THE CORPUS LUTEUM

ITS LIFE CYCLE AND ITS RÔLE IN MENSTRUAL DISORDERS *

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Since the publication of Fraenkel's paper,[1] in 1903, the study of the corpus luteum has been the point of departure in most of the investigations which have been made as to the cause and mechanism of menstruation. I shall not review the now voluminous literature of this subject, except perhaps to call attention to the definite advance made in 1911 by Robert Meyer,[2] who showed that the corpus luteum, like the endometrium, passes through certain stages corresponding to the various phases of the menstrual cycle.

The purpose of this present paper, aside from the study of the normal life cycle of the corpus luteum in relation to the menstrual cycle, includes an effort to determine whether any histologic variations in the lutein structures of the ovary can be found to explain the various menstrual disorders. Only the salient points of the inquiry can be sketched within the brief limits of this paper, leaving the more extended discussion of the various aspects of the subject for a more exhaustive report to be published later. My investigation so far has embraced the clinical and histologic study of 137 cases from the Gynecological Department of the Johns Hopkins Hospital. While these cases constitute the actual basis for the present paper, I have had the opportunity of studying a large number of corpora lutea from cases not included in the series.

* From the Gynecological Department of the Johns Hopkins Medical School.

1. Fraenkel, L.: Arch. f. Gynäk., 1903, lxviii, 438.
2. Meyer, Robert: Arch. f. Gynäk., 1911, xciii, 354.

In 102 of the 137 cases of the series studied, both ovaries had been removed, together with the uterus, so that it was possible to study the histologic picture of the endometrium side by side with the histologic variations in the removed ovaries. The latter were thoroughly ransacked, by numerous sections, for all traces of lutein tissue, as well as other characteristic structures which might be of functional importance. A careful study was thus made, not only of corpora lutea in various stages of development, but also of other structures, such as mature graafian follicles, atresic follicles, etc. In this way it would seem that the possibility of overlooking structures of functional importance could be reduced to a minimum, since the presence of such elements can usually be easily determined macroscopically. This is especially true, of course, of the yellow-walled corpus luteum in all except perhaps its earliest stages. Only by such thorough examination of both ovaries are any generalizations justified as to the significance of its various elements.

The mere presence or absence of corpora lutea on the surface of the ovary means very little. It is common to find well developed corpora lutea in ovaries which on their surface give little or no indication of their presence. For this reason, observations made during operations on ovaries which are not removed are far less valuable than the thorough examination of the ovaries after removal. As a matter of fact, the only indication of the site of even large corpora lutea is apt to be a slight hemorrhagic discoloration on the surface. Only by cutting into the ovarian substance is the true nature of the otherwise easily overlooked area revealed.

Again, since corpora lutea may be present in both ovaries, it is obvious that it would be hazardous to venture any very sweeping deductions unless both ovaries are studied. It is for these reasons that I have selected for this study chiefly those cases in which both

ovaries had been removed. The essential importance of accurate menstrual histories in such an investigation is obvious, as well as a knowledge of the full pathologic findings at operation and in the laboratory.

In a second smaller group of cases, numbering thirty-five, all ovarian tissue had not been removed at operation. Deductions from these cases cannot be included in any generalization concerning the rôle of lutein tissue in either normal or abnormal menstruation. They have been included in the study because the ovarian tissue removed from them has contained lutein structures which in one way or another are of interest from the standpoint of this investigation.

A careful study of the ovaries included in my material has enabled me to secure corpora lutea in practically all stages of development. One may thus trace the life history in a consecutive manner from beginning to end. Only in this way can an intelligent conception be gained as to the origin, development and ultimate fate of the structure derived from the rupture of the ripe graafian follicle.

With a few exceptions, those who have studied the corpus luteum in the past have seemed to disregard the fact that, like the endometrium, it undergoes a change from day to day. The stereotyped conception of the corpus luteum seems to have been that of a large structure, with brilliant yellow undulating walls, standing out sharply from the cut surface of the ovary. While this description fits the corpus luteum in certain stages of its development, it is altogether incorrect as applied to others. The above mentioned characteristics are apt to be those of the fully developed corpus luteum, which has, however, reached this stage only after a process of gradual development extending over many days. The presence of the large yellow walled corpus luteum does not, therefore, signify that ovulation has occurred just previously, as so many have assumed in discussing the subject.

In its earliest stages, just after rupture of the graafian follicle, the corpus luteum is usually a small, collapsed structure, with thin, moderately undulating walls, which are of grayish yellow hue instead of the brilliant yellow color of the later stages. For this reason the earliest stages are very inconspicuous and are usually overlooked. Indeed, their discovery, even with careful search, must be looked on as in large measure accidental. The difficulty of securing these early stages is increased by the uncertainty as to the exact time of ovulation, so that it is not possible, in the present stage of our knowledge, to arrange operations of election with a view of obtaining these early corpora lutea. Again, there is much evidence that the changes in the early history of the corpus luteum take place very rapidly, so that the earliest stages, speaking histologically, extend over a comparatively short time.

It is not surprising, therefore, that there have been very few observations in the human being on the earliest stages of the corpus luteum. Indeed, I know of no such observation, with the exception of the questionable one of Kreis[3] in 1899, until the report of Meyer's series of cases in 1911. And yet the study of the corpus luteum in its earliest stages throws a light otherwise unobtainable on such important questions as that of the origin of the lutein cells—the still open question as to whether they arise from the epithelial cells of the membrana granulosa or from the connective tissue cells of the theca interna. For this reason I have been especially on the alert in the investigation of my meterial for these early stages of corpus luteum development, and have been rewarded by finding five interesting examples. On account of the rarity with which such cases have been described, I shall refer briefly to the findings in these five cases.

