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13

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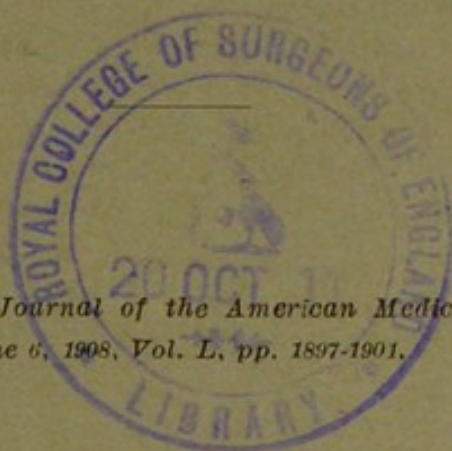
Relation between the Ovaries and the  
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LEO LOEB, M.D.

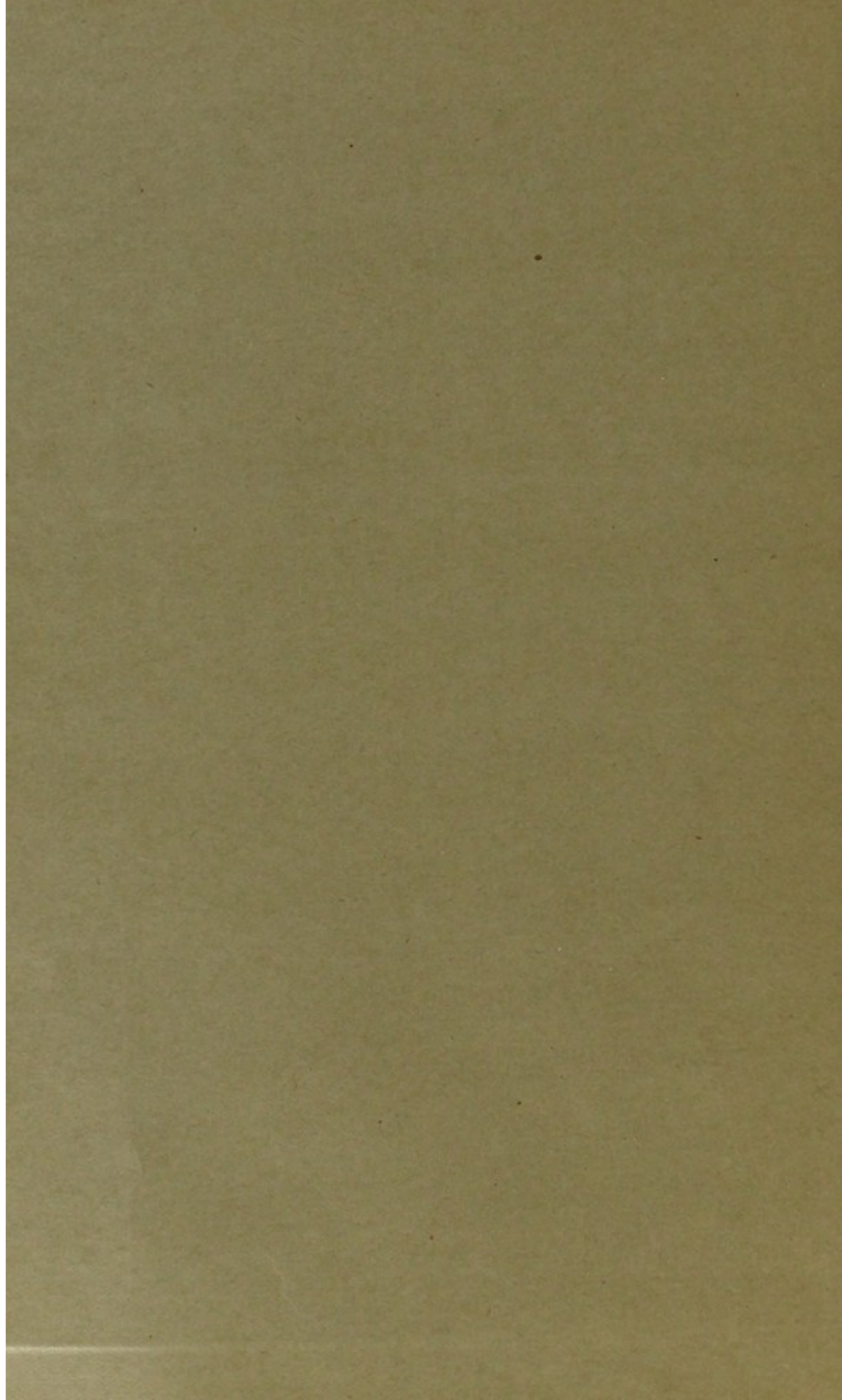
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ONE HUNDRED AND THREE DEARBORN AVENUE.  
CHICAGO.





