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The Effect of Follicular Extract on the Generative Organs of Hysterectomized Guinea Pigs.

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The corpus luteum has the following functions: (1) It sensitizes the uterine mucosa in such a way that mechanical stimuli applied to the sensitized tissue cause the production of placentomata, or the embedding of the ovum calls forth the production of maternal placenta. The corpus luteum also produces a slight predecidual proliferation in the mucosa.[1] (2) The corpus luteum induces a proliferation of the mammary gland,[2] and (3) The corpus luteum prevents ovulation.[3]

There are certain changes which occur in the sexual cycle previous to the development and functioning of the corpus luteum, namely, hyperemia and occasional mitoses in the mucosa of the uterus, a slight proliferation of the mammary gland and a marked proliferation of the vaginal epithelium. These latter phenomena are, therefore, not produced through the action of the corpus luteum, but they must be due to the influence of maturing or mature follicles, the development of which coincides with the occurrence of these latter changes. We divided, therefore, the sexual cycle into two phases, (1) the follicular phase and (2) the lutein phase, both of which are dominated by distinct hormones, although in certain respects their effects are similar.[4] Subsequently the experiments of Frank[6] and especially of Allen and Doisy,[5] and later, of many others proved that the contents of ovarian follicles produce certain changes in the sexual organs very similar to those observed during the follicular phase of the cycle. However, Allen, as well as Frank and others, on the basis of their observations, went so far as to identify the follicular hormone with the ovarian hormone in general. In their opinion the corpus luteum was merely a place where the follicular hormone was deposited.

These conclusions, according to our opinion, are not in accordance with the facts established during the last 25 years, and we believe that the interpretation of these authors is, in part at least, due to the circumstance that they depended largely on the mouse for the study of the sexual cycle, and used as the method of investigation principally the microscopic examination of vaginal smears devised by Stockard and Papanicolaou.[7] While the latter has the great ad-

vantage of simplicity, still it gives a very limited insight into what is actually taking place during the sexual cycle. As for the mouse and rat, their sexual cycle is peculiar in that the lutein phase is here developed only in a very rudimentary fashion. In order to clear up still more definitely the relation between follicular and corpus luteum hormones we turned to the guinea pig, in which both phases of the cycle are well developed and have been analyzed by us thoroughly in previous investigations. In addition, instead of applying the smear method we made a complete microscopic examination of the various generative organs of every guinea pig injected with follicular hormone. These investigations were begun about one and one-half years ago, and they comprise a series of different experiments. We shall limit ourselves in this communication to a consideration of those experiments in which, about 3 to 5 days following the period of heat, we extirpated completely or almost completely the uterus of guinea pigs, and after variable periods of time administered to such hysterectomized animals a series of injections of follicular extract extending over a period of 10 to 14 days. Usually two, but in one case three daily injections of 1 cc. of follicular extract were given to each animal.* At the end of the experiment the vagina, cervix, uterus, ovaries and mammary gland were examined microscopically. The ovaries were always studied in serial sections.

While in the guinea pigs injected during the sexual cycle, and also in immature or castrated guinea pigs the follicular extract caused opening of the vagina, proliferation of the vaginal epithelium, proliferation of the mammary gland, and in some cases hyperemia and an edematous condition of the uterus, in hysterectomized guinea pigs on the other hand, the vagina remained closed except that an occasional slight tear was seen, such as may occur in various conditions, perhaps as the result of injury; the vagina not only did not proliferate but was found to be more inactive than in immature guinea pigs, or even in guinea pigs during the second part of the cycle. The vaginal cells were very vacuolar, in some cases filled with large masses of mucus, and polymorphonuclear leucocytes migrated through the wall of the vagina in such large numbers that small abscesses were produced in the mucosa. The small remnants of the uterine mucosa did not show any predecidual proliferation. These

* In this series we used the preparation made and placed at our disposal by Parke, Davis & Company in Detroit. In other series of experiments we also used a follicular extract prepared by one of us (Kountz). The former preparation was tested in castrated guinea pigs and it was found that 12 injections of 1 cc. each administered on 6 successive days usually produced the characteristic changes.

peculiar results can be readily explained if we study the ovaries in such cases. In accordance with our previous experiments, we find that, in the guinea pig, extirpation of the uterus a few days following the oestrus prevents the degeneration of the corpus luteum which would normally occur within the next two weeks; instead, this organ remains alive and functioning for a period extending over at least 2 to 3 months.[8] In consequence of the persistence of the corpus luteum, ovulation is prevented, the vagina no longer opens, the vaginal epithelium becomes vacuolar and large masses of polynuclear leucocytes migrate through it; the sexual cycle is suspended and in certain respects the functioning of the generating system of the guinea pig becomes similar to that of the rabbit. However, the mammary gland under the stimulus of persisting corpus luteum secretion grows to a considerable size. In regard to the character of the vagina and mammary gland the condition in such animals resembles that obtaining in pregnancy. In both pregnant and hysterectomized guinea pigs, furthermore, the corpus luteum does not interfere with the development of the ovarian follicles, some of which mature, while all undergo the typical retrogressive changes in the course of time.

If we now inject follicular extract of moderate potency twice or three times daily into such pregnant or hysterectomized animals it is not able to counteract the effect of the corpus luteum, while the same injections in other guinea pigs would produce the typical changes. Furthermore it does not prevent the maturation of follicles which normally occurs in hysterectomized as well as in other guinea pigs. This latter fact is in accordance with the conclusion repeatedly emphasized by us that the corpus luteum does not inhibit maturation of follicles but only ovulation; in addition, we now find that it also inhibits the effect of follicular hormone on the vagina.

In this connection it may be stated that the follicular extract in general seems to promote the growth and full development of the follicles, while at the same time it not only does not accelerate, but on the contrary seems to inhibit, ovulation in the guinea pig. In a similar way to the persistent corpus luteum of the hysterectomized guinea pig the persistent corpus luteum of pregnancy likewise prevents the typical proliferative changes in the vagina; instead, this organ shows the characteristic degenerative condition found in hysterectomized guinea pigs. However, in this connection, we must recall the fact that, as we have found previously, there exist complicated conditions in pregnancy inasmuch as in this state certain factors prevent the typical predecidual reaction of the uterus from

taking place, in case an ovulation is called forth experimentally and a new corpus luteum is thus made to develop during pregnancy.

In conclusion, we may state that these investigations substantiate the interpretation of the mechanism of the sexual cycle given by us previously as to the existence of two different phases in the cycle; they also confirm our conclusions that in the regulation of the sexual cycle we do not have to deal with one single generative hormone residing in the follicles, but with the complex interaction of at least two and probably an even larger number of substances derived from corpus luteum as well as from follicles.

This is a preliminary report.

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Animal Passage Hypoglycaemia.*

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As the writer has never been able to duplicate the results obtained by him in connection with a study of plant extracts containing a hypoglycemia producing substance, and described as animal passage hypoglycemia,[1] he is now of the opinion that such results must have

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