

THE EXPERIMENTAL FORMATION OF DECIDUAL TISSUE

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The problem of the genesis of decidual tissue is of considerable complexity and is still largely unsolved, particularly with regard to the fact that the decidual reaction is found not only in the uterus but also occasionally elsewhere, for example, in the ovary, pelvic peritoneum, omentum, appendix and so on. Several workers have published in the literature [1, 3, 4] reports of endometrioid heterotopia and of ectopic decidual tissue. K. P. Ulezko-Stroganova [4] attaches great importance to hormonal and metabolic stimulation and at the same time considers that the development of endometrioid heterotopia may also be connected with the effect of a persistent inflammatory condition. V. S. Lisovtskii [2] considers that the development of decidual tissue is due to the hormonal effect of the corpus luteum and the growing ovum, inflammation being secondary.

Our concern in this problem derives from the results of our experiments on nonpregnant guinea pigs in which the phenomenon of hyperergasia had been produced in the uterus, where the development of decidual tissue was observed after an assaulting injection. The results of these experiments, carried out during a state of allergy, make us critical of certain statements of Loeb [7-9], and enable us to add new facts and to define certain points more precisely, which were incorrectly treated in the work of Loeb.

As a result of many experiments carried out in 1907-1910, Loeb came to the conclusion that the development of decidual tissue is possible without the participation of the ovum whose role is only that of a mechanical factor, providing a stimulus for the decidual conversion of the endometrium. The effect of the ovum can be replaced by other mechanical stimuli, for example an incision of the uterine wall, the injection of a foreign body into its cavity and so on. 24 hours after the application of the trauma proliferation of the interglandular tissue of the endometrium, may be found, and on the third day many mitoses and enlargement of the cells of the stroma, mainly beneath the integumentary epithelium. During 5-9 days after incision of the uterus may be observed the formation of small decidual nodules, which attain their full development on the 10th-11th day; after the 15th day the deciduum undergoes necrosis.

Loeb asserts that the decidual transformation of the endometrium under the influence of mechanical stimulation, just as after the action of the ovum itself, is possible only where there has been preliminary sensitization of the uterus to the hormones of the corpus luteum. This sensitization takes place from the 3rd to the 9th day after coitus. Loeb considers that the same interval (4-9 days) after menstruation is optimal for the development of decidual tissue without coitus. Since corpus luteum hormone is necessary not only for sensitization of the uterus but also for the life of the decidual tissue, regression of the corpus luteum and disappearance of its internal secretion leads to necrosis of the deciduum.

The results quoted were obtained by Loeb in nonsensitized guinea pigs. In our own experiments the guinea pigs were sensitized to horse serum and the development of decidual tissue took place in association with an allergic state. Loeb used for a stimulus incision or puncture of the uterus, and so on. Our stimulus was combined and consisted of injection of horse serum into the uterus supplemented by cooling of the experimental horn with ethyl chloride for 3 seconds or by the addition of ergotin to the serum. It is important to mention that the decidual reaction appears when the assaulting stimulus is applied at a particular stage of the sexual cycle — the

resting stage (dioestrus). Outside this stage the application of such a stimulus to the uterus resulted in a violent inflammatory reaction with formation of superficial and deep ulcers in the endometrium.

We give a short account of some of the experiments and of the histological findings.

EXPERIMENTAL METHOD AND RESULTS

Guinea pig No. 73, weight 456 g. Sensitization with 3 ml of horse serum 5 times at intervals of 6-7 days, starting on February 20. On March 25 vaginal smears showed the dioestrous stage. Laparotomy performed on the same day, with injection of 0.6 ml of serum into the right horn of the uterus. Immediately afterwards a stream of ethyl chloride is directed on to this horn for 3 seconds at a distance of 25-30 cm. The guinea pig was killed 4 hours after the assaulting stimulus. The right horn is thickened and hyperemic, with hemorrhages in the serosa.

Histological investigation. In places the uterine mucosa is more or less thickened, infiltrated with inflammatory elements and edematous. In the subepithelial zone there is irregular proliferation of the stroma which is undergoing a decidual metamorphosis. The mucosa here is poor in glands and mitoses are seen in the interstitial cells. Chorionic villi were not found. In the endometrium and circular musculature in places, areas of necrosis could be seen.

