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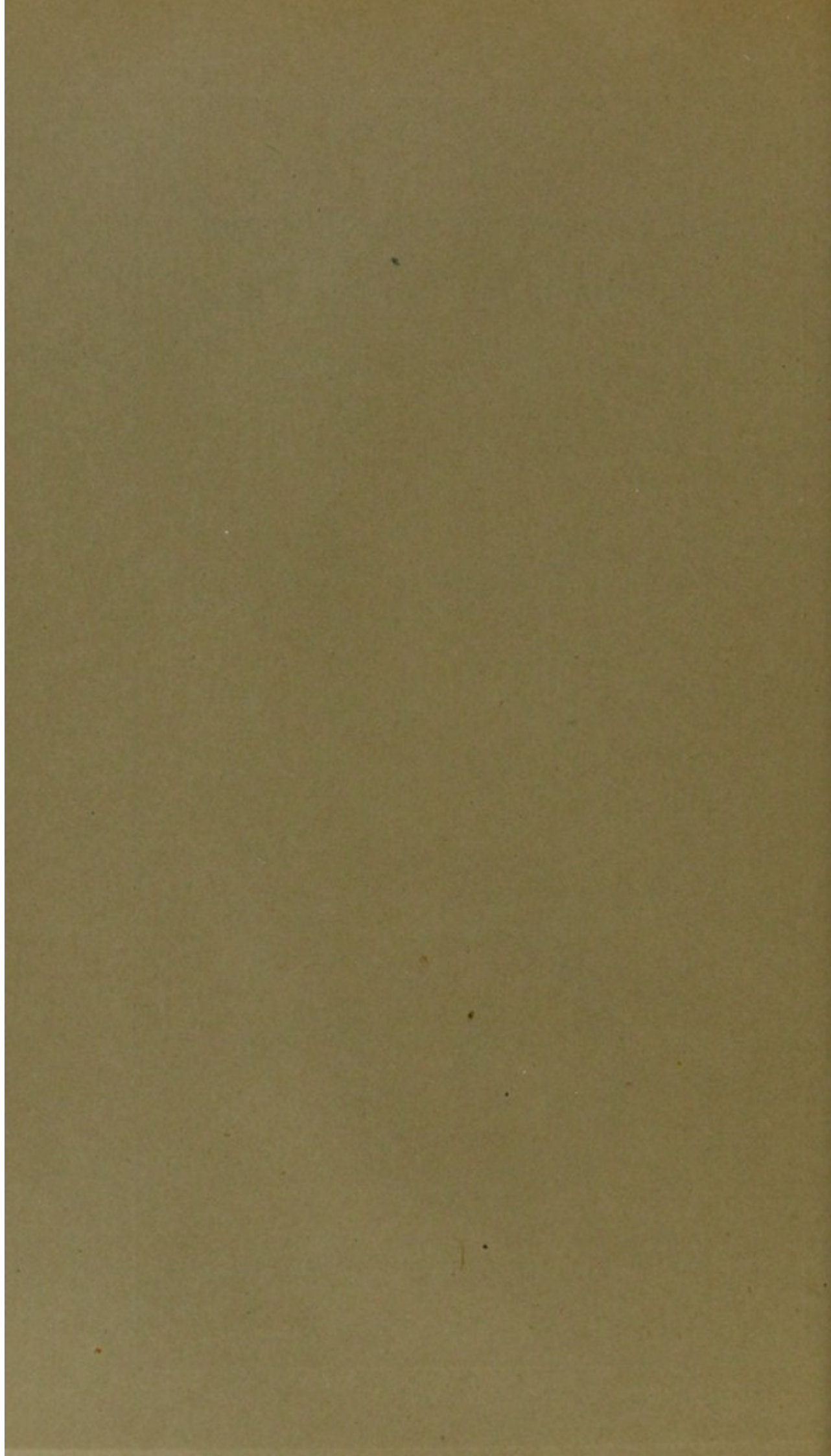
The Formation of the Corpus Luteum in the Guinea-Pig.

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THE FORMATION OF THE CORPUS LUTEUM
IN THE GUINEA-PIG.*

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HISTORY OF RESEARCH.

Three considerations make it desirable to undertake a detailed study of the development of the corpus luteum of the guinea-pig.

1. Although a number of very careful investigations on the development of the corpus luteum have been published within the last ten years, there are a number of essential points about which different writers still disagree. It is not necessary to give a review of the literature on this subject, as this has been done repeatedly within recent years.¹ In regard to the development of the corpus luteum of the guinea-pig, there exists a short paper of Belloy,² who does not give distinct statements in regard to the age of the different corpora lutea which he describes. His results are in some important points opposed to the results obtained in other animals by different investigators. The most recent paper on the development of the corpus luteum which refers, in part at least, to the guinea-pig is by Jankowski,³ who states that the corpus luteum is formed by theca interna and that the granulosa disintegrates after the

* From the Pathological Laboratory of the University of Pennsylvania, on grant of the committee of scientific research.

1. I refer especially to the very complete reviews of Sobotta in the *Ergebnisse d. Anatomie u. Entwicklungsgeschichte*, vol. viii, 1898, and vol. xi, 1902, and to the paper of F. G. Clark, "Ursprung, Wachstum u. Ende d. corpus luteum nach Beobachtungen am Ovarium des Schweins und des Menschen. *Arch. f. Anat. u. Physiol. Anat. Abteilung*, 1898.

2. G. Belloy: "Recherches sur l'origine des corps jaunes de Fovaire chez le rat et le cochon d'Inde, *Comptes rendus de l'Association des Anatomistes*," Paris, 1899.

3. J. Jankowski: "Beit. z. Entstehung d. corpus luteum d. Säugethiere." *Archiv. f. mikrosk. Anat.*, 1904, vol. lxi.

rupture of the follicle. His conclusions are based on insufficient evidence, as he has not examined a consecutive series of ovaries.

2. Former investigations into the normal and pathologic anatomy of the ovaries⁴ made it desirable to determine the origin of the cells which are characteristic of the corpus luteum. Similar cells can be found in certain pathologic new formations of the mammalian ovary. For an understanding of the processes leading to those new formations a study of the development of the normal corpus luteum was desired.

3. The formation of the corpus luteum represents a very interesting instance of growth, which constitutes an apparent transition between the processes found in wound healing and between processes observed in tumor growth. The structures recently described by me in the ovary of the guinea-pig show a still closer resemblance to "transitory tumors." The study of the development of the corpus luteum in the guinea-pig is, therefore, of a general pathologic interest.

MICROSCOPIC EXAMINATION OF OVARIES.

Sixty ovaries of thirty, mostly (about three months old), guinea-pigs, were used and cut into serial sections. Zenker's fluid, paraffin and celloidin, hematoxylin and eosin were used. At certain stages, which were of greater importance, more ovaries were investigated than at others.