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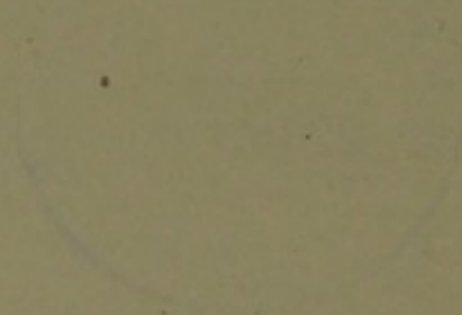
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# THE PRODUCTION OF DECIDUOMATA

## AND THE RELATION BETWEEN THE OVARIES AND THE FORMATION OF THE DECIDUA.\*

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Last summer I announced<sup>1</sup> that if an incision is made into the uterus of a guinea-pig at certain early stages of pregnancy, nodules will be formed that have the structure of the decidua of the guinea-pig. Since then these investigations have been continued. In the following I wish to summarize briefly some of the main results obtained:

1. The operative procedure consisted merely in making transverse and longitudinal cuts in the uterus of the anesthetized animal. In order to obtain a large number of deciduomata it is necessary to make many cuts that advantageously separate the continuity of the uterus in different directions. Under these conditions it is possible to obtain a very large number of deciduomata in the uterus of the guinea-pig.

2. The different stages in the development of these deciduomata were established by microscopic examination. In a number of cases serial sections of the nodules were made. These nodules originate through a proliferation of the interglandular connective tissue of the mucosa. The proliferation takes place through mitotic cell division. Occasionally apparent amitoses can be seen. At first a mass of myxoid tissue is formed underneath the epithelium of the mucosa. This newly-formed layer is very rich in blood capillaries, but extremely de-

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\*The term, "deciduoma" implies that the new formation consists of decidua-like tissue. Those tumors which formerly had been called deciduoma malignum are now almost universally designated as chorionepithelioma malignum.

1. Centralbl. f. allg. Path., 1907, xviii, No. 14.



ficient in glandular structures. The glands of the uterus participate in this proliferation not at all or only to a very slight degree.

As early as twenty-four hours after the operation it is possible to observe the beginning of the proliferative changes. On the third day small myxoid nodules are present, with many mitoses. The size of the cells, especially directly beneath the epithelial layer, is markedly increased. During the following days the cell proliferation continues. After five days small decidual nodules have formed, with many mitoses, which are also present in the endothelium of the blood vessels. The cells beneath the epithelium are very large, but have not yet attained their full size. As in the earlier stages, the blood vessels run at right angles to the myxoid cells. The deciduomata reach their full size ten to eleven days after the operation. Mitoses are still present at that time, but are not so frequent as before. They are usually found, not in the large cells, but in foci of small cells. The cells at this stage have commonly very much increased in size and resemble the decidual cells of the normal placenta. The superficial part of the mucosa frequently becomes necrotic under the influence of the pressure of the nodule, and is cast off. At other places we find inclusions of the surface epithelium in the tumor. This is due to an occasional papillomatous condition of the growth. The epithelium between papillæ may be included in the tumor. In the fully developed deciduomata the structure of the tumor resembles very much that of the ordinary decidua of the placenta of the guinea-pig.

3. After the deciduomata have reached their full growth the cells very rapidly die and the tumor becomes necrotic. Thirteen days after the operation was the latest period at which a few mitoses could still be seen. In one case, as late as seventeen days after the operation, the deciduomata were still alive, but no mitoses were present in these tumors; in the latter two cases the animals were pregnant at the same time. As a rule, fifteen days after the operation the deciduomata have become entirely necrotic and they gradually shrink.

