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Mechanism of Ovarian Control of Hypophyseal Gonadotrophic Function in Guinea Pig. (Experiments with Intrasplenic Grafts). (20294)

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Removal of one ovary does not affect the size of subsequent litters, *i.e.* the number of maturing follicles and of ova shed. Thus the conclusion was reached that follicular development is regulated by the production in the body of a fixed quantity of extra-ovarian substances ("law of follicular constancy") (1).† These extra-ovarian substances can now be identified with the pituitary gonadotrophins. On the other hand, it has been suggested that not only is follicular development quantitatively regulated by the production of these extra-ovarian substances but also that their use, or consumption, in the ripening follicles partakes in the maintenance of the normal ovarian and hypophyseal relationship; ovarian function would depend upon a balance between production and consumption of gonadotrophins(2). This concept though purely hypothetical was based on the experimental statement that an abnormal endocrine function of the ovary is observed after the removal of one entire ovary and the greater part of this second ovary. In similar animals with an ovarian fragment, or remnant, cystic hyperplasia of the endometrium, penetration of glands into the myometrium, uterine and extra-uterine tumors can be observed when the experiments are sufficiently prolonged(3). In the ovarian fragment signs of an abnormal follicular development may be present, as lutein cysts, occasionally also an hemorrhagic one. It was then assumed, though rather vaguely, that the overthrow of the normal ovarian hypophyseal relationship is due, under the described experimental conditions, to an imbalance between production and consumption of gonadotrophins in the ovarian remnant.

The concept of a regulatory influence exercised by the ovary on the hypophysis by the consumption of gonadotrophins was discarded when the control of the hypophysis by ovarian estrogens became a definitely established fact (4-6). The quantitative and timing conditions of this control are still under discussion (7,8). However, more recently the problem has been discussed on new experimental lines such as work with intrasplenic ovarian grafts in the rat; the important statement was made that the hypophysis of the female rat with both ovaries grafted into the spleen is not identical to that of a castrate in so far as it contains less gonadotrophins than the hypophysis of the castrated rat(9). This non-identity is shown also in the absence of castration cells in the hypophysis of castrated animals with intrasplenic ovarian grafts(10). These results were interpreted favoring the concept that consumption of gonadotrophins was a regulatory factor of the functional condition of the hypophysis(9). On the other hand, experiments made in this department have shown that in the guinea pig a small ovarian fragment *in situ* is capable of counteracting production of hemorrhagic follicles in the intrasplenic graft(11-13) even when follicular development in the fragment is very small, *i.e.*, when the assumed consumption of gonadotrophins apparently did not count(14).

In view of these discrepancies the following 2 comparative sets of experiments were made.

A. *Intrasplenic transplantation of variable*

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† Our concept was but a modernized and more "experimentalized" version of Hunter's, Heapes's, Sand's and Hammond's.

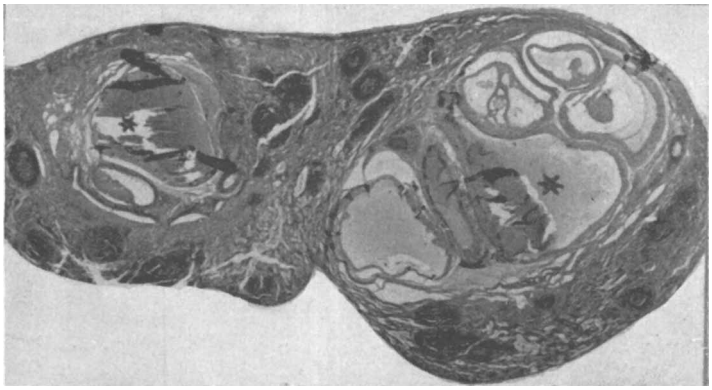

FIG. 1. Both entire ovaries grafted into the spleen; 2 months after grafting; autograft. *Hemorrhagic follicles in both ovaries*‡. Various *cystic* Graafian follicles; no corpora lutea (though they may be present). × 10 (CLVI. 8).