Copulation was observed and the ovaries were used at the following periods after copulation: Six hours, $7\frac{1}{4}$ hours, 9 hours (two guinea-pigs), 10 hours, 11 hours, $11\frac{1}{2}$ hours, 12 hours (two guinea-pigs), $12\frac{1}{4}$ hours, $12\frac{1}{2}$ hours, $14\frac{3}{4}$ hours, 15 hours, 17 hours 50 minutes, 22 hours, 24 hours, 25 hours 50 minutes, 28 hours, 30 hours 50 minutes, 32 hours 20 minutes, 34 hours, 36 hours, 38 hours, $49\frac{1}{2}$ hours, $50\frac{1}{2}$ hours, 60 hours, $74\frac{1}{2}$ hours, $77\frac{1}{2}$ hours, $100\frac{1}{2}$ hours, 127 hours.

1. *At Six Hours After Copulation* (Celloidin).—No ruptured follicle is visible.

2. *At Seven and One-Quarter Hours After Copulation* (Celliodin).—Place of rupture is visible. Granulosa is pre-

4. L. Loeb: "Ueber eine aus Luteingloebe Gewebe bestehende Neubildung in dem Ovarium eines Kalbes." *Virchow's Archiv.*, vol. cixvi, 1901. "On Progressive Changes in the Ova in Mammalian Ovaries." *Jour. Med. Research.* 1901, vol. vi. "Ueber hypertrophische Vorgänge bei der Follikelatresie, etc." *Arch. f. mik. Anatomie u. Entwicklungsgeschichte*, vol. lxxv, 1905.

served. In some of the granulosa cells karyorrhexis is present. Most of the cells are well preserved. Only very little extravasated blood is found in the ruptured follicle. Theca interna and granulosa can easily be distinguished. Theca interna is hyperemic. The granulosa cells are long drawn out. This guinea-pig was born a short time before copulation.

3. *At Nine Hours After Copulation* (Celloidin).—Two corpora lutea are present in one ovary. The place of rupture is visible. The lumen of the cavity persists. In one of the corpora lutea a part of the granulosa penetrates through the place of rupture into the abdominal cavity and lies on the germinal epithelium. *Liquor folliculi* is still present and it is drawn out in fibers. The granulosa is well preserved, only near the place of rupture the covering of the granulosa is very imperfect. Mitoses can not be seen in the granulosa cells. Some of the granulosa cells which have been lying free in the central cavity are karyorrhectic. Mitoses are present in the theca interna, which is hyperemic. At most places the demarcation between granulosa and theca interna is not sharp. At some places, however, the granulosa is somewhat detached from the theca interna and both layers can be easily distinguished. No blood is present in the ruptured follicle, with the exception of the immediate neighborhood of the place of rupture. Theca interna and granulosa form several folds. The granulosa cells are drawn out in the direction of the place of rupture. The theca interna cells are likewise drawn out at some places. Polynuclear leucocytes are present in the theca interna.

4. *At Nine Hours After Copulation* (Paraffin).—Ovaries are hyperemic; no ruptured follicle is present. Three old corpora lutea are visible.

5. *At Ten Hours After Copulation* (Paraffin).—A small cavity is preserved in each of the ruptured follicles. *Liquor folliculi* is present in the cavity. Polynuclear leucocytes are found in the central cavity. The granulosa is well preserved. The cells are partly vacuolar. Some of the central granulosa cells are karyorrhectic. The large majority of the granulosa cells are well preserved. The blood vessels of the theca interna are very much dilated. They contain polynuclear leucocytes. At some places between the vessels large cells are found which present the same appearances as granulosa cells. No mitoses can be seen in the granulosa cells. Mitoses are present at the borderline between theca interna and granulosa; they are probably situated in the interna cells. Granulosa and theca interna form folds.

6. *At Eleven Hours After Copulation* (Paraffin).—The place of rupture of the follicle is open. The corpus luteum is not prominent over the surface of the ovary. A small central cavity is present. In a few sections a few red blood corpuscles can be seen in the central cavity. The granulosa is well preserved. Many granulosa cells, especially the centrally situated

cells, show karyorrhexis. Some of the cells are vacuolar. Mitoses are not visible in the granulosa. The theca interna forms protrusions into the granulosa at some places. The blood vessels of the theca interna are very much dilated. Some of the granulosa cells are horizontally arranged (parallel to the theca interna); in some places, however, this arrangement does not exist. The interna cells may assume a polygonal shape with a round or oval nucleus. Such cells which are found around the blood vessels can not be distinguished from granulosa cells. Mitoses can be found in the theca interna cells. The line of demarcation between granulosa and theca interna is not sharp. (Two ruptured follicles.)

7. *At Eleven and One-Half Hours After Copulation* (Paraffin).—Two ruptured follicles. Place of rupture is still open; a small cavity is present. The opening at the place of rupture is very narrow. The follicle is very little prominent over the surface of the ovary at the place of rupture. The granulosa is well preserved. The granulosa cells are partly vacuolar. Cells of the inner half of the granulosa are drawn out into long threads. The nuclei in these cell threads become partially dissolved. A mitosis can be seen in the granulosa near the place of rupture. The direction of the spindle corresponds to the traction which is exerted toward the place of rupture. At one place two parallel rows of fusiform cells are seen extending into the granulosa from the theca interna. Mitoses are present in the theca interna near the border of the granulosa. The line of demarcation between theca interna and granulosa is not sharp, and some of the mitoses may therefore possibly belong to granulosa cells. Mitoses are present in the theca interna near the blood vessels and also at the border between theca interna and externa. Mitoses seen in the interna belong in part to dividing endothelial cells of capillaries. The theca interna cells may be very large, and those cells can not be distinguished from granulosa cells.

8. *At Twelve Hours After Copulation* (Celloidin).—Place of rupture is still visible; the cavity of the ruptured follicles preserved. Liquor folliculi is drawn out into fibers and some granulosa cells are drawn out in the same direction; the granulosa is well preserved. Hemorrhages are present in the tissue near the place of rupture. No mitoses are visible; the theca interna is very hyperemic.