4. I thought it possible that co-existing pregnancy might prolong the life of the deciduomata. In a series of experiments, therefore, I incised only one horn of the uterus, with the hope that in the other horn pregnancy might develop. In only three cases did I succeed. In



two of these, thirteen and seventeen days after the operation, respectively, the deciduomata were still alive; but in the latter case cell proliferation had ceased. In the third case, twenty-one days after the operation, the deciduomata were necrotic, notwithstanding the presence of living embryos in the other uterine horn. Necrosis, therefore, can not be prevented by the co-existence of pregnancy, although it is possible that the life of the deciduomata may be slightly prolonged under these conditions.

5. These deciduomata can not be produced in the uterus of every female guinea-pig. In cases in which they are not obtained the mucosa of the uterus shows merely an edematous, hyperemic condition, without cell proliferation. They can be produced at certain periods after copulation. In eight cases in which the operation was done inside of twenty-four hours after copulation no deciduomata formed. In only one case in which the operation was done eighteen hours after copulation was a trace of decidual tissue detected on microscopic examination.

Nine animals were operated on the second day after copulation. In these animals either no deciduomata developed or those that did develop were very small. In one case the operation was performed three days after copulation, and small deciduomata were found after ten days. Of twelve animals operated on four days after copulation, deciduomata developed in ten. In one case in which the animal was examined twenty days after operation, no deciduomata were found. Possibly, however, a small deciduoma may have been dissolved at a period so long after operation, so that this case can not be fully counted as negative. In the second negative case the animal had been dead a long time before autopsy. This case is probably to be regarded as negative.

Twenty-three guinea pigs were operated on five days after copulation. All of them developed deciduomata. Among eight guinea-pigs operated on six days after copulation seven developed deciduomata. One case was negative. In the latter case the autopsy was made twenty-one days after operation, and the animal had had young ones shortly before the operation. It is possible that in this case also the deciduoma may have disappeared. Thirteen guinea-pigs were operated on



seven days after copulation. Twelve of these developed deciduomata. One case was, perhaps, negative. Microscopic examination is still to be made in this case. This negative result may be explained through the special kind of incision used in this instance. Two guinea-pigs operated on eight days after copulation developed deciduomata. Four guinea-pigs were operated on nine and ten days after copulation, respectively. In one case, in which the operation was done not quite nine days after copulation, pregnancy developed, and simultaneously small decidual nodules were found. Two other cases were negative, and in the fourth case deciduomata developed. In five cases cuts were made into the uterus in more advanced stages of pregnancy, but in none of these did deciduomata develop.

From the fourth to the eighth day after copulation deciduomata almost invariably develop, if the correct incisions have been made. Inside the first day after copulation no deciduomata usually develop. On the second day only very small or no deciduomata develop. On the ninth and tenth days after copulation, again, the formation of deciduomata becomes very uncertain; and it is absent in the later stages of pregnancy. There exists, therefore, a definite curve that indicates the chances for the development of deciduomata after copulation.

The optimum lies between five and eight days thereafter, and this corresponds with the time when the uterus normally responds to the stimulation of the ovum with the formation of a decidua.

6. We see, therefore, that at certain stages after copulation the uterus is able to form a very large number of deciduomata, if it is stimulated in the proper way. Preceding copulation is not, however, necessary for the formation of deciduomata. At certain periods after the condition of heat has passed in animals the uterus likewise responds to the proper stimulation with the production of deciduomata.

Fifteen animals were operated on inside of the next ten days after the period of heat. In twelve of these cases deciduomata developed. In two of these the deciduomata were very small, namely, in the cases in which the animals were operated on very soon after the period of heat (twenty-one to thirty-six hours, respectively).



In the other positive cases the animals were operated on from four to six days after the period of heat. In the three other cases no deciduomata developed after the operation. In one of these the operation was done two days after the period of heat, in another three days thereafter, and in the third five days afterward.