Case 1 (private patient).—Mrs. L. M., aged 28, was operated on by me at Mercy Hospital, March 2, 1916, the operation consisting of left salpingo-oophorectomy, appendectomy

3. Kreis, O.: Arch. f. Gynäk., 1899, lviii, 426.

and resection of the right ovary. Menstruation had always been regular, lasting five days and being moderate in amount. The last period before operation commenced February 21, lasting five days, so that operation was done on the tenth day of the menstrual cycle.

Careful examination of the left ovary afterward failed to reveal any lutein structures. It contained, however, a follicular cyst about the size of a walnut, and numerous smaller cysts. The wedge of right ovary which had been removed, however, presented a small dark reddish discoloration on the surface. On section this was found to mark the site of a scalloped cavity, a little over 1 cm. in diameter, which contained no blood, the hemorrhagic appearance of the surface being apparently due to the excessive hyperemia of the walls. At one point there was a small eroded spot representing the point of rupture.

Microscopic sections revealed a picture which I had heretofore not observed, and which is well shown in Figures 2 and 3. The membrana granulosa is not only present, but there is not the slightest indication of degeneration. The cells are still quite compact, resembling those of the mature graafian follicle, except that they are more cylindric (compare Figure 1). The most remarkable change is evident in the cells of the theca interna. These have become large, epithelioid, and infiltrated with fat. The theca interna has become very vascular, its blood vessels, derived from the theca externa, pushing centripetally toward the granulosa, which, however, is not yet invaded. Especially striking is the vascular line of demarcation which has formed between the granulosa and the theca.

Case 2 (Gyn. Path. No. 21216).—The patient was a white woman of 46, on whom a radical operation for cancer of the cervix was done in Dr. Kelly's service, May 19, 1915. Menstruation was irregular on account of the carcinoma, a bloody discharge having been present for eight months. Both ovaries were small and cirrhotic. The surface of the right ovary showed a small hemorrhagic discoloration, beneath which was found a cavity with scalloped walls, measuring about 1 by 2 cm. The cavity itself contained no blood, but there was much hemorrhagic infiltration of its walls in places, especially near the surface. The microscopic picture was almost identical with that shown in Figure 1. The endometrium was of the interval type.

Case 3 (Gyn. Path. No. 21223).—This patient, a white woman of 38, was operated on in Dr. Kelly's service, May 24, 1915, for the radical removal of a carcinoma of the cervix. Preliminary cauterization was done, May 15, 1915. The last menstruation had begun May 2, although the intervening operation and the presence of the cancerous disease detract from the importance of the menstrual history. The right

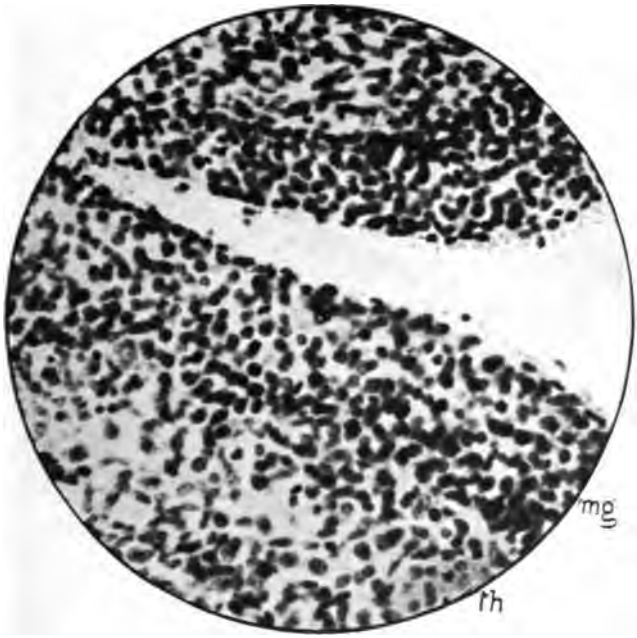

Fig. 1.—Portion of wall of mature graafian follicle, removed on fifth day of cycle (high power): mg, membrana granulosa; th, theca interna. All photomicrographs by Schapiro.

Fig. 2.—Portion of wall of early corpus luteum, removed on tenth day of cycle (low power): mg, membrana granulosa; th, theca interna. Note the vascular line of demarcation between these two layers.

Fig. 3.—High power picture of corpus luteum shown in Figure 2. Compare with Figure 1.