9. *At Twelve and One-Quarter Hours After Copulation* (Paraffin).—Three ruptured follicles are present. The place of rupture is still open. The central cavity is preserved. Liquor folliculi (or a viscid fluid of a similar character) is present. In one follicle this fluid protrudes through the place of rupture. The red viscid mass in the cavity is at least in part produced through the disintegration of the inner granulosa cells, the nuclei of which may become dissolved. The granulosa cells of the inner layer can be drawn out into long fibers

in which the nuclei may disappear. In the whole, the granulosa is well preserved, although it is in part vacuolar. Karyorrhetic cells are visible in the central part of the granulosa. A number of mitoses can be seen in the granulosa cells, in the outer, middle and inner layers of the granulosa. The diasters are arranged according to the direction in which the cells are drawn out. In the monaster stage the chromatin is sometimes drawn out in the same direction. In most places a sharp line of demarcation exists between the granulosa and the theca interna. Especially when the blood vessels and cells of the theca interna are running radially toward the granulosa it is difficult to determine where the granulosa begins. The distinction is easier when they are arranged in a horizontal direction. At places the line of demarcation between the two layers is still visible. Mitoses are present at the border between the two layers, and it is sometimes impossible to decide with certainty whether the mitoses belong to granulosa or to theca interna cells. The blood vessels are especially dilated near the place of rupture. Many mitoses are present in the interna. Some belong to endothelial cells of capillaries; others are found in cells near the blood vessels. Sometimes the central part of such a cell is in contact with the capillary, although the peripheral parts of the cell are removed from the vessel wall. It is frequently impossible to decide with certainty whether or not we have to deal in such cases with endothelial cells. The cells of the theca interna can be large and indistinguishable from the granulosa cells. Mitoses can also be present in endothelial cells of the blood vessels of the theca interna.

10. *At Twelve and One-Half Hours After Copulation (Paraffin).*—Place of rupture is still visible, but the follicle is no longer open. The granulosa cells of the opposite sides are in close contact; in this way the mouth of the follicle is closed. The defect in the granulosa at the place of rupture is repaired by the close attachment of the granulosa cells at the place of rupture. The ruptured follicle forms a little prominence over the surface of ovary at the place of rupture. A small cavity is present in the closed follicle. The granulosa cells are in part vacuolar. The nuclei of some of the inner granulosa cells become karyorrhetic, and some cells become dissolved. In many places the theca interna and granulosa are not distinct; the theca interna cells are large. At other places the line of demarcation is clear. The endothelial cells of the capillaries of the theca interna may become large and round. Mitoses are present in theca interna cells. Mitoses are also present in theca externa cells and in endothelial cells of the blood vessels of the theca externa. Blood vessels have not yet entered the granulosa.

11. *At Fourteen and Three-Quarter Hours After Copulation (Paraffin).*—Two ruptured follicles are present. The follicles

are closed merely through the granulosa. A small cavity with a little granular matter is seen in the center of the follicles. Many polynuclear leucocytes are present in the central cavity. A number of cells become dissolved in the central cavity. Near the place of rupture dilated blood vessels and lymph vessels are visible. Extravasated blood is also present in the connective tissue near the place of rupture. The granulosa is well preserved; its cells are partially drawn out; no blood vessels and connective tissue can be seen in the granulosa. The line of demarcation is visible between granulosa and theca interna at some places, not at others. Theca interna cells are in part large and polygonal. The blood vessels of the theca interna begin to assume a radial arrangement. At such places the cells of the theca interna and granulosa present frequently the same appearance, and the theca interna and granulosa can therefore not be distinguished. At other places the blood vessels of the theca interna are arranged horizontally, and here theca interna and granulosa can be distinguished. Mitoses are present in different parts of the theca interna near the blood vessels. When they are situated at the borderline between theca interna and granulosa, it is difficult to say to what kind of cells these mitoses belong. A number of the endothelial cells of the capillaries of the theca interna are much swollen, and it is sometimes difficult to determine whether or not a mitosis seen in the immediate neighborhood of a capillary belongs to such an endothelial cell. Many blood vessels of the theca interna are much dilated. The leucocytes seen in the interna stain frequently strongly red with eosin; the polynuclear leucocytes nearer the central cavity take less eosin.

12. *At Fifteen and One-Quarter Hours After Copulation (Celloidin).*—The follicles are closed by granulosa. Connective tissue has not yet regenerated at the place of rupture. A small cavity is present in the center of the follicles. The central mass which stains red with eosin is in part produced by disintegrating granulosa cells. Very little or no blood is present in the central cavity; a few leucocytes are, however, visible in the central cavity. Small hemorrhages may be found in the connective tissue near the place of rupture. The granulosa is well preserved. A few cells are disintegrated in the center. No vessels are visible in the granulosa. The borderline between the granulosa and the theca interna is wavy. Where the interna forms a fold its blood vessels are dilated; they are also dilated near the place of rupture. Mitoses are present in the theca interna, and at the borderline between the theca interna and granulosa. At some places a sharp line of demarcation exists between the theca interna and granulosa; at others no sharp line is visible. The theca interna is partly also drawn out and its blood vessels are dilated.

13. *At Seventeen Hours and Fifty Minutes After Copulation (Celloidin).*—The ruptured follicles are closed by granulosa

and by a homogeneous mass which stains red with eosin. Polynuclear leucocytes are present in this mass. The cavity of the follicle is small and does not contain blood. The follicle is somewhat prominent over the surface of the ovary. The lymph vessels in the albuginea near the place of rupture are dilated. In the inner zone of the granulosa there is a little karyorrhexis present. A part of the central granulosa cells are long drawn out and produce fibers when they disintegrate. No blood vessels or connective tissue can be seen in the granulosa. A part of the granulosa protrudes into the cavity. On the whole, the granulosa is well preserved, and mitoses can be seen in different parts of the granulosa. The boundary line between the granulosa and theca interna is wavy. The demarcation between these two layers is not sharp, neither is the theca interna sharply separated from the theca externa. Mitoses are present in the interna, in the endothelial cells of blood vessels as well as near the blood vessels. Two ruptured follicles are seen.

14. *At Twenty Hours After Copulation (Paraffin).*—A small cavity lies in the ruptured follicle. The place of rupture is closed by a red staining homogeneous mass. Near the place of rupture extravasation of blood is seen in the connective tissue and the lymph vessels are dilated. Old corpora lutea are present in both ovaries. The size of the granulosa cells is about the same as fifteen hours after copulation. The granulosa presents a vacuolar appearance. No blood vessels or connective tissue are visible in the granulosa. At many places no sharp line of demarcation exists between the theca interna and granulosa. At others a layer which is very poor in nuclei separates both layers. The cells of the theca interna frequently can not be distinguished from the granulosa cells, and at some places the interna seems to have disappeared. Mitoses are present in cells of the theca interna and in endothelial cells of its blood vessels. At some places the latter take a radial direction toward the granulosa. At the border between theca interna and granulosa mitoses can be seen. In this region some cells show karyorrhexis. Near the place of rupture mitoses are also visible in the theca interna. Mitoses are likewise present at the border between theca interna and externa. Mitoses are, furthermore, found in endothelial cells of blood vessels of the theca externa near the place of rupture, at a place where many large capillaries are seen, which are in part perhaps newly formed.