We know that even experiments performed two days after copulation are not always successful; and in the other two negative cases, namely, three and five days after the period of heat had passed respectively, a special method of incision was used. This incision was also used in a few other cases, and did not yield satisfactory results. In six of these fifteen cases the ovaries were examined microscopically in serial sections, and corpora lutea were found to be present.

7. We found that at a later period than ten days after copulation deciduomata did not develop. Correspondingly, we find that if we operate thirteen to sixteen days after the period of heat, deciduomata almost invariably do not develop. Eighteen animals were operated on at this period. Seventeen did not develop deciduomata. In only one case did the deciduomata develop. It is, of course, not impossible that in this case either a mistake may have been made in determining the period of heat, or some complicating factor was added. In four of these eighteen cases, ovaries of which were examined microscopically in serial sections, no corpora lutea were present.

8. The period at which no deciduomata are formed is followed by another period in which the uterus again becomes responsive.

9. We see, therefore, that animals, at certain stages of their sexual life, can form deciduomata without a preceding copulation. Here also we notice the presence of a certain curve, the optimum of which lies approximately at four to nine days after the period of heat. From thirteen to sixteen days the chances for decidual formation are almost nil, and then gradually the uterus seems again to become responsive.

10. The ovaries of six guinea-pigs that had been operated on inside of ten days after the period of heat were examined microscopically in serial sections. They all showed the presence of corpora lutea. In all these animals deciduomata developed. The ovaries of five of the guinea-pigs that had been operated on thirteen to sixteen days after the period of heat were likewise examined in



serial sections microscopically. In four cases no corpora lutea were found. In one case the corpora lutea had been present. At this time the deciduomata, as I stated above, do not develop. The ovaries of three guinea-pigs that, according to the statement of the breeder, had been in the period of heat inside of ten days (but that did not after operation, develop deciduomata), did not on microscopic examination show the presence of any corpora lutea. Four guinea-pigs that had apparently not been in heat for some time were operated on in the usual way. Only one of these developed deciduomata. Eight guinea-pigs in which the period of heat had not been determined previously were taken at random and operated on in the usual way. In these cases, of course, it is possible that a certain number or the majority of the animals may have been in a favorable condition for the development of the deciduomata, but after operation in seven the uterus healed without the formation of deciduomata, and only in one of them did deciduomata develop.

11. These differences between the results obtained after operation on animals from the third to the ninth day after the period of heat, on the one hand, and those obtained with guinea-pigs operated on at other periods, on the other hand, are so striking that we may conclude that the development of the deciduomata depends on a certain condition in the sexual cycle of the animal at the time of operation.

12. In order to obtain a deeper insight into the causes that lead to this peculiar predisposition to the development of deciduomata, several series of experiments were made. It was possible that the contact of the ovum with the mucous membrane might cause the predisposition of the mucous membrane to the development of the deciduomata. This, however, is very improbable, because the deciduomata can develop in horns of the uterus without the corresponding ovaries containing a corpus luteum. It is, furthermore, improbable, because the deciduomata can develop below the seats of pregnancy. I could exclude this hypothesis with certainty in the following way:

One or two days after copulation, before the ovum had passed into the lower part of the uterus, a ligature was applied to the center of both horns. This prevented the ovum from touching the mucous membrane of the



lower half of the uterus. A few days later, the uterus below and above the ligature was incised in the usual way, and in three cases treated in this manner, deciduomata developed both above and below the ligature. We may, therefore, state that the contact of the ovum with the mucous membrane is not necessary for the development of the deciduomata.

13. The second series of experiments that we made in order to clear up the peculiar predisposition of the uterus in certain animals, consisted in the extirpation of the ovaries before the incisions into the uterus were made in guinea-pigs that had been previously copulated. Twenty-nine guinea-pigs were operated on in this way. In twenty-one of them, the incisions into the uterus were made from two to five days after the extirpation of the ovaries. In seventeen of these no deciduomata developed. In one animal there developed only microscopically recognizable deciduomata. Two died prematurely, and one developed an abscess. Of eighteen guinea-pigs, therefore, seventeen were without deciduomata, and one had only a microscopically recognizable deciduoma, although all of them had been operated on at the most favorable time after copulation. In eight guinea-pigs, incisions were made into the uterus immediately after the ovaries had been extirpated, or one day later. In three of them, at most places of incision, no deciduomata developed, and only at one or two places, small microscopic deciduomata were found. In one a somewhat larger microscopic deciduoma developed; the others were entirely free from deciduomata.

