitary hormone, although the first effect may occur without being followed by the second effect.

Some doubt remains in regard to several points. There is associated with the action of the hormone I, which causes enlargement and maturation of the granulosa, a marked development of interstitial gland around atretic follicles and in the medulla of the ovary. These effects are usually more marked than the corresponding ones connected with hormone II. Shall we ascribe these hypertrophic changes in both cases to the presence of the hormone II? Or do they represent a further development of the changes initiated by the hormone I?

[2] Loeb, Leo, *J. Morphol.*, 1911, **22**, 37; *Virchow's Arch.*, 1911, **206**, 278.

Pending the outcome of these investigations we may provisionally characterize hormone I as responsible for the development of follicles to large size and for the maturation of the granulosa, and hormone II as inhibiting the growth of follicles and causing the degeneration of granulosa in species in which the granulosa cells are very labile and show little resistance to injurious factors; this hormone also leads to hypertrophic changes in the theca interna and in certain connective tissue cells, especially those which are active during atresia of follicles, although we cannot as yet be quite certain as to the possible relationship of these effects to hormones I and II. It seems probable that the anterior pituitaries of different species each contain both hormones, but that the proportions differ much in different species.

The luteinization of granulosa is associated with a process and is due to a hormone different from the process and hormone concerned with the luteinization which takes place during atresia of non-mature follicles. It is therefore necessary to distinguish between different processes which in the end may lead to the production either of corpora lutea or of lutein-like structures.

The hormone acting as stimulator of the thyroid gland can be independent of the follicular growth and maturation hormone I, but we have always found it associated with hormone II and the formation of interstitial gland and other pseudolutein structures, which we may tentatively attribute to hormone II. This thyroid effect appears after inoculation of anterior pituitaries relatively rich in hormone I (rat, rabbit, guinea pig), only if at the same time interstitial gland and other types of lutein-like tissue are produced. The interpretation of this fact will vary in accordance with our interpretation of the relations which exist between the follicular growth and maturation promoting hormone (I) and the production of lutein-like structures. If we assume the latter also to be a function of hormone I, but to appear only if hormone I is present in larger quantity, then we would have to conclude that the thyroid stimulating hormone occurs also in association with hormone I.

In addition to the character of the active hormone, the type of the soil on which the hormone acts determines the resulting effects. We have previously shown that the thyroid of the guinea pig is much more responsive to stimulation by anterior pituitary than the thyroid of the rat. We thus reproduce in the guinea pig but not in the rat all the essential characteristics of Graves' disease. Similarly the ovary responds in the guinea pig more readily to an-

terior pituitary hormones than in the rat, due to a considerable extent to a greater inertia and to a lessened sensitiveness on the part of the granulosa in the rat. These properties of the granulosa make possible the short duration of the sexual cycle in the rat.

On the other hand, there is some indication that the fully formed corpora lutea are less resistant in the rat than in the guinea pig. This is also a necessary requisite, if the sexual cycle shall have a short duration, because as I have shown previously[3] the corpus luteum inhibits ovulation. Probably this greater sensitiveness of the corpora lutea to unfavorable conditions and their greater tendency to degeneration in the rat, as compared with the guinea pig, makes impossible the long-continued preservation of the corpora lutea following complete hysterectomy in the rat, an effect which can be easily accomplished in the guinea pig.

A further variable factor modifies the response of the ovary to the anterior pituitary hormones, namely the immunity which develops after long-continued application of these hormones in thyroid as well as in ovary.[4] We have furthermore shown that this state of immunity does not depend upon the production of antibodies in the blood serum.

The effects which these ovarian changes have on uterus, vagina and mammary gland can be predicted from what we know of the characteristic effects of the follicular and corpus luteum hormones during the normal cycle and during pregnancy. The follicular hormone causes proliferation of vagina, hyperemia and marked epithelial hypertrophy and very slight proliferation in the connective tissue of the uterine mucosa, as well as growth in the mammary gland, while the corpus luteum hormone causes predecidual proliferation in the mucosa and sensitizes the mucosa in such a way that various kinds of stimuli can then produce placenta and placentomata. The corpus luteum also inhibits ovulation and proliferation of the vaginal epithelium.[5] We find corresponding effects, if follicles are stimulated or on the contrary depressed and lutein tissue is produced experimentally in the ovary. In particular, do we find after inoculation of cattle anterior pituitary a resting stage in the vagina of the guinea pig, while the uterus may under certain

[3] Loeb, Leo, *D. med. Wochenschr.*, 1911, **37**, 17; *Biol. Bull.*, 1914, **27**, 1; Papanicolaou, G. N., *Anat. Rec.*, 1920, **18**, 251.

[4] Loeb, Leo, and Friedman, Hilda, PROC. SOC. EXP. BIOL. AND MED., 1931, **29**, 172.

[5] Loeb, Leo, PROC. SOC. EXP. BIOL. AND MED., 1923, **20**, 441; *Am. J. Physiol.*, 1927, **83**, 202; Loeb, Leo, and Kountz, W. B., *Am. J. Physiol.*, 1928, **84**, 283.

conditions present the typical picture of predecidual proliferation. On the other hand, the inhibiting effect of certain lutein-like formations produced in the ovary under the influence of rat, rabbit or guinea pig anterior pituitary allows, in many cases, only a partial proliferation of the vaginal epithelium, notwithstanding the presence of many fully developed mature follicles which otherwise should be expected to lead to keratinization of the vaginal epithelium.

6921

Diseased Rats Showing Increase of Giardia and a Septicemic Bacillus coli.

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During a recent series of experiments by the Department of Physiology of the University of California there appeared a very high rate of mortality in young rats. These rats, ranging in age from 3 to 8 weeks, were brought to us for protozoological examination. The symptoms were as follows: yellowish watery faeces; haemoglobinuria in some cases; anemia; and decided lack of muscular coordination. Twenty-three such rats were examined by us. They were on a *raw* milk diet.

At biopsy and autopsy the duodenum was quite inflamed, while the jejunum and ileum were frequently black with congested blood. The lungs were often hyperemic. The macroscopic appearance of the liver, spleen, and kidneys was normal.

Microscopic examination revealed the presence of a far greater number of *Giardia* than ever before observed by us in rats. They were most abundant between the limits of 6 and 20 inches below the stomach in the jejunum and ileum. They were so abundant that the microscopic field contained countless numbers of these protozoa, while tissue scrapings from the wall of the intestine revealed them massed on the surface of the cells, apparently feeding on tissue juices.

Potter[1] distinguishes 2 species of *Giardia* from the rat: *G. lamblia* and *G. muris*. The forms found in these rats were of the *G. lamblia* type in the majority of cases, occasionally accompanied by *G. muris*.

[1] Potter, L. A., *Am. J. Hyg.*, 1928, **8**, 77.