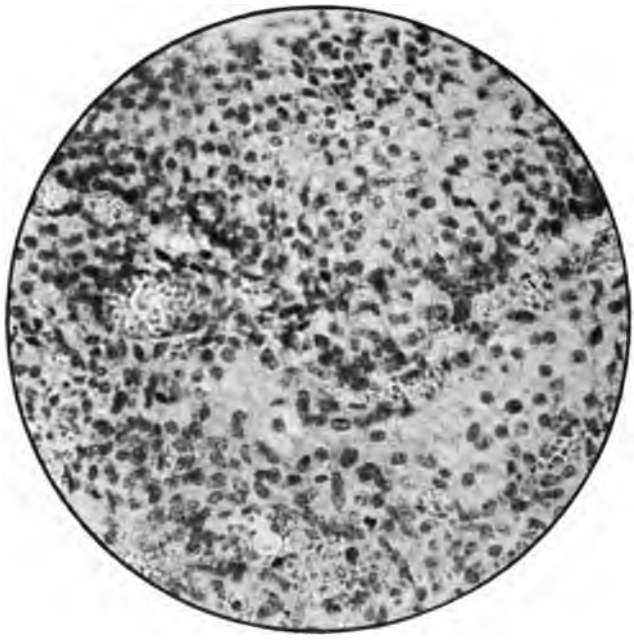

Fig. 4.—Wall of early corpus luteum, slightly more advanced than that shown in Figure 3 (high power). Note the lutein-like change of granulosa cells, and beginning retrogression of theca cells.

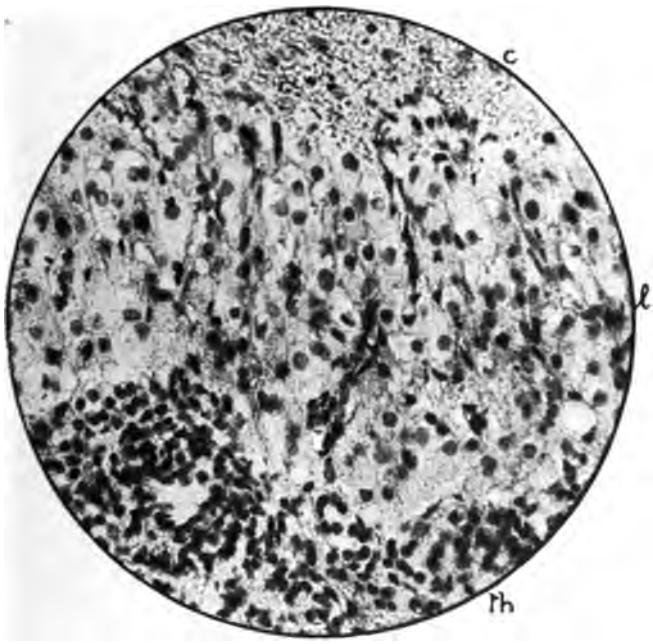

Fig. 5.—Wall of corpus luteum in stage of early vascularization, sixteenth day (high power). Blood vessels from the theca are pushing into the granulosa layer (*l*), which now possesses definite lutein characteristics. The theca cells (*th*) have lost their fat and are retrogressing. Note the beginning invasion of the blood in the cavity (*c*) by endothelial cells.

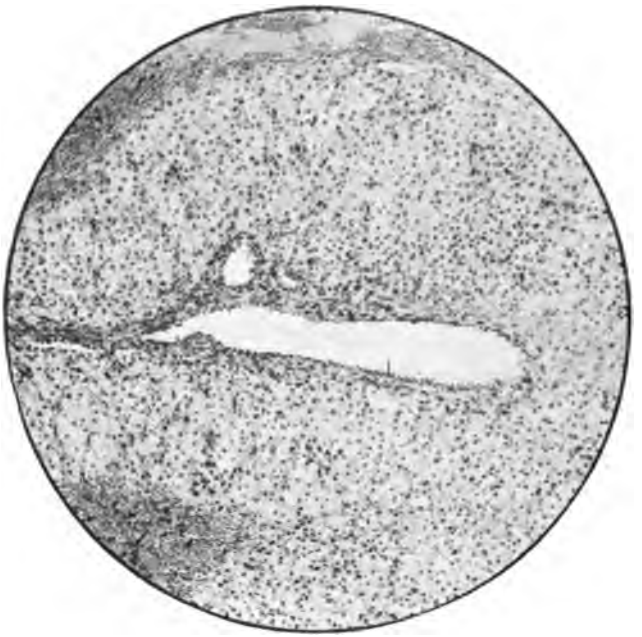

Fig. 6.—Wall of corpus luteum in stage of late vascularization, approaching maturity (low power).

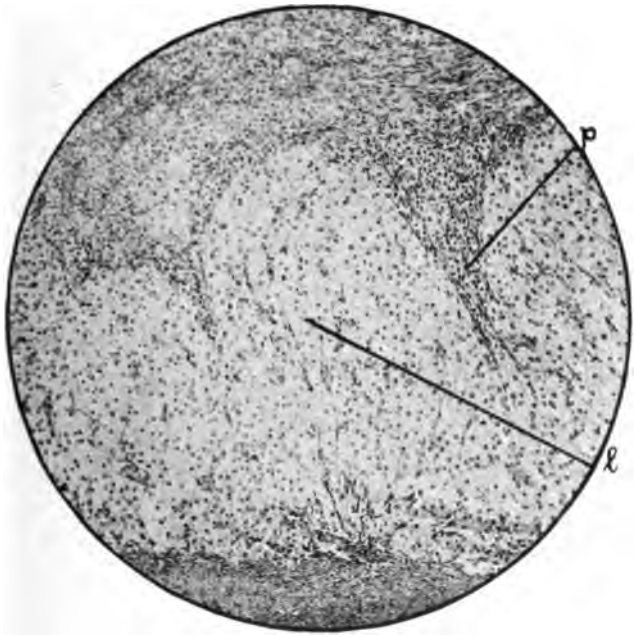

Fig. 7.—Wall of mature corpus luteum, twenty-seventh day (low power), showing lutein (*l*) and paralutein (*p*) cells. The latter are found in the wedgelike septa.