From these experiments we may conclude that extirpation of the ovaries in most cases prevents entirely the formation of deciduomata in animals that are operated on at the most favorable period after copulation.

14. In accordance with the results of these experiments it was found that of five guinea-pigs that had been taken from the common stock without any knowledge of the period of heat and whose ovaries had been extirpated, after a subsequent incision of the uterus four did not develop deciduomata. In one case, small microscopic deciduomata were found.

15. In order to rule out the objection that a previous operation had in itself prevented the formation of deciduomata, in three guinea-pigs another series of experiments was carried out, in which the ovaries were



merely pulled out of the wound without being extirpated. In all cases a second operation was followed by the formation of deciduomata.

16. In eight other guinea-pigs that had been previously copulated, the ovaries were cauterized at various places several days before incising the uterus. Six of these developed deciduomata. One died prematurely, and in one case a microscopic examination has still to be made to determine the outcome. We see, therefore, that a previous ovarian operation does not in itself interfere with the formation of the deciduomata, if, after the first operation, the uterus is later incised in the usual way during a second operation.

17. These experiments establish the fact that the presence of the ovaries is responsible for the peculiar predisposition of the uterus at certain periods, which enables it to form deciduomata under the influence of certain indifferent stimuli. The question next to be determined was, whether the influence of the ovaries is transmitted through nerves, or whether we have to deal with the effect of chemical substances secreted by the ovaries. In order to determine this problem I transplanted pieces of the uterus of guinea-pigs into the subcutaneous tissue at the proper time after copulation. It was found that in two cases deciduomata developed in pieces of uterus transplanted into the subcutaneous tissue. This makes it probable<sup>2</sup> that an internal secretion of the ovaries is responsible for the above mentioned predisposition of the uterus to form deciduomata.

18. Certain facts that have been mentioned before suggest that the corpora lutea which are present in the ovaries after copulation, and probably at certain times after the period of heat, represent that part of the ovary that secretes the substance necessary for the development of the deciduomata. In nineteen guinea-pigs, we, accordingly, attempted to burn out the corpora lutea soon after copulation and, at a second operation, the usual incisions into the uterus were made. One of these nineteen animals died too early to be used. Of the others, four developed good deciduomata; but the microscopic examination of the ovaries showed that not all the corpora lutea had been destroyed. In each of these

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2. It is very improbable that such a proliferation in the transplanted uterus would take place under any conditions irrespective of the state of the ovaries. Further experiments will decide these points with certainty.



cases corpora lutea had been left in the ovaries. In the four other cases in which deciduomata were produced, a complete examination of the ovaries has not yet been made. Four other guinea-pigs did not develop deciduomata. Microscopic examination of their ovaries showed the absence of corpora lutea. In one of these four cases one ovary only has so far been examined. In two animals in which only small microscopic deciduomatous areas developed, the corpora lutea were almost entirely destroyed. In four cases no deciduomata developed; but the ovaries have not as yet been examined.

19. In seven guinea-pigs, only one ovary was removed. Five of them developed deciduomata. In two of these cases, the ovaries were examined microscopically and corpora lutea were found in the remaining ovary. In one, no deciduomata developed, and the examination showed that no corpus luteum was present in the remaining ovary. In one case only small doubtful nodules were found, without a microscopic examination of the uterus or ovaries having as yet been made.

20. All these facts show that a certain substance secreted by the ovaries is responsible for the formation of the deciduomata, and make it at least very probable that the corpora lutea represent that part of the ovary which secretes this substance. This latter point, however, can be made certain only by further experiments, which are under way at the present time.

21. A certain substance present in the ovaries is necessary for the production of deciduomata. If, as we found, very small deciduomata can be formed even after the extirpation of the ovaries, it is most likely that a certain amount of this substance is still present in the circulation at the time of the incision into the uterus. We noticed especially the fact that extirpation of the ovaries is followed by the formation of microscopic deciduomata in such cases in which the uterine operation was carried out very soon after the extirpation of the ovaries, and this circumstance speaks in favor of the interpretation just given.

