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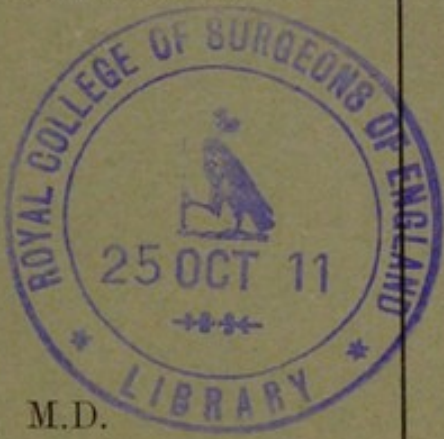
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The Experimental Production of the Maternal Placenta

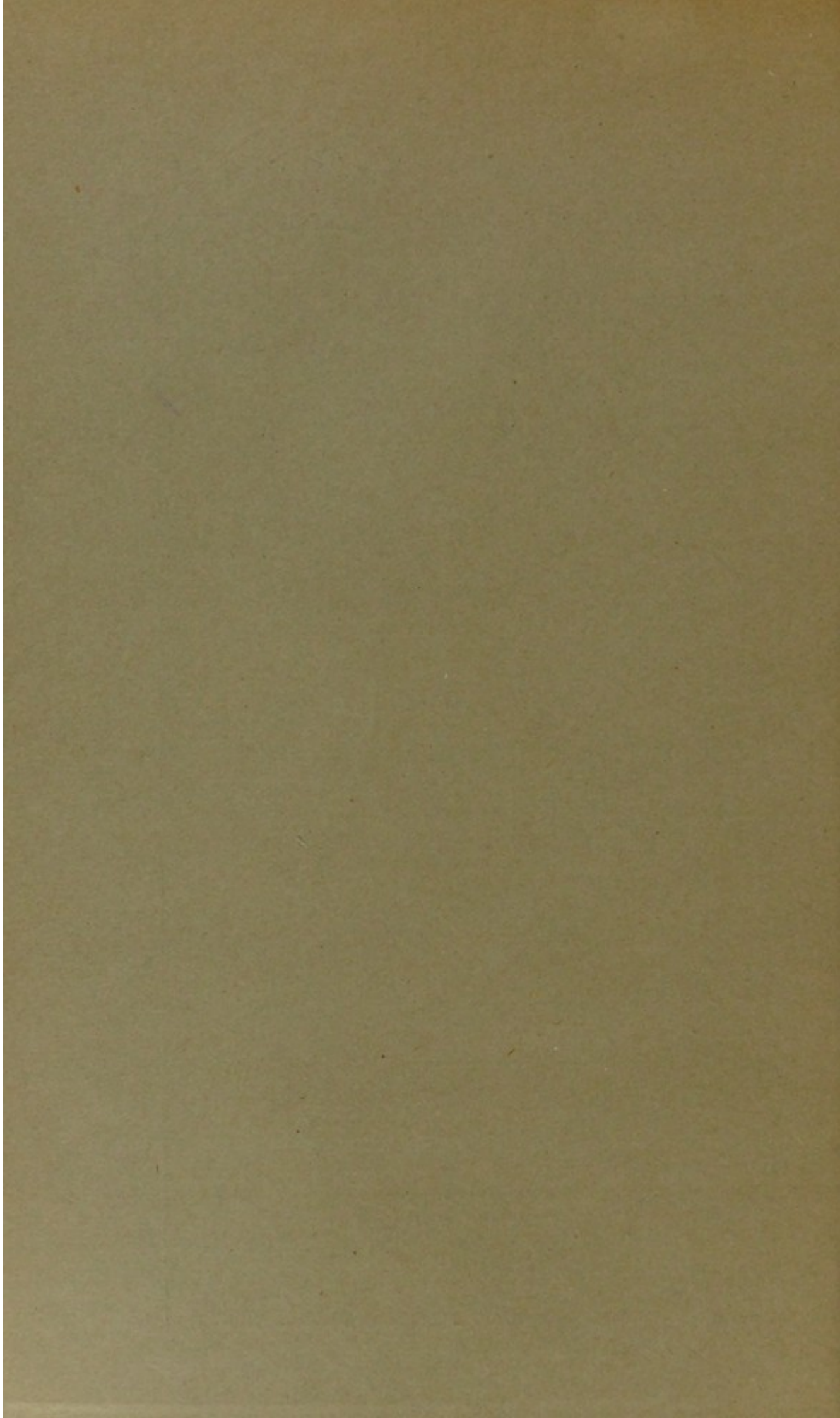
And the Function of the Corpus Luteum



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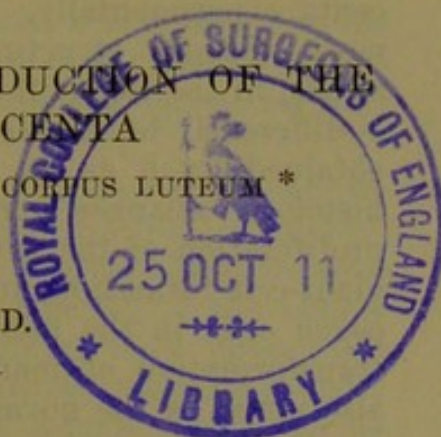
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THE EXPERIMENTAL PRODUCTION OF THE
MATERNAL PLACENTA

AND THE FUNCTION OF THE CORPUS LUTEUM *

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In former work I have shown that it is possible to produce at will any desired number of maternal placentas or deciduomata in the guinea-pig, if we make incisions into the uterus at a certain period after ovulation. Here I shall report on the continuation of my work¹ without, however, attempting to go into any details or to give definite figures.

1. In the beginning I may state that the experimental production of the maternal placenta depends primarily on three factors: first, on a chemical sensitizing of the uterine mucosa; second, on an additional mechanical stimulus applied to the uterus, and, third, on a certain condition of the body fluids of the animal.

2. In my former publication I described only the changes produced in the guinea-pig after incisions made into the sensitized mucosa. Since then I have carried out similar experiments in rabbits and I find that in the

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* From the Laboratory of Experimental Pathology of the University of Pennsylvania.

1. In regard to this work, see the following articles:

Loeb, Leo: The Production of Deciduomata, *THE JOURNAL A. M. A.*, 1908, L. 1897.

Ueber die experimentelle Erzeugung von Knoten von Decidua-gewebe, etc., *Centralbl. f. allg. Path. u. path. Anat.*, 1907, xviii, No. 14; Die Erzeugung von Decidua in d. Uterus des Kaninchens, *Arch. f. Entwcklgsmech. d. Organ*, January, 1909, xxvii; Zur Analyse der Wachstumsbedingungen des mütterlichen Telles der Placenta beim Kaninchen, *Arch. f. Entwsklgsmech. d. Organ.*, 1909, xxvii; Ueber die Bedeutung des Corpus luteum, *Centralbl. f. Physiol.*, November 3, 1909, xxiii; The Formation of the Corpus Luteum in the Guinea-Pig, *THE JOURNAL A. M. A.*, 1906, xlvi, 416. For a review of the literature concerning the corpus luteum see Birnbaum, R.: *Sammelreferat, Ztschr. f. allg. Physiol.*, 1908, viii.