Guinea pig No. 47, weight 420 g. Sensitization and experimental procedure as in the previous example. Stage of the sexual cycle - dioestrus. Animal killed 48 hours after assaulting injection of 0.6 ml of horse serum into the left horn of the uterus, followed by cooling with ethyl chloride for 3 seconds at a distance of 25-30 cm.

Histological investigation. Under the integumentary epithelium is seen a decidual transformation of the stroma, the cells of which become round in shape and increased in size. There are many mitotic figures and few glands here. In places the mucosa forms polypi of decidual cells, among which mitoses are clearly visible. In some preparations an isolated islet of tissue, a transverse section through the apical portion of a decidual polypus, can be seen in the cavity of the cornu. Some of the vessels are dilated and filled with blood. Chorionic villi are not found.

Guinea pig No. 76, weight 478 g. Sensitization and conduct of the experiment as in guinea pig No. 73. Stage of the sexual cycle - dioestrus. Animal killed 72 hours after assaulting injection of 0.6 ml of horse serum into the left horn and the simultaneous action on this structure of a stream of ethyl chloride for 3 seconds from a distance of 25-30 cm.

Histological investigation. Part of the mucosa of the left horn is more or less thickened and consists, as it were, of two layers. The first - subepithelial, compact - is formed of decidual cells among which mitoses are seen. Glands are few or completely absent. The second layer - beneath the first - is in direct contact with the circular musculature and contains a comparatively large number of glands. The stroma is infiltrated with eosinophils. In one place the mucosa forms a decidual polypus. Chorionic villi nowhere to be seen.

Guinea pig No. 51, weight 488 g. Sensitization and experimental procedure: as in guinea pig No. 73. Stage of the sexual cycle - dioestrus. Animal killed 80 hours after assaulting injection into the left horn of 0.6 ml of horse serum mixed with one drop of a 10% solution of ergotin.

Histological investigation. In the superficial zone of the endometrium is observed proliferation of interstitial tissue, which in the caudal section of the horn forms a polypus of decidual cells, covered at the apex with prismatic, and elsewhere with elongated, simple squamous epithelium. In the central portion of the polypus a barely perceptible hyaline droplet degeneration of the decidual cells may be observed. At the base of the polypus is a small hemorrhage.

Guinea pig No. 53, weight 375 g. Sensitization and experimental procedure as in guinea pig No. 73. Stage of the sexual cycle - dioestrus. Animal killed 96 hours after assaulting injection of 0.6 ml of horse serum into the left horn and the simultaneous application of a stream of ethyl chloride for 3 seconds from a distance of 25-30 cm.

Histological investigation. The superficial layer of the mucosa consists of decidual tissue forming decidual processes into the cavity of the horn which is thereby diminished in size and in places is obliterated. In the peripheral zone of the polypi there are many mitoses but no glands. The cells of the central zone are enlarged and their large nuclei are oval or round in shape. The capillaries in this part of the polypus are compressed and hyaline droplet degeneration of the decidual cells is observed. Their protoplasm has disintegrated into a multitude of large and small homogeneous blocks, red in color. The nuclei of many of the cells have become pale and reduced in size. As a result of the penetration into this region of segmented neutrophil leucocytes some liquefaction of the

tissue takes place with the formation of cavities filled with a rose-colored fluid containing white blood cells and remnants of disintegrating cells. Outside the zones of cytolysis no leucocytes are visible. Chorionic villi are not seen. The basal layer of the endometrium consists of ordinary stroma with a small number of compressed glands.

From these descriptions it can be seen that in allergic conditions, after the application of a stimulus in the stage of dioestrus the rate of decidual transformation is speeded up. In guinea pigs Nos. 7, 24 and 73, for example, the beginning of the decidual reaction is already visible 4-6 hours after the assaulting injection. Beneath the integumentary epithelium of the endometrium proliferation of the stroma and the appearance of mitoses among its cells are observed. Later on the number of mitoses increases, the glands in this zone disappear and on the 3rd day polypi of decidual cells are observed (guinea pigs Nos. 43, 47, 76 etc.). By comparison with the periphery the cells of the central part of the decidual polypi are increased in size. In guinea pigs Nos. 51, 42 and 53, after 80, 91 and 96 hours respectively from the assaulting injection, hyaline droplet degeneration of decidual cells is found in the central part of the decidual mass, with subsequent liquefaction of these cells as a result of the enzymic activity of leucocytes which penetrate the area.