22. The process leading to the formation of deciduomata differs in essential points from the connective tissue proliferation in ordinary wound healing. (a) The production of new cells by mitotic division is incomparably more extensive in the development of the deciduomata. For some time the proliferative energy re-



sembles closely the growth of a malignant sarcoma. (b) Instead of forming mainly connective tissue fibrils, the new cells enlarge and assume more or less the appearance of decidua cells. Scar tissue is not produced. (c) Instead of growing into the wounds and filling the defects, the cells grow upward between the glands of the uterine mucosa and raise the epithelial covering of the uterine mucosa. (d) At a certain stage of the development the whole new formation becomes necrotic.

23. As we stated above, the deciduomata invariably become entirely necrotic twelve to twenty days after operation. This might be due to interference with the circulation. In cases of rapid cell-proliferation the development of the blood vessels does not proceed adequately and frequently we find, therefore, in rapidly growing tumors, areas of necrosis. Such an interpretation can not, however, explain the invariable necrosis of the deciduomata at a certain period of their development. Such a necrosis takes place quite independently of the condition under which they develop; it is always complete, even if at certain places the blood vessel supply is quite sufficient. This necrosis must be compared to the general disappearance of the corpus luteum after the causative factors leading to its development have ceased to exist. We saw that certain substances prepare the uterine connective tissue cells to proliferate and to form decidua. It seems, therefore, evident that the same substances which prepared the cells for the cell-proliferation are necessary for their life. The cells die, as soon as the "growth substances" have disappeared.

24. A problem of great interest which at the present we merely wish to state as such, is the limitation of the proliferation to the connective tissue of the uterus. The subserous or subcutaneous connective tissue which is likewise incised, does not form nodules. Does that depend on a physico-chemical difference of connective tissue cells in different parts of the body, or does it depend on the specific relation of connective tissue cells to certain differentiated cells in their neighborhood, in this case on the influence of the uterine epithelium? The latter interpretation seems to be the more probable one.

25. If as we saw, a certain "internal secretion" of the ovaries is of great significance for the production of deciduomata, we are justified in concluding that it has the same significance for the formation of the placental decidua. The early extirpation of the ovaries and not



unlikely the early destruction of the corpora lutea interferes with the normal course of pregnancy, because the substance which is necessary for the development of the decidua is absent.

26. Towards the end of the first week following copulation the ovum implants itself into the uterine wall and causes the decidua formation which is necessary for embryonic production. We have here an instance of an especial adaptation. The uterus responds at the proper time in the proper way to insure the development of the embryos. Our experiments permit us a further analysis of this adaptive process. We saw, first, that an ovum is not necessary for the stimulation of the uterine mucosa—that we have to deal with a two-fold cause; second, that the uterus has the potential power to produce many more placentas than it can ever be called on to produce under normal conditions; third, that the stimulus of the ovum alone would probably be powerless without secretion of the predisposing substance by the ovary. It is especially noticeable that the action of this “preparing” substance becomes potent at the time when the ovum is ready for implantation; but as we saw, even without copulation this substance is secreted and acts on the uterus.

27. In conclusion I wish to point out a certain analogy which exists between these artificially produced deciduomata and a variety of multiple tumors that are limited to certain organs, as for instance, multiple fibro-neuromata, enchondromata, symmetric lipomata, or adenomata of the intestinal mucosa; they might be called multiple systemic tumors. The deciduomata represent a type of new formations which I designated “transitory tumors.” If the substance were secreted by the ovaries continuously, instead of intermittently, the tumors would lose their transitory character and would become permanent new growths. In the case of the systemic tumors and of the deciduomata we have to deal with multiple benign tumors of a more or less transitory character affecting one organ or one tissue. We know that the origin of the deciduomata depends on two sets of conditions: (a) That a predisposing chemical substance be produced by a certain organ; and (b) that such a substance having been produced, indifferent stimuli, for instance, traumatisms, are sufficient to produce the tumors. Clinical observation makes it likely



that certain tumors, as for instance, sarcomata, have at times been caused by traumatisms. Experimentally, attempts to produce tumors through traumatism or through long continued irritation have never been successful. It may be suggested that such attempts could have been successful only if the necessary "preparatory" substance had been secreted prior to the action of the indifferent stimuli.

