

and have so far given only apparent normals. There is no marked difference in the division rate of apparent normals and of abnormals.

Further experiments on the heritability of this abnormality of form are now in progress.

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The production of certain distinct types of reactions by the use of ovarian extracts.¹

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The present status of our knowledge on the rôle of the ovary as an endocrine gland, and on the exact physiological effects produced by the use of ovarian preparations and extracts, is far from being satisfactory. Though the importance of the ovary as an internal gland is well recognized, there is yet much controversy regarding the interpretation of its particular functions. Some investigators consider the *corpus luteum* as the only or chief active endocrine part of the ovary, while others attribute more importance to the interstitial tissue or to the follicular complex. This divergence of opinions is partly due to the fact that the methods used for the study of this problem have been somewhat incomplete and the conclusions drawn more or less exclusive. The *corpus luteum*, for instance, has been repeatedly underestimated in its importance as an endocrine gland since no positive results have been obtained by certain investigators, who have tried several luteal preparations. The fact that one type of ovarian extract may be inactive in a case where another is active must not be taken as a proof that the former does not possess a certain hormonal action which might be detected by the use of other methods. The ovary is a complex gland and possibly secretes more than one active substance. Such a view is well

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supported by a large number of facts. The great diversity of the phenomena characterizing the sexual functions of the female could hardly be the result of a single factor or hormone. The structural complexity of the ovary and its diversity at different developmental stages, with the presence in it of several types of cells seemingly secreting actively in an alternating fashion, are also indicative of a multiple secretory function.

Such views as the above seem to be justified by some experiments carried out in this laboratory during the years 1922 and 1923. These experiments were done in cooperation with Dr. F. N. Blau and Dr. John D. Rogers. A large number of extracts prepared from ovaries or *corpora lutea* of pigs and cows were tested especially in regard to their effect upon the sexual organs of the guinea pig. Control extracts of other organs and different solvents have been administered for testing the specificity of the results obtained. The extracts were prepared by Dr. Blau, while the writer made the physiological tests. A careful examination of the vaginal smears of the treated animals was made. A number of animals have also been killed at different stages and their reproductive organs examined in sections. The guinea pigs used as test animals consisted of a group of normal and a group of ovariectomized females. The extracts were given in three different ways—by mouth, by subcutaneous injections and by intracardiac injections.

The results obtained gave indications of different types of reactions, which may be classified in three different groups:

The first group consists only of one set of extracts of lipid nature prepared from the *corpus luteum*. Such extracts, when given by injections to normal animals, produce certain effects which seem to me entirely characteristic of an active *corpus luteum*. No effect is produced by mouth administration. Under the effect of the injections the large follicles begin to regress in the ovary, the process of ovulation stops and the oestrous or menstrual phenomena are suppressed. An active *corpus luteum* produces the same effects; it prevents the growth of the follicles and suppresses the oestrous or menstrual activities. This reaction seems to be specific and is evidently due to an hormone secreted by the *corpus luteum*.

A second group of reactions is produced by the administration of follicular and cystic fluid extracts and also of ovarian

residue extracts. The effect of these extracts is, as pointed out recently by Allen and Doisy,² to induce congestive and hypertrophic reactions in the genital tract, similar to those produced normally during the oestrous activities. This hormone, though entirely different in action from the first one, is contained also in lipid extracts and is not effective by mouth.

A third group of reactions is produced by some water-soluble fractions of alcoholic extracts of whole ovaries, and of *corpora lutea*, when given by injections and to some extent by mouth. These extracts stimulate the functions of the sexual organs. The cycle shows a well-regulated periodicity, and a tendency to be somewhat shortened. The ovary functions properly with a slightly increased activity. This stimulating effect is of a different nature from the one produced by the second hormone. This affects more the ovary and stimulates its functions, without producing some of the hypertrophic oestrous reactions in the uterus and the vagina, which characterize the second group. The factor responsible for these effects cannot be confused with the previous ones as it is contained in watery soluble fractions from alcoholic extracts, while the first and second are obtainable only in oil soluble fractions.

The recognition of these three different types of reactions is very important in the final analysis of the ovarian functions. The more active secretions of an hormone of one or the other type may explain why at a certain time the ovary or the uterus reacts in one or the other way. The complicated changes occurring in the sexual organs in a well-regulated cyclic form could not be explained as due to the effect of only one hormone factor. More extensive experimental work which is now under way indicates the possibility of isolating and purifying these ovarian hormones, especially those giving the first and third type reactions. The second type has been greatly advanced by the very important and energetic work of Allen and Doisy.

² *J. Am. Med. Assn.*, 1923, lxxxi, 819-821. *J. Biol. Chem.*, 1924, lxi, 711-727.