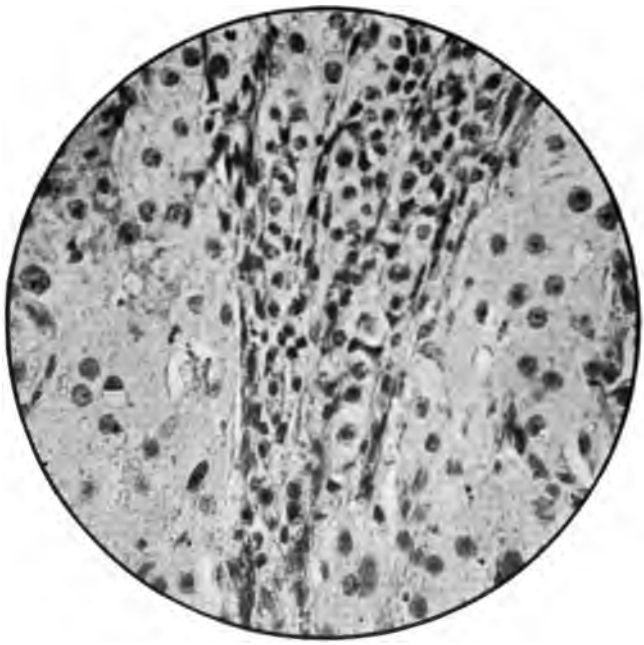

Fig. 8.—Contrast between lutein and paralutein cells, near top of septum shown at *p*, in Figure 7 (high power).

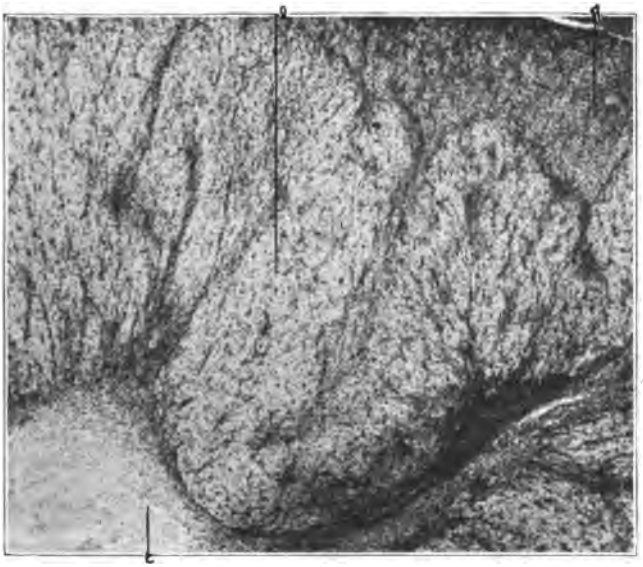

Fig. 9.—Corpus luteum in a case of early tubal pregnancy (low power), showing lutein cells (*l*), paralutein cells (*q*), and organization of contents (*c*).

ovary contained an early corpus luteum similar to those in Cases 1 and 2. There was in this case, however, a very great hemorrhagic extravasation surrounding the wall of the corpus, in many places obscuring the cells of the theca. The endometrium was of the interval type.

CASE 4 (Gyn. Path. No. 21195).—A white woman, aged 34, was operated on in Dr. Kelly's service, May 13, 1915, for chronic pelvic inflammatory disease, with left tubo-ovarian abscess. Panhysterectomy, with double salpingo-oophorectomy, was performed. Irregular bleeding had been present for two months. The right ovary contained a small cavity, a microscopic section of which is pictured in Figure 4. The same ovary contained a large corpus luteum in the stage of retrogression. The endometrium was of the interval type. The corpus luteum pictured in Figure 4 differs from that represented in Figures 2 and 3 in that the granulosa cells are losing their long cylindric shape and are becoming larger and more polygonal. In other words, they are beginning to assume the morphologic characteristics of lutein cells. On the other hand, the theca cells are much less conspicuous than in the earlier stage, having lost much of their fatty content.

CASE 5 (Gyn. Path. No. 21333).—This patient was a colored woman, aged 43, who was operated on in Dr. Kelly's service, July 6. The operation was hysterectomy with double salpingo-oophorectomy, on account of extensive inflammatory disease with cystic degeneration of both ovaries. Menstruation had always been regular, lasting two or three days, with moderate flow. The date of the last menstruation was June 20, so that the operation was done on the sixteenth day of the menstrual cycle. In the right ovary was a blood-filled cavity measuring 3.5 by 1.5 cm. which proved to be a corpus luteum cyst. Between this and the surface of the ovary, just beneath the latter, was a rather flattened cavity which on microscopic examination was found to be an early corpus luteum, similar to that found in the preceding case.