15. *At Twenty-two Hours After Copulation (Paraffin).*—Two ruptured follicles are closed by cells which are large and resemble the granulosa and large theca interna cells. Capillaries are seen in this tissue. Spindle-shaped cells cover the large cells. The spindle cells may be either connective tissue cells or regenerating cells of the germinal epithelium. Mitoses are seen in spindle cells as

well as in the large cells and in the capillaries and in the connective tissue of the albuginea near the place of rupture. In the connective tissue near the place of rupture red blood corpuscles are still present. The central cavity of the new follicle begins to enlarge; it is larger in the one follicle than in the other. Both corpora lutea are protruding over the surface of the ovary. No boundary line is visible between granulosa and theca interna; the cells of both layers show the same character. The number of cell layers and the size of the cells of the corpus luteum are not markedly different from those of former stages. The central granulosa cells are still vacuolar. From the neighborhood of the blood vessels of the former interna tubes are formed by two parallel layers of drawn-out, spindle-shaped cells, and extend into the former granulosa about half way from the central cavity or still further. The direction of these tubes is radial. In the endothelial cells of the former theca interna, which are often very large, mitoses are present; mitoses are likewise seen in cells lying directly in contact with the endothelial cells. In the theca interna and externa many leucocytes are seen, which stain strongly with eosin. The blood vessels of the theca interna and of the surrounding connective tissue are much dilated. Some old corpora lutea are present in these ovaries.

16. *At Twenty-four Hours After Copulation* (Celloidin).—A small prominence of the follicle is visible at the place of rupture. The follicle is closed by the granulosa; the granulosa at the place of rupture is covered by cells, which may be either connective tissue cells or cells of the germinal epithelium. The germinal epithelium, however, has certainly not yet completely regenerated. Only little blood extravasation is present at the place of rupture. The central cavity of the follicle is closed. The theca interna and granulosa can not very well be distinguished. Mitoses are present at the border between the two layers, and it is difficult to recognize to which of those two layers the mitoses belong. Blood vessels are only found in the outer zone of the follicle; they are not very dilated. No connective tissue or blood vessels are visible in the former granulosa.

17. *At Twenty-five Hours After Copulation* (Paraffin).—The cavity of the corpus luteum is much larger. Pressure is exerted on the cells which line the cavity; they are flat. The number of cell rows or the size of the cells is not markedly changed. No line of demarcation between the granulosa and theca interna can be seen. The blood vessels of the theca interna are much dilated. Mitoses are present in the endothelial cells of the capillaries. Mitoses are also present in the long-drawn out cells which invade the granulosa. The tubes formed by these cells are occluded presumably by the pressure which is exerted by the fluid present in the central cavity. No blood is to be found in these tubes. The pressure exerted from the

central cavity is probably also the cause that ~~these~~ these rows of new-formed cells do not run in an absolutely radial direction, but in a more oblique way.

18. *At Twenty-eight and One-Half Hours After Copulation* (Celloidin).—Ruptured follicles are prominent over the surface of the ovary at the former place of rupture. The place of rupture is covered by large cells (former granulosa and interna cells) with blood vessels. Spindle cells are also present, which perhaps are regenerating cells of the germinal epithelium. Near the place of rupture mitoses are seen in the albuginea and also in the endothelial cells of the blood vessels. The central cavity is not large and contains a red-staining, granular substance. No line of demarcation between granulosa and theca interna is visible. In the direct neighborhood of the theca interna of the developing corpus luteum, blood vessels are dilated and mitoses are present in the endothelial cells. The capillaries in the peripheral part of the corpus luteum (in the former theca interna) send out processes toward the central cavity. These capillaries do not yet penetrate deeply into the corpus luteum. Mitoses are present in the endothelial cells of these capillaries and also in many cells in the direct neighborhood of the capillaries. It is sometimes difficult to decide whether or not such mitoses belong to endothelial cells. Mitoses are also present in the former granulosa, in cells which have the appearance of granulosa cells, which may nevertheless be immigrated cells. Besides distinct capillaries, we see spindle-shaped cells penetrating into the granulosa. These spindle-shaped cells may in part at least also represent advancing endothelial cells of capillaries. At some places the tubes formed by the ingrowing spindle-shaped cells (endothelial cells) may extend much further into the corpus luteum. The central part of the corpus luteum, near the central cavity, is free from such cells. The direction of the ingrowing cells is a radial one. In the outer part of the developing corpus luteum many polynuclear leucocytes which stain deeply with eosin are seen. Some karyorrhexis and karyolysis are visible in the cells lying in the central cavity. Three developing corpora lutea.

19. *At Thirty-one Hours After Copulation* (Paraffin).—The corpora lutea are closed; the place of rupture is covered by large cells of the character of granulosa and the large theca interna cells and by regenerating cells, which are probably derived from the germinal epithelium. In one of the developing corpora lutea the follicle forms a marked prominence over the surface of the ovary, the prominence consisting mainly in connective tissue rich in blood vessels. The central cavity has increased in size, cells which have the appearance of detached granulosa cells, which show karyolysis and become dissolved are visible in the central cavity; occasionally a string of cells becomes necrotic. A marked tension seems to exist

in the central cavity. The cells lining this cavity are stretched very markedly. No distinction exists between granulosa and theca interna. Dilated blood vessels are visible at the border between theca externa and the developing corpus luteum. In the outer part of the latter, capillaries are seen. Mitoses are present in the endothelial cells of these vessels, as well as in the vessels at the border of the theca externa. Mitoses are also seen in cells in the close neighborhood of the capillaries. From these capillaries or from their neighborhood tubes are growing deeper into the former granulosa. In two of the developing corpora lutea these tubes remain open until they almost reach the central cavity; in the third they are not open so far. Mitoses are also seen in the cells of these tubes. The latter do not run entirely radially, but obliquely, and they frequently turn in a horizontal direction at the inner end. At one place a cell tube, which is without doubt a blood vessel, penetrates almost to the central cavity. In that corpus luteum in which the cell tubes remain open, the course of the latter is more radial than in the other corpus luteum. One old corpus luteum is present.

20. *At Thirty-two and One-Half Hours After Copulation (Paraffin).*—The cavities found in this corpus luteum are very similar to those seen in the corpus luteum of the preceding stage. The developing corpus luteum is closed mainly through the granulosa cells, which occlude the former place of rupture. They are covered by cells, which are probably derived from the germinal epithelium. The similarity between the large granulosa cells and the regenerated cells of the germinal epithelium, which probably cover the wound, is, however, so great that it is impossible to distinguish with certainty between these two kinds of cells. Some of the covering cells degenerate. The connective tissue near the place of rupture is very rich in enlarged blood vessels, whose endothelial cells are frequently seen to be in mitotic division. Some extravasated blood can also be found here. The corpus luteum is not prominent in this ovary; in this case a retraction of the ovary is found at the former place of rupture. The central cavity is large and it contains a little blood; some cells are disintegrating in the central cavity. Granulosa and theca interna can not be distinguished. Mitoses are found in cells of theca externa and in endothelial cells of the capillaries. At places the blood vessels of the theca externa are very much dilated and the surrounding tissue is edematous. The cells which surround the central cavity are arranged in a concentric manner. The central granulosa cells are vacuolar and small; it appears as if the exudate present in the central cavity, by means of the pressure exerted by it, separated these cells. Cell tubes are extending from the periphery of the developing corpus luteum into the central part. In part they almost reach the central cavity. Others turn around at different heights. Some of these tubes

are wide open; most of them are closed and seem to be compressed. In one developing corpus luteum they run in a radial direction, in the other their direction is more oblique. Mitoses are present in the endothelial cells of the blood vessels and in the cell tubes, which in all probability represent new-formed capillaries, although some of them may be ingrowing connective tissue. The cells of these tubes which are in mitotic division are sometimes found in the lumen of the tube; in other places at the outer side, and it is not always possible to exclude with certainty that a neighboring cell is in mitotic division. In the developing corpus luteum other mitoses are visible without any apparent connection with the capillaries. The capillaries in the outer part of the corpus luteum are much dilated, and they run in horizontal direction. An old corpus luteum is present.