Thus, our results bring new facts to the problem of the times of development and involution of the decidua. The beginning of the decidual transformation of the endometrium, for example, was already marked in our experiments 4 hours after the assaulting injection, while in Loeb's series this time was lengthened to 24 hours. We observed the appearance of a formed decidua on the 3rd day, i.e., 8 days before Loeb. Finally, the beginning of regression of the decidua, in the form of hyaline droplet degeneration and cytolysis was found in our experiments on the 4th day, whereas in Loeb's experiments involution of the decidua began 13-15 days after trauma.

In Loeb's opinion the development of decidual tissue is influenced only by mechanical stimulation of the endometrium previously sensitized with corpus luteum hormone. The question naturally arises: under the influence of what impulses does development of decidual tissue take place during extrauterine pregnancy, when the endometrium is not subjected to mechanical stimulation from the ovum, which is arrested in some extrauterine position? It is quite obvious that mechanical stimulation of the mucosa of the uterus or Fallopian tube causes not only damage of the tissue but also stimulation of receptors. An assaulting action on the nerve structures is also shown by the absorption of products of disintegration resulting from mechanical trauma to the mucosa, whether due to artificial means (incision of the uterus) or to the ovum.

Afferent signals arising at the site of the trauma are effected by means of impulses which pass through the central nervous system along efferent paths directly to the ovary, or by a combined-reflex route, through intensification of the hormonopoietic function of the pituitary, or else by a short pathway directly to the uterus, stimulating the proliferation and decidual transformation of the endometrium previously sensitized with corpus luteum hormone. It is quite possible that this mechanism takes place during the development of decidual tissue in the uterus during extrauterine pregnancy and during decidual transformation of endometrial heterotopias.

The experiments of I. A. Eskin [5, 6] showed that if rats were injected subcutaneously for 3 days (on the day of estrus and the following two days) with a-folliculin in a dose of 4000-6000 international units, dioestrus is produced and lasts for 13.1 days on the average. On the 6th day after the injection of folliculin the uterus of three of the animals was sewn through with thread and in two of these a placentoma was found 5 days later. I. A. Eskin points out that the state of dioestrus caused by injection of folliculin is similar, both in its duration and in the decidual metamorphosis of the endometrium, to the normal pseudopregnancy of the rabbit and is accompanied by an active lutein phase in the ovary.

If a prolonged dioestrous state similar to that in pseudopregnancy is obtained as a result of appropriate stimulation of the nervous system (injection of folliculin or adrenalin, mechanical or electrical stimulation of the cervix of the uterus), it can be assumed that a similar phenomenon took place in our experiments also. This means that in our experiments the act of sensitization must be regarded as a stimulus of the nervous system. Probably the preparatory injection of serum, like the injection of folliculin in I. A. Eskin's experiments, coincided in some of our animals with the time of oestrus, and caused in these animals a prolonged dioestrus with activation of the corpora lutea arising during natural ovulation. With such an assumption it is not difficult to explain why the assaulting injection results in the formation of decidual tissue.

So far as the shortening of the periods of development and involution of the decidual tissue are concerned, the former, obviously, is connected with stimulation and the latter with the subsequent depression of nervous activity. Because of this the trophic influence of the nervous system during a state of allergy and in the absence of the ovum

is modified and is expressed early, presumably through reflex suppression of the function of the corpus luteum, in the decidual tissue which undergoes rapid regression. This type of mechanism probably lies at the root of some cases of early interruption of pregnancy and incomplete abortion in women who are of an allergic disposition.

SUMMARY

Nonpregnant guinea pigs were sensitized by horse serum. Then one of the horns of the uterus was cooled after a booster dose. Development of decidual tissue in the uterus was observed in these conditions. The initial signs of formation of this tissue was noted in 4 hours while completely formed decidual tissue was found in 3 days.

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* In Russian.