The five specimens of early corpus luteum here reported are alike in the very important particular that in all of them the epithelial cells of the granulosa are, to say the least, quite intact. This fact is of prime importance in the consideration of the origin of the lutein cells. One of the strongest arguments against the epithelial origin of these cells has been the alleged degeneration and disappearance of the membrana granulosa after rupture of the follicle. In each of my five specimens, however, the epithelium is well pre-

served. Moreover, in Cases 4 and 5, it exhibits definite signs of a lutein-like transformation. This I look on as a vital point — *the* vital point — in connection with the question of the origin of the lutein cell. If we can demonstrate in human beings, as Sobotta[4] seems to have shown in lower animals, that there is a direct transformation of the granulosa cell into the lutein cell, the problem is solved. I believe that Figures 1, 2, 3 and 4 illustrate such a beginning transition of the granulosa cell to the lutein cell. It will be noted that this transformation is already well under way before there is any evidence of vascular invasion of the granulosa layer, and that as the granulosa cells assume lutein characteristics, the cells of the theca become less conspicuous, giving up much of their fatty content. This may be observed from a comparison of Figures 3 and 4. From this it might be inferred that the theca cells, with their rich fatty content, fulfil an important nutritive function, as Meyer has suggested. The gradual retrogression of the theca cells, moreover, is another indication that it is not they that are to be transformed into lutein cells.

That the structures which I have described are really corpora lutea and not merely mature and unruptured follicles is evidenced, not only by the demonstration of a definite point of rupture in at least two of the cases, but also by the many layers of the epithelium, by the cylindric shape and large size of the cells, by the striking fatty deposit in the theca interna, and by the pronounced and characteristic hyperemia (Compare Figures 1 and 3).

As to the time relation of these early corpora lutea to the menstrual cycle, only two of the five cases, unfortunately, can give any trustworthy evidence, owing to the irregular bleeding present in the others. The structure found in Case 1 and pictured in Figure 2 was obtained on the tenth day of the menstrual cycle. For the absolute accuracy of the menstrual history in

4. Sobotta, J.: Arch. f. mikrosk. Anat., 1896, xlvii, 261.

the case I can vouch. In Case 5, on the other hand, the patient was operated on on the sixteenth day of the menstrual cycle, although histologically it represents only a slightly later stage than that seen in Case 1. Meyer's earliest corpus luteum was found on the twelfth day of the cycle. The unruptured follicle pictured in Figure 1 was removed on the fifth day of the cycle. It would be indiscreet to draw from this small group of cases any conclusions as to the time of follicular rupture. Indeed, it does not seem to me that a sufficient number of cases have as yet been studied by all investigators collectively to warrant any such generalization. I may simply state that in the five cases reported by me ovulation seems definitely to have occurred in the first half, or perhaps we may say the second quarter, of the intermenstrual period, and that the time of follicular rupture is subject to a certain—perhaps a considerable—degree of individual variation.

The later stages of the development of the corpus luteum I shall pass over much more briefly, as my observations differ in no important respect from those of Meyer. In the five cases above described, there was no evidence of invasion of the epithelium by the blood vessels of the theca. Figure 5, which pictures a corpus luteum removed on the fourteenth day of the menstrual cycle, shows a somewhat later stage. The granulosa cells are large and epithelioid, and contain some fat. In other words, they now possess all the morphologic characteristics of lutein cells. The lutein zone is still rather narrow and only slightly undulating.

The most significant feature of this stage, however, is the invasion of the lutein layer by small blood channels. These are clearly traceable back to the ring of blood vessels which marks the division between the granulosa and the theca, as described in connection with the earlier stages. Some of the blood in the lutein zone is present in definite endothelium-lined vessels, while some lies free between the cells, making its way to and into the cavity of the corpus. Even in this

early stage, endothelial cells may be observed here and there to push out into the lumen, forecasting the organization of the blood contents which takes place in the late stages of the corpus luteum. It will also be seen that vascularization of the lutein layer is chiefly responsible for the bleeding into the cavity of the corpus, and for the organization of the lumen contents. From a physiologic point of view, it is of great importance because, in addition to carrying nutriment to the lutein cells, it enables their secretion to be emptied directly into the blood stream. Together with the advance in the development of the lutein cells, there is a corresponding retrogression in the theca cells. They have lost most of their fat, and are apparently reverting to the type of ordinary connective tissue cells.

In Figure 6, which represents a considerably later stage, the theca cells are inconspicuous, while the lutein layer appears as a broad festooned zone irrigated by numerous blood channels. The corpus luteum in this picture is rapidly approaching the stage of maturity, which is illustrated in Figure 7. Here one sees the corpus luteum in full bloom. Operation in this case had been done on the twenty-seventh day of the menstrual cycle. The lutein cells are large and polygonal, and give every histologic appearance of active function. Toward the lumen they are separated from the contents by a delicate layer of organized tissue, whose formation from the septa penetrating the lutein layer from the theca is clearly traceable. Meyer attaches great physiologic importance to this layer, as indicating that the secretion of the lutein cells can no longer be given off into the lumen, but must pass back into the blood stream. In many mature corpora lutea which I have examined, however, this layer is very poorly marked, and I believe that irrigation of the lutein zone by the vascular channels is more important than the formation of this organized layer in determining the internal secretory function of the corpus luteum.

The present series included twenty-four corpora lutea classified histologically as mature. Reference to the menstrual histories in these cases showed that operation had been done at periods varying from the eighteenth to the twenty-seventh days of the cycle. In other words, the mature corpus luteum is found during that portion of the cycle in which the endometrium exhibits the premenstrual hypertrophy.