21. *At Thirty-four Hours After Copulation (Paraffin).*—The place of rupture is covered by germinal epithelium, which, however, does not yet provide a perfect covering. The follicle forms a small prominence at the former place of rupture. The blood vessels near by are dilated. At one place the blood vessels of the theca externa are dilated and the tissue around these vessels is edematous. The capillaries in the neighborhood of the developing corpus luteum are dilated. In the capillaries of the young corpus luteum mitoses are present, even near the central cavity. At various points cell tubes, which are probably newly formed capillaries, give off branches; the cell tubes may split in several branches. The cells lining the central cavity are flat, perhaps as a result of the pressure exerted by the fluid in the central cavity.

22. *At Thirty-six Hours After Copulation (Celloidin).*—The central cavity is much enlarged. The fluid filling it seems to exert a strong pressure on the corpus luteum. The corpus luteum represents a vesicle with a relatively thin wall traversed in a radial direction by cell tubes and spindle-shaped cells, which latter, perhaps, are connective tissue cells. Mitoses are frequent, especially in the outer part of the corpus luteum; they are, however, also present in the inner half near the central cavity. They can be found in endothelial cells and in the spindle-shaped cells of the corpus luteum. They are also present in the direct neighborhood of the endothelial cells. A part of the capillaries run in a horizontal direction. The cells surrounding the central cavity are flat. They are probably granulosa cells, although it can not be excluded with certainty that they are immigrated connective tissue cells. No line of demarcation exists between granulosa and theca interna.

23. *At Thirty-eight and One-Half Hours After Copulation (Paraffin).*—The corpora lutea protrude somewhat over the surface of the ovaries at the place of the former rupture. Long drawn-out cells, which are probably regenerating cells

of the germinal epithelium, cover this prominence. The central cavity of the corpus luteum is very large. The shape of one corpus luteum is markedly irregular; protrusions of the corpus luteum into the surrounding tissue are formed. No demarcation exists between theca interna and granulosa. In the outer half open capillaries are present; they run radially or horizontally. In the inner half open tubes are also present, but frequently no lumen can be seen between the rows of spindle cells, which grow into the inner half and which may split in different directions. At one place large capillaries traverse almost the whole thickness of the corpus luteum. Mitoses are present in the endothelial cells of the capillaries and in cells lying in contact with the capillaries. The majority of the mitoses are found in the outer half. There are, however, mitoses present near the inner cavity. The cells of the outer half of the corpus luteum are different from the more centrally situated cells, insofar as the latter are more vacuolar than the former. Two old corpora lutea are present.

24. *At Forty-nine and One-Half Hours After Copulation (Celloidin).*—The corpora lutea are closed; they form small prominences over the surface of the ovary. The wound at the place of rupture has healed. It is covered by cells of the germinal epithelium, which have not yet regained their normal shape, but are still long drawn out. Beneath the germinal epithelium connective tissue of the albuginea is found. The central cavity is larger than at the former stage; new liquor folliculi is present. Spindle-shaped cells line the peripheral part of the central cavity. It is not certain that all of these cells are connective tissue cells; some may be granulosa cells drawn out by the pressure exerted by the liquor folliculi. Some of these cells become transformed into fibers. Leucocytes are present in the central cavity. Parallel rows of spindle-shaped cells, the majority of which are probably new-formed endothelial cells of capillaries, traverse the corpus luteum; they may penetrate to the central cavity or they may form loops enveloping groups of lutein cells. The direction of these capillaries is not entirely radial; they run in part in a horizontal direction, which is perhaps due to the pressure exerted by the liquor folliculi. Many mitoses are found in the endothelial cells and in cells in their immediate neighborhood. A part of the invading spindle-shaped cells may be connective tissue cells.

25. *At Fifty and One-Half Hours After Copulation (Paraffin).*—The corpora lutea are closed and covered by germinal epithelium. The latter cells are still spindle-shaped. Beneath the germinal epithelium the connective tissue of the albuginea covers the former place of rupture. One corpus luteum protrudes only slightly over the surface of the ovary, the other somewhat more. The central cavity is still present, although

somewhat encroached on by connective tissue which envelops the central part of the cavity in concentric layers. The blood vessels pass through the whole corpus luteum so that at such a place very little or no lutein tissue is left. The outlines and shape of the corpus luteum may become very irregular, probably as a result of this ingrowth the corpus luteum of blood vessels forms irregular protuberances into the surrounding connective tissue. Probably because of the better blood supply the character of the corpus luteum cells changes; they are less vacuolar and stain well with eosin. The capillaries are still partially compressed; they run either radially or bend over into a horizontal direction; they may also split into two branches at different levels, even near the central connective tissue. They penetrate into the central connective tissue. Probably as a result of this new formation of capillaries a small hemorrhage with many leucocytes is found in the central cavity. A new formation of capillaries has apparently likewise taken place in the theca externa at a place where the latter protrudes into the corpus luteum. Many mitoses can be seen in the endothelial cells of the capillaries in all parts of the corpus luteum, near the border of the theca externa as well as near the central cavity. Mitoses are also present in cells which are in direct contact with the capillaries. An endothelial cell in mitotic division may, with its fusiform ends, overlap neighboring endothelial cells. Mitoses are likewise seen in the cells of the connective tissue which fills the peripheral part of the central cavity. The large majority of all mitoses are certainly in endothelial cells. It sometimes appears as if the connective tissue cells of the central connective tissue might be derived from the endothelial cells of the capillaries. It is, however, not possible to prove it. Both corpora lutea have about the same character. Some old corpora lutea are present.

26. *At Sixty Hours After Copulation* (Celloidin).—Two corpora lutea of the same character are present. The periphery of the central cavity is filled by connective tissue and new-formed capillaries which penetrate into the connective tissue from the corpus luteum tissue proper. The latter is traversed by capillaries, mostly in a radial direction. The cells of the corpus luteum are somewhat larger than at earlier stages and stain well. The new-formed blood vessels have probably a favorable effect on the character of the lutein cells. Many mitoses are present in endothelial cells of the capillaries in different parts of the corpus luteum, and also in other cells which are probably lutein cells. Mitoses are also present in the connective tissue cells of the central cavity. Hemorrhages are seen in the central cavity and in the connective tissue of the central cavity probably as a result of the intrusion of new capillaries in the central cavity.