quantities of ovary. Whereas in our former work only one ovary was grafted into the spleen, the second one being excised, in new work *both* whole ovaries were grafted into the spleen. Animals were necropsied 2 months after transplantation. Only those experiments have been included in the results in which both ovaries survived in the spleen. There were 36 animals with 2 ovaries in the spleen (5 series operated on different occasions); in 24 out of these 36 animals (67%), hemorrhagic follicles demonstrating uncontrolled hypophyseal activity were found. In many cases both the ovaries grafted had hemorrhagic follicles (Fig. 1). The frequency of hemorrhagic follicles in experiments with one ovary in the spleen was higher; with one ovary in the spleen, 90-100% of grafts with hemorrhagic follicles were found. This was also the case in 3 series of 22 animals (out of the total of 5 series) with 2 ovaries in the spleen; 19 out of these 22 animals, or 86% had hemorrhagic follicles. The smaller average in the whole group of 36 animals with 67% was due to a failure in 2 series of 14 animals with 2 ovaries in the spleen; only 5 of these had hemorrhagic follicles. The most probable is that a tiny fragment of ovary was involuntarily left in the body of some of these animals. There was among the group of 36 animals a series of 9 animals in which besides the 2 autografts, 2 homoiografts were also made simultaneously but did not take. Cystic condition of Graafian follicles, hemorrhagic or not, was frequent. Corpora lutea were probably less frequent than when only one ovary was grafted. The above results give evidence that both ovaries present simultaneously in the spleen are as incapable as one ovary of controlling the gonadotrophic function of the hypophysis. Certainly, the results do not disprove the concept of a regulatory influence of the ovary on the hypophysis by the means of consumption of gonadotrophins; but they show clearly that such an influence is not sufficient to maintain the gonadotrophic hypophyseal function on a normal level.

B. *Simultaneous transplantation of one ovary into the spleen and of the second one into the kidney* (Fig. 2 and 3). Under these experimental conditions it is to be supposed that consumption of gonadotrophins will be the same as with two ovaries in the spleen, whereas estrogens from the intrarenal graft will reach the general circulation. Animals were again necropsied 2 months after transplantation and only those animals were considered in which grafts survived both in the spleen and in the kidney. There were 10 such animals and there was none with hemorrhagic follicles in the intrasplenic graft.‡ Cystic condition of Graafian follicles was less frequent.

Summary. Hemorrhagic follicles in intrasplenic ovarian grafts in castrated guinea pigs

‡ We have found hemorrhagic follicles, exceptionally, even in intrarenal ovarian grafts (see 16, p. 178). The intrarenal graft, like the intrasplenic one, is incapable of affording a complete control of the hypophysis. This is likewise true for subcutaneous ovarian grafts(3,17).

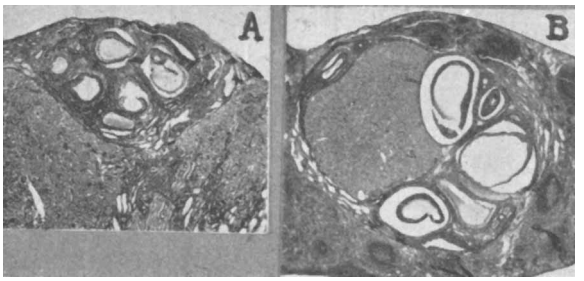

FIG. 2. One ovary grafted into the kidney (A); the whole ovary slipt out to the surface of the kidney. The second ovary grafted into the spleen (B). 2 months; autograft. *No hemorrhagic follicle in B.* No cystic Graafian follicles; very large corpus luteum in B. × 10. (CXXXVIII. 121).

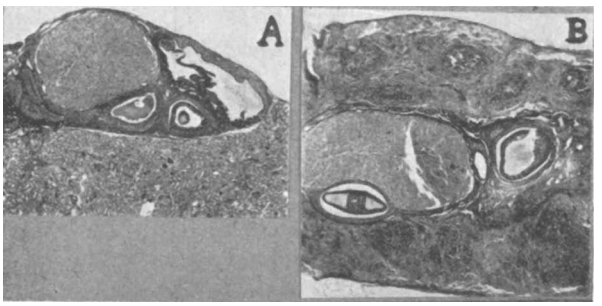

FIG. 3. One ovary grafted into the kidney (A); the greater part of the ovary is on the surface of the kidney. The second ovary grafted into the spleen (B). 2 months; autograft. *No hemorrhagic follicle in B.* No cystic Graafian follicles. [The cystic formation in A is Wolffian; this we consider as indicative of an ovarian-hypophyseal imbalance(15), though of small degree.] Corpora lutea both in A and B. × 10. (CXXXVIII. 133).

appear irrespectively whether one or 2 ovaries are grafted into the spleen. On the contrary, hemorrhagic follicles fail to appear in an intrasplenic graft of the castrated guinea pig when the second ovary is grafted into the kidney. These experiments give definite evidence that the ovarian control of the hypophyseal gonadotrophic function depends not only, if at all, on consumption of gonadotrophins but certainly also on ovarian hormones which reach the general circulation.

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