An exceedingly interesting feature of many corpora lutea, especially near the stage of maturity, is the remarkable development of the theca interna cells. This is well shown in Figure 7, and, more highly magnified, in Figure 8. The theca cells are seen to be fully as well developed as are the lutein cells, though they are of quite a different type. The contrast is very striking. The large size of the theca cells, their alveolar arrangement, the richness of their blood supply, all suggest a glandular structure and function. I cannot believe, as does Meyer, that the theca cells, after fulfilling a nutritive function in the earliest stages of the corpus luteum, retrogress and serve no further purpose. The name of "paralutein" cells was given to these cells by Pinto,[5] who, however, credits them with no special function. Such pictures as that shown in Figure 8 speak strongly against such a view. The corpus luteum pictured in Figure 9 shows a similar theca change occurring with an early tubal pregnancy. Incidentally it illustrates also the broader lutein zone and the more advanced organization of the corpus luteum of pregnancy. The theca changes represented in Figures 7 and 9 are practically the same, though one patient was pregnant and the other was not.

There can be little doubt that the corpus luteum possesses at least a dual function. Even Fraenkel attributed to it not only the causation of menstruation but also the fixation of the ovum in the early part of pregnancy. Since the luetin cells proper are almost

5. Pinto, C.: Ann. di obstet. e ginec., 1905 (quoted by Seitz, Footnote 6).

certainly concerned in the causation of the menstrual phenomena, perhaps the paralutein cells are in some way concerned in the other important function ascribed to the corpus luteum. This, however, is a problem of biologic chemistry. I may simply state that in nineteen corpora lutea exhibiting marked development of these paralutein cells, all except a few were removed from patients who gave histories of profuse and, in a few instances, irregular menstruation. It is curious to note, also, that many of the patients were sterile. In some cases pregnancy had never occurred although the patient had been married many years, while in others, again, there had been a long period of secondary sterility.

There is no sharp dividing line between the stage of maturity and that of retrogression. One blends gradually into the other. I have often found it impossible to distinguish corpora lutea removed just after menstruation from those removed just before, even though retrogressive changes are said to set in with the onset of menstruation. The individual variation in the rapidity of retrogression is illustrated by the fact that in some ovaries four or five well marked corpora lutea in various stages of retrogression may be observed, while in other cases only one is to be noted. There has been much discussion as to the significance of fatty changes in the lutein cells. It is a prominent though probably not characteristic feature of this stage. Together with this will be seen that the connective tissue trabeculae ramify more boldly through the lutein zone, while organization of the contents becomes more advanced, the process being due to invasion of the endothelial and connective tissue cells of the lutein layer. The central core of organizing tissue on the inner side and the theca to the outside are thus connected by a gradually shrinking fibrous meshwork, showing more and more evidence of hyaline change. Little by little the lutein cells are crushed out, until finally, in the corpus albicans there remains

only the shrunken and hyalinized outline of the wavy lutein layer surrounding the central core of well formed connective tissue. The sharp outline of the hyalinized lutein layer, both internally and externally, is worthy of note, indicating the remarkable special reaction of the lutein cell even after its death.

ORIGIN OF THE LUTEIN CELLS

Such a complex question as this cannot, of course, be adequately discussed in the limits of the present paper. I shall merely indicate one or two facts which the study of my cases has brought out and which seem to throw light on this problem. The theory of the connective tissue origin of the lutein cells was supported by von Baer, the discoverer of the human ovum, and, after him, by His, von Köllicker, Spiegelberg, Paladino, Schottländer, Clark, Holzl, Nagel and others. On the other hand, the theory of the epithelial genesis of the lutein cells has found able supporters in Bischoff, Pflüger, Call and Exner, Schulin, Waldeyer, Sobotta and others. The latter theory, moreover, is favored by most of the modern German school of investigators who have contributed so much to our knowledge of the corpus luteum.

The question of the origin of the lutein cells in the lower animals has been conclusively settled by the exhaustive studies of Sobotta[4] on mice, rabbits, guinea-pigs and other mammals. Sobotta's studies indicate that in the lower animals, at least, it is from the epithelial cells of the membrana granulosa that the lutein cells are derived. It is questionable, however, whether these findings may be taken as applying to the human corpus luteum, especially since there has been such a paucity of accurate studies of the human structures.

Without going into the evidence pro and con, I may say that the balance was thrown decidedly in favor of the epithelial origin of the lutein cells by the studies of Robert Meyer on very early stages of corpus luteum development, as already mentioned. The early corpora

lutea described by me in this paper fully confirm Meyer's claim that the cells of the membrana granulosa do not undergo degeneration after follicular rupture. Furthermore, the "paralutein" cells found in many corpora lutea, constituting a distinct zone between the lutein layer within and the theca externa to the outer side, are, with scarcely a doubt, developed from the theca interna. If this be true, there is no reasonable doubt of the origin of the lutein cells from the epithelium of the membrana granulosa.

Finally, the demonstration, as seen in Figures 1, 2, 3, 4 and 5, of a direct transformation of the granulosa cells into, first, lutein-like cells and then into actual lutein cells, is the strongest and most direct histologic evidence that can be brought to bear on this question. The great desideratum at the present time is the secural of many more early corpora lutea, so that all possible stages may be described in the actual conversion of granulosa cells into lutein cells. Such evidence is infinitely more valuable than any that can be obtained from the study of the mature corpus luteum.