27. *At Seventy-four and One-Half Hours After Copulation*

(Paraffin).—The corpora lutea are not much larger than in the former stage. The central cavity is not yet entirely filled out by connective tissue, which latter is arranged concentrically in the peripheral part of the central cavity. The corpus luteum cells are well formed. The cell membrane is distinct. Some vacuoles appear in cells, which are large and assume the character of typical lutein cells. Mitoses are present in endothelial cells of the capillaries and in cells near capillaries which are probably lutein cells. Mitoses are also visible in the central connective tissue. Many polynuclear leucocytes are found in the corpus luteum.

28. *At Seventy-seven and One-Half Hours After Copulation* (Celloidin).—The central cavity is almost entirely filled by connective tissue. Mitoses are seen in capillaries of the central connective tissue. The corpus luteum cells are larger than in former stages and are well formed. The corpus luteum as a whole is also larger. No distinction exists between granulosa and theca interna. Many capillaries traverse the corpus luteum. Mitoses are present in the endothelial cells of the blood vessels and also in cells near the capillaries. Such cells are probably lutein cells. Mitoses in lutein cells are found in the central as well as in the peripheral parts of the corpus luteum. Such mitoses may cause a protrusion of the endothelial cells of the capillaries.

29. *At One Hundred and One-Half Hours After Copulation* (Celloidin).—The central cavity is filled by connective tissue. In this connective tissue capillaries are present. The corpus luteum proper is relatively large, the central connective tissue at the place of the former central cavity occupies only a relatively small area. The corpus luteum cells are large and show well-formed vesicular nuclei. The cytoplasm is somewhat spongy; it stains purple with hematoxylin and eosin. Mitoses are present in endothelial cells of capillaries, as well as in lutein cells. One corpus luteum still protrudes somewhat over the surface of the ovary. The connective tissue covering the former place of rupture is compressed so that the typical albuginea has not yet been restored. Polynuclear leucocytes are present in the peripheral part of the corpus luteum. The character of a typical corpus luteum has been acquired.

30. *At One Hundred and Twenty-seven Hours After Copulation* (Celloidin).—The corpus luteum is typical. Large capillaries traverse the corpus luteum. The central connective tissue is small in quantity. The lutein cells stain well (purple). No mitoses can be seen. The corpus luteum forms many irregular protrusions into the surrounding tissue.

DISCUSSION OF RESULTS.

1. Ovaries of thirty guinea-pigs were examined. The ovaries of two animals showed no ruptured follicle. In one of these cases, six hours after copulation, the time

elapsed after copulation had perhaps been too short for the rupture to take place. In the other the ovaries were examined nine hours after copulation and some hyperemia was found, but there was no indication that a follicle was near rupturing.

2. One of the questions most discussed is: Is the granulosa preserved after the rupture of the follicle, and does it take part in the formation of the corpus luteum? It can be stated with certainty that the granulosa remains preserved and takes part in the formation of the corpus luteum. A distinct defect in the granulosa can be noticed at the place of rupture nine and eleven and one-half hours after copulation. The cells are on the whole well preserved; in part they show some vacuoles. From twelve and one-half hours on, the defect in the granulosa is no longer visible, as the granulosa cells which surround the place of rupture form one continuous layer. The vacuolar character is especially noticeable in the centrally-situated cells. From fifty to sixty hours on, the lutein cells become somewhat larger and stain well. On the fourth day the cells show the typical appearance of the lutein cells. On the fifth day we see typical lutein cells with well-formed vesicular nuclei. The cytoplasm is spongy and it stains purple with hematoxylin and eosin. The change in the character of the cells seems to coincide with the penetration of the blood vessels into the former granulosa. When the whole corpus luteum is supplied with a network of capillaries the cells seem to get larger and to stain better.

3. Nine hours after copulation, a short time after the rupture has taken place, a part of the granulosa on the surface of the ovary is seen extending through the place of rupture into the peritoneal cavity. This is a frequent occurrence and tumors are not known to originate from such displaced cells. After twelve and one-quarter hours liquor folliculi penetrates through the place of rupture into the peritoneal cavity instead of granulosa; the place of rupture is now closed and internal pressure causes the granulosa to protrude partially into the cavity of the follicle. That can be seen seventeen hours fifty minutes after copulation.

4. Not all the granulosa cells remain alive. In the first hours after the rupture, and as late as eighteen hours after copulation, a number of centrally-situated

granulosa cells show karyorrhexis and disappearance of their nuclei, followed by dissolution of the cells. At twenty hours we see some karyorrhexis at the border between the granulosa and theca interna, and as late as twenty-eight and one-half hours and thirty-one hours karyorrhexis and karyolysis and dissolution of some cells take place.

5. At an early period after the rupture some granulosa cells are long drawn out in the direction of the place of rupture. It appears as if traction were exerted on the cells in that direction. A number of such cells may degenerate, lose their nuclei and form fibers which stain red by eosin. A part of the red-staining mass which is present in the central cavity is therefore a direct product of degenerating cells.

6. In a similar way the viscid red-staining mass which fills the cavity of the follicle can be drawn out into fibers nine and twelve hours after copulation. At an early period after the rupture a red-staining, homogeneous mass or a somewhat granular material is still present in the central cavity. From forty-nine and one-half hours on the liquor follicule is increasing again.

7. As stated, a number of granulosa cells are lost after the rupture of the follicle. To compensate for this loss mitotic divisions take place in granulosa cells. One mitosis is visible near the place of rupture eleven and one-half hours after copulation. At twelve and one-half hours we see a number of mitoses, diasters and monasters, in all layers of granulosa. The diasters are drawn out as the cells are drawn out—toward the place of rupture. At seventeen hours fifty minutes we see mitoses in different parts of the granulosa. In other specimens mitoses can be seen at the margin of granulosa and theca interna, and it is difficult to be sure whether some mitoses lie in the outer part of the granulosa or in the inner part of the theca interna. At twenty-six hours and at later stages we see mitoses in the cells which invade the granulosa from the theca interna. At twenty-eight and one-half hours we see in the area of the former granulosa mitoses in cells which may have been granulosa cells, but which possibly were immigrated cells. No mitoses could be seen in the granulosa nine, ten, eleven and twelve hours after copulation.

8. Soon after the rupture of the follicle, nine and

ten hours after copulation, the boundary line between granulosa and theca interna form folds. At eleven hours the theca interna forms protrusions into the granulosa at some places. At eleven and one-half hours two parallel rows of fusiform cells are seen at one place to extend into the granulosa from the theca interna; at fifteen and one-half hours and seventeen hours fifty minutes the border between granulosa and theca interna is wavy. The theca interna cells may be drawn out in the same direction as the granulosa cells.