rabbit it is also possible to produce the maternal placenta experimentally. But while in the guinea-pig the newly formed structures somewhat resemble the adrenals, in the rabbit the experimental maternal placenta is differently built. Here usually no distinct tumors are obtained, such as we find in the guinea-pig, but the histologic changes are very marked; they consist in proliferation of the surface epithelium leading often to giant-cell formation, in the production of nests of glycogen cells in the uterine papillæ and in a plasmodial transformation of many uterine blood vessels, changes also noted in the normal placenta of the rabbit. These results enable us to analyze the factors leading to the building up of the maternal placenta and to state that these structures are produced independently of any specific action of the ovum, because experimentally they can be produced, without any previous contact with the ovum having taken place. I have not yet succeeded in reproducing Minot's monster cells or the multinucleated glycogen cells. At present, therefore, we can not exclude the possibility that these latter structures may owe their origin to a specific action of the ovum.

It will be of great interest to use these methods for the analysis of the formation of the placenta in other mammals.

3. In my former publication I stated that after extirpation of the ovaries the formation of the maternal placenta takes place only in a small minority of all cases and that in the few positive cases the resulting deciduomata are very small. Since then I have continued these experiments and in a large series I have noted that the only tissue in the ovaries which is concerned in the production of the sensitizing substance is the corpus luteum. Even after extirpation of the corpora lutea small deciduomata may be produced in a small minority of cases; and in one experiment, indeed, I found a pregnancy to be established notwithstanding the absence of the corpora lutea (which was in every case proved by examining the ovaries in serial sections). The few positive results obtained after the removal of the corpora lutea are in all probability to be ascribed to the fact that in my experiments the lutein tissue was removed several days after ovulation and at that period a partial sensitization of the uterine mucosa may very well have taken place already. In future experiments it

will be necessary to remove the corpora lutea or the ovaries very soon after ovulation before the specific substance has been formed, and in such cases no maternal placentas ought to develop after subsequent incision into the uterus.