ATRESIA FOLLICULI AND THE THECA LUTEIN CELLS

Only a very small percentage of the follicles in the ovary attain maturity, with the discharge of their ova and the development of corpora lutea. The great number sooner or later exhibit the phenomenon of atresia, which is characterized by degeneration of the ovum and of the epithelial cells of the granulosa. I shall not here discuss the influence which brings about this arrest in the development of the follicles, except to say that it seems to emanate from the discharged ovum. The cystlike cavities resulting from atresia are found in practically all ovaries during the reproductive period, and not infrequently even in the ovaries of fetuses and young children. When present in excessive number, they give rise to the well known fibrocystic disease of the ovary. The later history of the cystic atresic follicle is a gradual process of oblitera-

tion. In other words, the two varieties of atresia folliculi described by Seitz,[6] the cystic and obliterative, are in reality only different stages of the same process.

The theca cells of the atresic follicle, as is well known, exhibit a striking change during pregnancy, giving rise to the so-called "interstitial glands." Although no special attention seems to have been paid to their behavior in the nonpregnant condition, the arrangement of these cells strongly suggests that these cells possess some sort of function. What the relation of the theca lutein cell is to the paralutein cell already described I do not believe can be stated in the present stage of our knowledge.

As to the clinical significance of atresia folliculi, we may look on the process as, within certain limits, physiologic. On the other hand, the so-called fibrocystic ovary, to which so much pathologic importance was attached in the past, represents usually a marked exaggeration in the number and size of the atresic follicles. The particular point which struck me in going over my cases was that the ovaries which exhibited extreme degrees of follicular atresia, i. e., the fibrocystic ovaries, were almost always associated with excessive menstruation. I hasten to add that I do not look on the fibrocystic disease as the cause of the excessive menstruation. I do believe, however, that, like the latter, it is an evidence of excessive ovarian function. The majority of these ovaries are found in association with pelvic inflammatory disease, which brings about a greater or less increase in the blood supply of the ovary with hyperfunction as the natural result. Another result of the ovarian hyperemia is a stimulation of the growth of the follicles throughout the ovary. Only one of these each month, as a rule, comes to rupture, the others forming the numerous cavities of varying size, with or without epithelium, scattered throughout the ovary. If this view is correct, the presence of the fibrocystic ovary is an important index

6. Seitz, L.: Arch. f. Gynäk., 1906, lxxvii, 203.

of ovarian hyperemia and hyperfunction, with excessive menstruation as the most frequent clinical symptom. This would explain, moreover, the frequent good results obtained by resection of a greater or less amount of ovarian tissue in cases of this type.

LUTEIN CYSTS

In the series of cases forming the basis of this paper, thirteen instances were encountered of cystlike cavities lined either completely or incompletely with lutein elements. This number is altogether too small to justify any conclusions as to the various types of these cysts or their significance. The discussion of such a complex subject, furthermore, would be out of place in a paper whose purpose is so general as this. I may simply say that the thirteen lutein cysts were all of moderate size, varying from 1 to 5 cm. in diameter, and all contained blood, this being especially characteristic. Furthermore, in all but four of the cases menstruation was described as more profuse than normally.

CLINICAL CONSIDERATIONS

One of the purposes of this study has been to determine whether any characteristic anatomic changes in the ovaries, especially as regards lutein tissue, are associated with the various disorders of menstruation. The histologic appearance of a tissue cannot be taken as an index of its functional activity. It would be of value, however, to know whether amenorrhea on the one hand or excessive menstruation on the other are associated with differences in the lutein cell content of the ovary, as one would expect might be the case.

One of the most important methods of studying the function of an organ is to study the results of its removal. I need only mention the valuable results yielded by this method of study in the case of other endocrine glands, such as the thyroid, parathyroid, suprarenal or pituitary. Fraenkel's plan of destroying the corpus luteum by the cautery point, crude and

imperfect as it was, is an illustration of the same method as applied to this structure. The indispensability of the corpus luteum to menstruation can be determined with far greater accuracy, however, by the histologic method. During the menstrual life of the normal woman, lutein tissue in some stage or another of development is always to be found in the ovaries. On the other hand, in the nonmenstruating woman corpora lutea are absent. Many cases might be described to illustrate this fundamental rôle of the corpus luteum in menstruation.

While it is true that a greater or less degree of maturation of graafian follicles is frequently observed in the ovaries of girls before puberty, and even in those of fetuses and new-born children, corpora lutea are never found. Although I have studied a considerable number of very young ovaries, I have never observed a corpus luteum in them. On the other hand, I have frequently seen well developed graafian follicles and atresic follicles.

To pass to the other extreme of menstrual life, corpora lutea are never found in the ovaries of women who have ceased to menstruate. For a number of months after the last menstrual flow, retrogressive corpora lutea are, of course, present, and degenerated lutein cells may be observed; but this does not alter the general rule.

Of especial interest in this connection is the amenorrhea of lactation. That ovulation occurs during this period is obvious from the frequency with which impregnation occurs among nursing women. Certainly, therefore, one must expect to find corpora lutea in the ovaries of lactating women. Why, then, is menstruation so frequently absent during lactation? The evidence all indicates that the menstrual function of the corpus luteum is nullified by the new element which comes into activity during lactation, i. e., the influence of the functioning mammary gland. This influence is exerted through the medium of a hormone, which

tends to inhibit or to counteract the secretion of the corpus luteum. A similar explanation suggests itself with regard to the amenorrhea of hypopituitary obesity (dystrophia adiposogenitalis), while the amenorrhea of anemia, phthisis and other debilitating conditions is due either to an inhibitory effect on the secretory cells of the corpus luteum, or, more probably, to the failure of ovulation itself. Which of these two factors is responsible can be determined only by the careful study of ovaries from women suffering from these various diseases. So far as I know, such studies have not yet been made.