9. Soon after the rupture of the follicle the theca interna is very hyperemic. This condition is marked until fifteen hours after copulation. From twelve hours up to thirty hours the blood and lymph vessels near the place of rupture are dilated. The hyperemia extends to the connective tissue surrounding the place of rupture, especially to the albuginea. From twenty-two hours on, the blood vessels of the theca externa become dilated and the hyperemia passes to the connective tissue directly surrounding the corpus luteum. The hyperemia is quite marked thirty-one and thirty-four hours after copulation. This change in the area of hyperemia from theca interna to theca externa is perhaps due to the pressure exerted in the corpus luteum itself after the rupture has been closed more firmly.

10. Mitoses in the theca interna can be seen soon after the rupture up to the time when the theca interna and the granulosa can no longer be distinguished in the corpus luteum. From nine to twenty-four and thirty-one hours mitoses can be seen near the granulosa as well as in the peripheral part of the theca interna, in endothelial cells and in interna cells proper at the side of the capillaries. It is not possible in each case to decide with certainty whether a mitosis belongs to an endothelial cell or to a cell lying in close proximity to an endothelial cell. Mitoses in endothelial cells are present as early as eleven and one-half hours after copulation and can be seen at different periods up to thirty-two and one-half hours; at that time one can only approximately determine which part of the vessels belongs to the former theca interna and which belongs to the former granulosa. Between twenty and thirty hours mitoses are present near the place of rupture in endothelial cells as well as in other cells.

11. In the theca externa mitoses can also be seen in

endothelial cells of blood vessels as well as in connective tissue cells. They are present twelve and one-quarter and twelve and one-half hours after copulation. The larger number of mitoses is visible in the theca externa, and in the blood vessels of the theca externa between twenty and thirty-two and one-half hours, perhaps in connection with the hyperemia which is more marked here at that period. At a later period, fifty and one-half hours after copulation, capillaries seem to be newly formed in the theca externa, and these capillaries enter the corpus luteum.

12. A number of cells of the theca interna become large and polygonal and can no longer be distinguished from the granulosa cells. At some places such cells can be seen between the blood vessels ten, eleven and twelve and one-half hours after copulation. The endothelial cells of capillaries may likewise swell. The interna cells assume more and more this character, and if the blood vessels of the interna run in a radial direction toward the granulosa, both layers are in part or in their entirety indistinguishable. At seven and one-quarter hours both layers can still be easily distinguished. From nine hours to twenty hours in many cases the line of demarcation can be made out. At fourteen and three-quarter hours they can, for instance, easily be distinguished where the theca interna cells and their blood vessels show a concentric arrangement to the follicle. At twenty hours a zone, which is very poor in nuclei, separates both layers. Where the direction of the capillaries is a radial one the distinction between the two layers is no longer possible. Both layers take part in the formation of the corpus luteum.

13. Mitoses in blood vessels of the theca interna can be seen very early after the rupture of the follicle. Twenty hours after copulation the blood vessels of the theca interna have a radial direction in some places. Twenty-two hours after copulation, tubes, formed by two parallel layers of spindle-shaped cells and with a radial direction, extend from the neighborhood of the blood vessels of the former interna half way or further into the former granulosa. At twenty-four hours we see blood vessels only in the outer zone of the follicle. At twenty-six hours cell tubes enter the former granulosa. At twenty-eight and one-half hours we see capillaries in the peripheral part of the corpus luteum (the former

theca interna) sending out processes toward the central cavity. Cell tubes extend at some places far into the corpus luteum, the central part near the central cavity remaining free from capillaries. The direction is radial. At the same time we see spindle-shaped cells which represent endothelial cells of capillaries or perhaps connective tissue cells entering the former granulosa. At thirty-one hours capillaries are present in the outer part of the corpus luteum. From these outer capillaries or from their neighborhood cell tubes are growing deeply into the former granulosa. In two of the corpora lutea these tubes preserve a distinct lumen until they almost reach the central cavity and their course is radial; in the third corpus luteum they do not remain open so far and their course is more oblique. At the central end the cell tubes turn frequently in a horizontal direction. Between thirty and forty hours such cell tubes traverse the corpus luteum either radially or obliquely. They have a lumen in the outer part of the corpus luteum. In the inner half open tubes are also present, but frequently no lumen can be seen between the rows of spindle cells. The rows of spindle cells give off branches which run obliquely or horizontally and begin to envelop the corpus luteum cells. Besides the distinct cell tubes we see spindle-shaped cells without apparent connection with such cell tubes. As early as thirty-eight and one-half hours after copulation at one place large capillaries traverse almost the whole thickness of the corpus luteum. At forty-nine and one-half and at fifty and one-half hours capillaries pass through the corpus luteum to the central cavity. In the connective tissue which is present in the peripheral part of the central cavity the tubes may lose their lumen. These capillaries may split into two branches at different levels, even near the central connective tissue. At some places the blood vessels and connective tissue pass directly from the theca externa through the whole corpus luteum in a radial direction into the central tissue. At such a place very little corpus luteum tissue is left. At sixty hours and later many well developed capillaries pass through the corpus luteum.

Two questions arise: Are the spindle-shaped cells invading the granulosa, endothelial cells of capillaries, or are they in part ordinary connective tissue cells; and what is the origin of these cells? We see that these cell

tubes originate near the capillaries of the former theca interna. The endothelial cells of the latter show at the same time mitoses. These facts make it probable that at least a great part, perhaps all, of these tubes are derived from the blood vessels of the theca interna. The fact that a lumen is not present in all cell rows might be explained by the pressure exerted at certain stages of the developing corpus luteum from the direction of the central cavity toward the periphery. Nevertheless it is likely that a part of the spindle-shaped cells are connective tissue cells, but I could not find any definite indication that the ordinary theca interna or theca externa cells infiltrate the granulosa. This fact, however, does not exclude the possibility that nevertheless such an infiltration might take place. At a later stage we see blood vessels and connective tissue pass from the theca externa to the central part of the corpus luteum.

14. Between thirty and forty hours mitoses are found in the newly-formed cell tubes of the corpus luteum. They are present in the central, and more frequently, in the peripheral part of the corpus luteum. Mitoses are also found in spindle-shaped cells which do not distinctly belong to the cell tubes, and in cells which lie in close approximation to the cell tubes. Not in every case is it possible to state with certainty whether a mitosis is seen in a cell belonging to the tubes described above or to a lutein cell lying near it, because during mitotic division the endothelial cells may change somewhat their position; they may protrude toward the lumen of the cell tubes as well as toward the outer side.