4. I have, therefore, been able to ascribe a definite function to the corpus luteum, namely, that of supplying a sensitizing substance to the uterus which prepares the latter to respond with the production of the maternal placenta, if an external stimulus of a mechanical nature is added. A number of investigators, especially Born and Fraenkel, believed the corpus luteum to be indispensable for the attachment of the ovum at the surface of or inside the uterine mucosa and consequently also for the initial stages of pregnancy. Furthermore, the periodic function of the corpus luteum was believed to be responsible for menstruation and other sexual processes. No definite proof for these hypotheses, however, has been given so far; and the experimental evidence was, on the whole, unsatisfactory. My investigations led to an exact method of experimentation which permitted us to determine definitely the function of the corpus luteum, namely, that of supplying a substance which sensitizes the uterus and thus enables it to produce the maternal placenta.

5. In order to correlate the functions of the corpus luteum and the formation of the maternal placenta it was necessary to study the growth and the retrogression of the corpus luteum in the guinea-pig. Only a few data of interest may be mentioned here. The corpus luteum in the guinea-pig is formed principally through a transformation of the granulosa cells of the follicle.

6. The formation of the corpus luteum follows the spontaneous rupture of the follicle (ovulation) which usually takes place approximately six to ten hours after copulation. But ovulation with the subsequent formation of corpora lutea may take place independently of a preceding copulation. Such a spontaneous ovulation usually occurs in the mother inside the next ten hours after the young have been born; it also occurs in many cases spontaneously—approximately nineteen to twenty-four days after a preceding ovulation without the presence of a male. But such a spontaneous ovulation without a preceding labor and without a previous copulation does not take place in every case. Under ordinary con-

ditions the corpus luteum grows actively for approximately eighteen days; then a spontaneous degeneration and retrogression sets in. In the case of a concomitant pregnancy, however, the period of retrogression is deferred considerably and only begins sixty days after copulation or later.

7. Although the life and growth of the corpus luteum lasts, therefore, usually eighteen days, and much longer in the case of pregnancy, the uterus is not sensitized during the whole of this period, but only approximately from the second to the ninth days after copulation. If the mechanical stimulus of the uterus is applied after the ninth day, the uterus does not usually respond with the formation of a maternal placenta. This may perhaps be due to the fact that within nine days after copulation the uterus becomes saturated with the sensitizing substance and that, after such a state of saturation has been reached, fatigue sets in and the uterine mucosa becomes unresponsive. It may be that only a dynamic process, namely, the constant addition of the corpus luteum substance, has a sensitizing effect. However that may be, this curious relation between corpus luteum and uterine mucosa exists and is easily interpreted in a teleologic sense in the following manner:

8. We see that the uterus is sensitized approximately three to nine days after copulation. If we wished, therefore, to select the safest period for the egg to attach itself to a sensitized uterine mucosa and to be sure to be welcomed at its new habitat, and to find a responsive environment, we would choose the middle of this period, namely, approximately the sixth day after copulation, and this is precisely the term at which under normal conditions the ovum does begin to enter the uterine mucosa in the guinea-pig.

We have here an example of a highly useful adaptation, most important for the propagation of mammals, and we, furthermore, recognize the fact that this adaptation is based on a biochemical correlation between different organs.

9. In this connection I may briefly mention a few other facts concerning the life-history and the possible function of the corpus luteum. The retrogression of the corpus luteum sets in apparently spontaneously at the period mentioned above; it is not dependent on nor is

it caused by a preceding new ovulation and the formation of a new corpus luteum. The retrogressive changes in the corpus luteum set in even without the previous rupture of a follicle.

On the other hand, in a number of cases I found that an early extirpation of the corpora lutea led to an acceleration of the following ovulation and consequently to an earlier formation of new corpora lutea. This observation suggests that the existence of growing corpora lutea has an inhibiting effect on the growth and rupture of ovarian follicles. Such an inhibiting action does not, however, consist in a mechanical influence exerted by the corpus luteum, inasmuch as the follicles rupture as soon as the retrogressive changes set in in the corpora lutea, although the site of the corpus luteum and, therefore, its mechanical significance has not yet changed at that time. It is, therefore, a justifiable hypothesis, if we assume that the functional, probably chemical activity of the corpus luteum is one of the factors determining the time of the rupture of the follicle and the subsequent formation of the new corpora lutea. Such an influence of the corpus luteum is, however, not the sole determining, but only a concomitant factor in ovulation; it would explain why during pregnancy a further rupture of follicles usually does not take place.