As stated above, the new formations which we produced differ in several essential aspects from regenerative proliferation of the connective tissue during wound healing. Furthermore, the processes leading to the formation of deciduomata have nothing in common with so-called inflammatory reactions. Neither do they represent an example of compensatory hypertrophy although there exist cases of compensatory hypertrophy, which apparently almost imperceptibly merge into adenomatous new formations, just as certain hypertrophic processes taking place in the connective tissue in connection with wound healing lead to the production of keloids, which are usually classed among the fibrous tumors. If we injure the perichondrium near the ear cartilage the regenerative processes setting in may lead to the formation of small nests of cartilage. A similar result can be obtained, if we transplant pieces of perichondrium. It is very doubtful whether we should call such small cartilaginous areas, "chondromata." But let us assume that under the influence of an abnormal internal secretion, which suddenly comes into play, the connective tissue of the mucosa of the intestines began to proliferate at circumscribed areas in the neighborhood of places of injury, raising up the epithelium and forming relatively large polypoid out-growths covered by epithelium, we should be much tempted to regard such multiple polypoid out-growths as related to tumor formation, especially if the connective tissue of the mucosa showed a metaplasia into another variety of connective tissue. A sharp line of demarcation between regenerative and tumorous new formations does not exist. We are inclined to use the term "tumor" if the cell proliferation is very marked and limited to a certain circumscribed area and leads to a well defined formation and if—and this is an essential point—we can not entirely account for the tissue proliferation by including it among the regenera-



tive or inflammatory reactions—if there exists an unknown factor leading to the cell growth.

In the case of deciduoma we have found the definite cause for its formation; and it is very desirable to emphasize certain similarities between the deciduoma and various other tumors in order to indicate the possible presence of predisposing “preparing” substances, as the unknown cause of certain tumors. Given such a “preparing” substance, otherwise indifferent stimuli would be sufficient to excite the potential proliferative energy of the tissues. The fact that the deciduomata degenerate as soon as the “preparing” substance ceases to be active is no valid reason for denying the designation “tumor” to these new formations. In order to indicate the ephemeral character of such new formations they may be called, “transitory tumors.” Even carcinomata may retrogress spontaneously. As I have pointed out in another paper,<sup>3</sup> the presence of “preparing” substance can only explain the formation of a “transitory tumor” or at the best, of a tumor that grows indefinitely in the same individual in which it originated, but it can not explain the growth of a tumor which can be transplanted into many other individuals in which such a “growth” substance is not likely to be present. In order to explain on such a basis the inoculability of tumors we should have to assume the hereditary transmission of an increased energy of growth to the following generations of tumor cells which thus would be able to continue to proliferate without the further presence of the growth substance in the inoculated animal. The possibility of such a transmission into later generations has not yet been established. Until such a proof has been given we must assume that transplantable tumors carry with them in the tumor cells or in their direct neighborhood the stimulus which enables them to proliferate in a new host. But it is quite possible that a non-transplantable tumor which originated through the action of a “preparing” substance may grow very rapidly and be, therefore, malignant. Transplantable tumors, on the other hand, do not need to be very malignant. As I have pointed out,<sup>4</sup> the degree of inoculability and energy of

3. Über einige Probleme der experimentellen Tumorforschung, Ztschr. f. Krebsforsch., 1907, v, p. 17.

4. Über einige Probleme der experimentellen Tumorforschung, Ztschr. f. Krebsforsch., 1907, v, p. 18.



tumor growth are two distinct properties which do not need to be associated in the same tumor. But the transplantability of tumors depends, in all probability, not only on the presence of a permanent stimulus in or near the tumor cells, but on some other factors, as yet unknown. The presence or absence of such secondary factors might determine the inoculability or non-inoculability of a tumor, even if the essential cause in the tumor formation was the same in both cases.