From fifty to sixty hours in all parts of the corpus luteum many mitoses can be seen in endothelial cells and in cells which are situated between the capillaries. These latter cells are probably lutein cells. Mitoses are also present in the connective tissue of the central cavity. The same conditions prevail up to 100 hours after copulation. At 127 hours mitoses are no longer visible.

15. The place of rupture of the follicle is open in the first few hours. It becomes occluded by granulosa cells twelve and one-half hours after copulation. Six hours later we find between the occluding granulosa cells a homogeneous mass which stains red with eosin. Perhaps some liquor folliculi was pressed out through the granulosa, or it is possible that it was formed through the degeneration of some granulosa cells. Between twenty-two

and thirty hours we find the place of rupture occluded by larger corpus luteum cells which contain capillaries. These large cells again are covered by spindle-shaped cells which may be in part at least regenerating cells of the germinal epithelium; there were perhaps connective tissue cells admixed. Mitoses can be found in the endothelial cells of the blood vessels as well as in the large cells.

Mitoses are also present in the connective tissue of the albuginea near by. Between thirty and forty hours no marked change takes place; the regeneration of the germinal epithelium becomes more marked, mitoses still occur and the surrounding connective tissue is hyperemic. The covering of the albuginea is, however, not yet perfect. About fifty hours after copulation the regenerating cells of the germinal epithelium are in part still somewhat spindle-shaped; beneath them the connective tissue is visible.

We have to assume that the first temporary occlusion by granulosa cells is caused by the pressure of the ovarian tissue surrounding the follicle, only somewhat later an actual wound healing takes place and leads to a solid closure of the opening.

16. That a pressure of the surrounding ovarian tissue is exerted on the ruptured follicle is perhaps also indicated by the fact that after eleven and one-half hours we find a more or less marked prominence of the ruptured follicle over the surface of the ovary. It is quite marked twenty-two hours and thirty-one hours after copulation. It is, however, not necessarily always present. We find even a retraction at the place of rupture thirty-two and one-half hours after copulation.

17. After the rupture of the follicle a small cavity remains preserved in the center of the follicle. As soon as the granulosa covering of the follicle becomes stronger and with the simultaneous ingrowth of capillaries the cavity begins to enlarge, slowly from twenty-two to thirty hours after copulation, more rapidly between thirty and forty hours. At forty-nine and one-half hours the cavity is large, new liquor folliculi is formed, and connective tissue becomes visible in the peripheral parts of the central cavity. At seventy-seven and one-half hours the cavity is almost entirely filled by connective tissue. At 100½ hours the central cavity is entirely filled by connective tissue which contains capillaries.

18. The increase in the size of the central cavity, combined with the increase in the quantity of the liquor folliculi, seems to exert a pressure on the structures surrounding the central cavity. This is indicated, for instance, by the flattening of the centrally situated granulosa cells, which is noticeable twenty-six hours after copulation. From now on flattened cells line the central cavity. At first they are in all probability granulosa cells. The flattened cells are probably granulosa cells between thirty and forty hours, although at that period connective tissue cells may be admixed. After fifty hours we have to deal mainly or exclusively with connective tissue cells. As indications of pressure exerted by the fluid of the central cavity may perhaps be considered the fact that at early periods the cell tubes traverse the corpus luteum, frequently not in a directly radial, but in a more oblique direction, and that from twenty-six hours on the blood seems to be pressed out of the vessels of the corpus luteum proper into the surrounding connective tissue for a certain period. This interpretation, however, is only a tentative one.

19. It is an interesting fact that the connective tissue which fills gradually the central cavity grows along the border of the cavity in a concentric direction and that in this way it gradually fills the central cavity. Mitoses can be seen in the connective tissue cells of the central cavity at different periods, for instance, fifty and one-half and seventy-four and one-half hours after copulation. Cell tubes and distinct capillaries grow into it. At fifty and one-half hours cell tubes can be seen, and at sixty hours distinct capillaries are visible. Mitoses are also found in endothelial cells of capillaries. It is uncertain whether the mode of ingrowth of connective tissue is due to contact irritability of the connective tissue or to the pressure exerted by the fluid of the cavity.

20. At various periods the developing corpora lutea show a very irregular shape and they form protrusions into the surrounding connective tissue. Corpora lutea of that character were visible at thirty-eight and one-half hours, at fifty and one-half hours and 100½ hours. In one case (at fifty and one-half hours) it appeared as if the ingrowth of large blood vessels from the theca externa had caused those irregular formations.

21. The rupture of the follicle seems to be accompanied by very little hemorrhage. In a number of follicles we

see a slight amount of extravasated blood in the connective tissue near the place of rupture as late as thirty-two hours after copulation. In some follicles we see a small number of red blood corpuscles in the central cavity eleven, twelve and fifteen and one-quarter hours after copulation. Later, at fifty and one-half hours and at sixty hours we see slight hemorrhages in the central cavity. This blood has, however, probably a different origin and is in all likelihood extravasated from the new-formed blood vessels of the corpus luteum.

22. Polynuclear leucocytes are seen in the central cavity, and in the theca interna soon after the rupture of the follicle, in variable numbers. The leucocytes in the central cavity take up the eosin to a much less degree than the leucocytes which have just left the vessels. Later, at forty-nine and one-half hours and fifty and one-half hours, we see leucocytes in the central cavity. Their presence is in part due to hemorrhage from the new-formed vessels.

23. The size of the corpus luteum and of the individual cells does not increase much at early stages of the developing corpus luteum. At seventy-seven and one-half hours, however, the corpus luteum begins to become distinctly larger and at 100½ hours the central connective tissue occupies a relatively small area as compared to the lutein tissue proper.

24. We found that the large theca interna cells and the granulosa cells assume the same appearance in the ruptured follicle of the guinea-pig. We are, therefore, unable to distinguish between the two kinds of cells composing the corpus luteum after development has advanced to a certain stage. We can state that the large cells which are characteristic of the corpus luteum are derived from two different sources, namely, from the granulosa and from the theca interna. Although these two varieties of cells can not be distinguished morphologically after the corpus luteum has been formed, we can not say with certainty that there might not exist some chemical or physicochemical differences. We have, however, no indications of the presence of such differences, which become especially doubtful as we know that both the large cells of the theca interna as well as the granulosa cells may contain lutein, and that both may show the same tendency to fatty changes.

25. If we now compare the formation of the corpus

luteum with the atresia of the follicles we see two principal differences between the development of these two structures. (a) During the atresia of follicles the granulosa degenerates entirely; in the corpus luteum it remains preserved and the cells increase in size and in number. A number of granulosa cells degenerate, however, even in the follicle which has ruptured. (b) In the atretic follicle the ingrowth of connective tissue predominates. A new formation of blood vessels does not take place, or is only very slight. In the corpus luteum, on the other hand, the new formation of blood vessels and their ingrowth into the former granulosa, and even into the central connective tissue, is very prominent.

For a further deeper analysis of these differences of growth, experimental investigations will be necessary.