10. At present we do not know why the spontaneous rupture of follicles is followed by the formation of a corpus luteum. Two years ago I carried out a number of experiments, in which at various times, preferably near the period of ovulation, I made incisions into the ovaries, in order to open follicles and thus, if possible, produce corpora lutea experimentally, but in no case did I succeed. The cuts in follicles were not followed by the formation of corpora lutea. These experiments I intend to take up again. Perhaps some variations in the technic may give positive results, but at present it appears as if only at certain periods and under certain conditions the opening of a follicle would lead to the formation of a corpus luteum.

11. Three factors are, as stated, primarily concerned in the experimental production of the maternal placenta: (1) the sensitizing substance of the corpus luteum; (2) the mechanical stimulus exerted directly on the uterine mucosa; (3) the character of the body

fluids, which is more or less specific for each individual of a certain species.

It is, however, possible to make a more far-reaching analysis of these phenomena and to reveal quantitative relations between the causative factors and the size of the deciduomata.

I mentioned above that sometimes after extirpation of the corpora lutea, deciduomata develop, which, however, under those conditions were usually very small. This can best be explained if it be assumed that a relatively small quantity of this corpus luteum substance enables the mucosa merely to form small deciduomata.

In a similar manner incisions made into the uterus inside of the first forty-eight hours lead usually only to the development of small nodules, and probably for the same reason; at that period after application of the mechanical stimulus, when the uterus begins to react, only a relatively small quantity of the sensitizing substance had been secreted and had had time to unite with the uterine mucosa.

12. Definite quantitative relations exist also between the mechanical stimulus and the size of the maternal placenta.

The volume of the deciduomata grows in direct ratio to the area of the uterine mucosa exposed by the incision. The direction of the incision is, therefore, of importance and, furthermore, it is found that the deciduomata are very small in cases in which the incision had been made near the tubal end of the uterus, inasmuch as such an incision renders possible the exposure of only a very small area of the uterine mucosa.

13. Of the three factors concerned in the development of the maternal placenta, the sensitizing substance of the corpus luteum shows the highest degree of specificity, while the mechanical factor is the least specific, inasmuch as its place can be taken by an apparently totally different process, namely, the insertion of the ovum.

It is, therefore, not to be wondered at that even the stimuli always present in normal tissue life have some effect in exciting certain reactions in a uterine mucosa which has previously been sensitized by the specific substance of the corpus luteum. In experiments in which I prevented the ova from entering the uterine

cavity after ovulation I found, indeed, that even without a preceding incision at a certain period after ovulation, when the uterine mucosa has been sensitized, certain predecidual changes take place normally and rhythmically, leading in the guinea-pig to the appearance of many mitoses and to a myxomatous condition in the connective tissue, and in the rabbit to an amitotic division of the epithelial nuclei.

Here, again, a quantitative relation is seen between exciting conditions and the extent of the changes produced. The normal stimuli of tissue life are quantitatively very much inferior to the experimental incisions and to the insertion of the ovum and lead, therefore, only to the beginning of placental changes.

14. The experimental facts just mentioned may explain the difference in the structure of uterine and tubal mucosa in the guinea-pig. The former is very rich, the latter is very poor in cells. Correspondingly we find that the uterine mucosa can be sensitized by the corpus luteum substance, while, as we shall see later, the tubal mucosa in the guinea-pig can not be sensitized.

This process of sensitizing enables the connective tissue of the uterine mucosa to proliferate periodically, to be more or less in a rhythmic condition of growth, while the tubal connective tissue is resting. After cessation of sexual activity the uterine mucosa must become atrophic, being no longer under the influence of the sensitizing substance of the corpus luteum.

These observations enable us, therefore, to correlate structural differences between the mucosa of the uterus and the Fallopian tube with certain dynamic biochemical differences, namely, difference in the ability of certain tissues to combine with the sensitizing substance provided by the corpus luteum.