With regard to the opposite condition of excessive menstruation, the problem is much more difficult and complex. Many factors are to be considered in attempting to explain uterine bleeding, as emphasized in a previous paper before this section.[7] At present, however, we are dealing only with the possible rôle of the ovary in this connection.

As is well known, Hitschmann and Adler[8] have attempted to show that in the great majority of cases uterine bleeding is due to either functional or organic disturbance in the ovaries. For example, such conditions as salpingitis are especially apt to produce excessive menstruation when the ovary is involved in the inflammatory disease. When the ovary is free, there is less likelihood of menorrhagia or metrorrhagia. This rule, if I may so speak of it, does not, of course, apply to diseases such as carcinoma of the uterus, in which the bleeding is due to actual local destruction of tissue and invasion of blood vessels by the disease.

Since it seems to be demonstrated that the corpus luteum is the cause of normal menstruation, it would seem most probable that we must look to disturbance of this structure for an explanation of the disorders of menstruation. The histologic evidences of hyperfunction would naturally be either overdevelopment of the normal corpus luteum, of the presence of other

7. Novak, Emil: The Pathologic Physiology of Uterine Bleeding, THE JOURNAL A. M. A., Aug. 22, 1914, p. 617.
8. Hitschmann and Adler: Arch. f. Gynäk., 1913, c, 233.

lutein tissue than that to be found in the corpus luteum (accessory corpora lutea, corpus luteum cysts, etc.). A careful analysis of my cases has failed to reveal anything like a direct relation between the degree of lutein the menstrual flow. Speaking generally, the corpus development in the ovary and the clinical intensity of luteum from a case of excessive menstruation shows no greater development than that from a case of scanty menstruation at a corresponding stage in the menstrual cycle. Such a conclusion is not justified unless both ovaries are thoroughly ransacked in all pa.+s so that no lutein tissue structures will be overlooked. This was done, as has been mentioned, in 102 cases of this series, and it is of course on these alone that I have based the assertion that variations in the amount of menstrual flow are not due to differences in the degree of development of the lutein tissue of the ovary. This does not, however, preclude the possibility of functional increase or decrease being the cause of increase or decrease in the menstrual reaction. Nor can we forget the all important fact that even though the ovarian secretion is the immediate cause of menstruation, this function is also influenced by practically all the other endocrine glands of the body. The ovary is merely the portal through which the entire ductless gland change exerts its influence on the functions of the female generative organs. Whereas formerly anatomic causes were presupposed in practically all cases of uterine bleeding, now the evidence is pointing more and more clearly toward the importance of functional disturbances in the ovary and of the endocrine system of which it is a part. To this general principle, the bleeding caused by such actually destructive lesions as cancer is of course an exception.

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ABSTRACT OF DISCUSSION

Dr. Carey Culbertson, Chicago: I was pleased that Dr. Novak regards the lutein cell as the histologic derivative of the membrana granulosa—hence of embryonic epithelial origin

—rather than as modified from the internal theca. This opinion is in accord with my own teaching during the past ten years. The corpus luteum must be thought of as implying not only folliculation, but ovulation, hence I agree with the speaker again in his remarks anent Dr. Reynold's description of the atretic follicles, that is, that in the atretic follicle the band of more or less degenerated cells does not represent lutein cells. A follicle that has become cystic before casting off its ovule can never develop a corpus luteum, hence, can never produce a hormone, nor eventually result in a corpus albicans. Another point in Dr. Novak's paper which requires reinforcement is that pertaining to the theca interna. This represents a very interesting cell change, indeed, on which the corpus luteum seems to be absolutely dependent. The corpus luteum must not be thought of as a histologic entity in that it can exist by itself, be transplanted, etc. It depends for its cell development, for its activation, directly on the underlying theca wherein we find the essential blood supply. Indeed, after all, the term "activation" may mean nothing but vascularization—the dilatation of capillaries with the consequent imbibition of serum whereby certain special cells reach the height of development and are thereby able to produce a certain active principle called a hormone.

Dr. E. Novak, Baltimore: As Dr. Culbertson remarked, the tendency in this country has apparently been in favor of the connective tissue origin of the lutein cell, probably as a result of the influence of certain American writers. If such observations as those which I have reported are confirmed, it will be necessary to revise this teaching. The evidence of the epithelial origin of these cells is based on the following observations: (1) The membrana granulosa is not lost after follicular rupture, but remains practically intact and virile; (2) a direct transformation of the granulosa cells seems to have been demonstrated; (3) the theca cells, while epithelioid and fatty shortly after follicular rupture, soon exhibit a retrogression to the ordinary connective tissue type; (4) if, as seems almost certain, the paralutein cells are derived from the theca interna, the lutein zone must represent the transformed granulosa; (5) exhaustive studies of the corpus luteum in lower animals have clearly demonstrated the epithelial origin of the lutein tissue in these animals. The time is soon coming when the mystery which has always enshrouded the menstrual phenomenon will be dissipated. We are rapidly accumulating facts which will sometime enable us to treat menstrual disorders as rationally as we treat such analogous disorders as those of the thyroid gland. There can be little doubt that perfected organotherapy will play a more important rôle in the management of many of these cases in the future than it has in the past.