15. The substance which is produced in the corpus luteum and which sensitizes the mucosa of the uterus has a specific affinity to the uterine tissue. In a number of experiments I made incisions into the peritoneal wall, into the ovaries, into the Fallopian tubes of the guinea-pig, into the subcutaneous tissue, and I transplanted skin in animals at the critical period, but in no case did I find any unusual reaction in these tissues, none of these tissues or organs having become sensitized.

This is especially noteworthy if we consider that apparently the ordinary connective tissue is the same everywhere in the body.

This specific affinity of a certain chemical substance could be explained, however, if we assume that the identity of the different connective tissues of the body does really not exist, or, as an alternative, we could refer the specificity, not to the connective tissue, but to the surrounding epithelium, of which we know that it differs in structure and, therefore, in metabolism from other epithelial structures. The connective tissue would then receive the stimulus only through the intermediate action of some other cells.

16. This specificity which is established experimentally clears up another related problem.

On the basis of many experiments I can state that in the guinea-pig it is impossible to produce at will an extrauterine tubal or abdominal pregnancy. The ovum which after fertilization is prevented from attaching itself to the uterine wall perishes without forming an embryo.

We are now able to state why an extrauterine pregnancy is impossible in the guinea-pig: Neither the tube nor the peritoneal lining nor the ovarian tissues are able to produce the maternal part of the placenta in response to the stimulus of the ovum touching the uterus, and without a maternal placenta the egg is unable to develop.

In man we occasionally do find such a response in the case of tubal pregnancy; here the specificity in the fixation of the corpus luteum substance is less marked than in the guinea-pig.

17. I have already stated in a former communication that it is possible to obtain growth of the decidua in a piece of uterine tissue which is excised and transplanted into the subcutaneous tissue of the same animal. This proves that the formation of the placenta does not stand under the regulative influence of the central nervous system, and probably not of local nerves, it being very unlikely that such peripheral nerves and ganglia cells would functionate after transplantation of a small segment of the uterus. In the large majority of my experiments the pieces were transplanted several days after ovulation; therefore, at a time when the sensitizing of the uterine tissue in all

probability had already taken place. Such experiments, therefore, do not prove that the sensitizing takes place through a chemical agency carried to the uterus through the circulation and not through the nerves. In two cases, however, in which the transplantation was done within the first twenty hours after ovulation and in which, therefore, in all probability the uterine tissue has not yet been sensitized before transplantation small deciduomatous areas formed in the transplanted uterus. This indicates that the sensitizing substance is carried from the corpus luteum to the uterus through the circulation and that it is not transmitted through the nerves.

18. But is it possible to obtain a decidua in the transplanted uterus only after transplantation into the same animal? I have so far not been able to obtain the formation of a well-developed decidua after transplantation into a male guinea-pig. In a large series of experiments I exchanged the uteri in animals which were known to be at the same period after ovulation, in animals therefore, in both of which the sensitizing substance was present. Notwithstanding this equality of conditions there was a notable difference in the results. After transplantation into the same female the number of deciduas formed in the various experiments was greater and the size of the deciduas was larger in the positive cases. These experiments I intend to extend still further. But at present it is very likely that the body fluids are different in the different individuals of the same species and that this difference is of importance for the cell growth and that at least some tissues show a specific adaptation to their individual body fluids and that such an adaptation becomes especially apparent in certain conditions of unusual functional activity. This result is a further confirmation of my former findings, according to which certain tumor tissues remain alive after transplantation into the individual in which they originated, but die after transplantation into other individuals of the same species.

19. We see that in the transplanted uterus a decidua can be produced under the conditions valid in the case of the untransplanted uterus.

Where and from what kind of cells does the decidua form in the transplanted uterus? Do the invading connective-tissue cells of the host tissue become converted

into decidua in contact with the uterine structures? In examining the uterus at various stages after transplantation, it becomes apparent that not only the transplanted glands remain alive, but also the connective-tissue cells in the neighborhood of the glands, and precisely at this place, the deciduomata are formed; we have therefore, sufficient reason for believing that the connective tissue of the transplanted tissue of the host gives origin to the deciduomata—just as in tumor transplantation, sarcoma and carcinomata arise from transplanted cells and a new infection of the host cells does usually not take place.

20. It will not be necessary here to discuss the bearing which these experiments have on the analysis of tissue and of tumor growth, as I have done this at some previous occasions. It may suffice to state that I have here been able to demonstrate the interaction of various sets of factors which all have to participate in a quantitatively determined way at stated periods in order to produce a growth which differs from the ordinary regenerative and bears some resemblance to tumor growth.

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