RELATION OF THE OVARIAN CYCLE TO ENDOCRINOLOGY*

BY

NINIAN McI. FALKINER, Sc.D., M.B., B.Ch.
F.R.C.P.I.

VISITING GYNAECOLOGIST, ROYAL CITY OF DUBLIN HOSPITAL;
ASSISTANT TO MASTER, ROTUNDA HOSPITAL, DUBLIN

Opening this discussion I shall confine myself to that part of the ovarian cycle which is under the influence of the corpus luteum. I hope, however, that other speakers will fully discuss the role of the anterior pituitary gland and of the follicle system in the ovaries.

The material which I have at my disposal consists of eight specimens of corpora lutea from the menstrual cycle and from pregnancy; some of these are accompanied by the corresponding uterine mucosa. Some of the specimens have been illustrated in an article published in the *Irish Journal of Medical Science* (January, 1933). In this paper an effort was made to elucidate the significance of haemorrhage in the human corpus luteum.

At the meeting of the British Medical Association in Dublin in 1933 Professor Novak stated that Hartman's views with regard to an active substance derived from the anterior pituitary gland as a cause of the onset of menstrual bleeding had been abandoned. I had endeavoured to show that in the human corpus luteum the onset of haemorrhage in the uterine mucosa was accompanied by a synchronous haemorrhage in the corpus luteum. This, to my mind, explained the very rapid degeneration of the corpus luteum of menstruation. On the other hand, in the corpora lutea of pregnancy that I had had the opportunity of examining I had never been able to demonstrate gross bleeding. Novak did not agree with my interpretation of the series that I had collected. However, he thought that further investigation might do something towards elucidating the problem.

There is no doubt that haemorrhage occurs in the corpus luteum at various stages of its history, and this fact makes it very difficult to state that a haemorrhage seen at the time of the onset of menstruation can be attributed to any specific cause. The one conclusion in my study of the past two years is that no corpus luteum from pregnancy has shown the presence of bleeding.

First Specimen

No. 7749, iii, 20; examined July 19th, 1932. In an unmarried patient, aged 18, menstruation had been irregular, but as a rule there was a twenty-eight-day interval. She had pain in the left side, but the uterus was normal in position. Laparotomy was performed on August 3rd (fourteenth day of cycle), when a retrocaecal appendix was found showing signs of recent inflammation. Appendicectomy was performed, and the corpus luteum was resected from the left ovary. Bleeding or menstruation occurred within forty-eight hours of the operation.

Macroscopically the section through the meridian of the corpus luteum showed a very definite stigma. The measurements after fixation were 2 cm. by 0.9 cm. The history and the appearance of the corpus luteum suggested that ovulation had preceded the operation by a comparatively short period, possibly two days or less.

Apparently a resected corpus luteum separates from the ovarian tissue, carrying with it both the theca externa and the theca interna. This was certainly the case in this specimen and in other corpora lutea that I have resected.

A photomicrograph ($\times 7$) depicted the general characteristics. At this magnification the main features recognized

were: (1) A central cavity occupied by a clear coagulum at the pole further from the stigma. A collection of extravasated blood occupied that part of the cavity near the stigma. Although this blood extravasation was most marked at this part of the cavity small quantities were present contiguous with the inner limits of the luteal cells. (2) The luteal tissue was not markedly folded, and thus varied greatly in depth. Its inner margin was somewhat irregular, a feature more easily recognized at the higher magnification.

Under a high magnification further features were revealed. The cells of the theca interna were easily distinguished lying in irregular wedge-shaped masses among the luteal cells, which were larger and showed varying degrees of vacuolation. Tracing the theca interna cells towards the centre of the corpus luteum it became increasingly difficult to identify them. The luteal tissue was vascularized to a great degree, but not completely. Where the luteal cells were contiguous with the central cavity there was at some places no connective tissue limiting their border. In the main, however, there was a definite layer of loosely arranged connective tissue cells bordering the internal surface of the luteal cells and separating it from the central cavity.

A remarkable feature of these cells was their arrangement into centripetal strands, especially where they were in contact with the blood extravasation. In the cytoplasm of such cells small granules of blood pigment were seen.

Summary.—This was a very young corpus luteum, as instanced by the incomplete development of its fibrous and vascular structure. The degree of vacuolation in the luteal cells suggested an already active function. The extravasated blood was in all probability derived from the vessels broken at ovulation, but the distribution of the blood around the margin of the central cavity was possibly the result of haemorrhage arising from the vessels of the theca interna. Williams regards this latter source as the most important; Novak, however, does not confirm Williams's opinion.

Second Specimen

This was also a comparatively young corpus luteum, taken out on the thirteenth day of the menstrual cycle, but in this case the cycle was only twenty-one days. It showed many characteristics of the previous specimen, but appeared to be more fully formed, and might be regarded as being four days after the date of ovulation. The distribution of bleeding was very wide. This type of haemorrhagic corpus luteum is responsible for the difficulty in making an estimate of the significance of the haemorrhage in the corpus luteum.

Third Specimen

No. 100, iii, 42; examined April 29th, 1932. In an unmarried woman, aged 34, menstruation was regular, with a periodicity of twenty-eight days. She had pain in the back, and there was retroversion of the uterus. Appendicectomy was performed on May 9th, 1932, the twenty-seventh day of the cycle (Gilliam suspension; corpus luteum resected). The specimen was fixed in Da Fano's solution. The measurements of an approximately meridian section, after fixation, were 1.8 cm. by 1.2 cm. The removal of this corpus was followed by the onset of menstrual bleeding on the following day.

A photomicrograph ($\times 7$) depicted the general characteristics of this specimen. The main features to be recognized were: (1) a central cavity occupied by a clear coagulum, in the midst of which was a curious tongue of luteal tissue which was really contiguous with the rest of the luteal cells, but projected into the cavity in a remarkable fashion; (2) a fairly even layer of luteal

* Read in opening a discussion in the Section of Obstetrics and Gynaecology at the Annual Meeting of the British Medical Association, Melbourne, 1935.

tissue, averaging about 2 mm. in depth and presenting a moderately folded appearance, seen especially at the lower pole; (3) the connective tissue strands among the luteal cells and bordering their internal limits was well marked. This layer, dividing the luteal cells, showed up as a dark line, owing to the deep staining of the connective tissue cells, and the presence of a moderate amount of red blood cells which were possibly already extravasated.

High-power magnification revealed a very definite differentiation of the theca externa from the theca interna. The former was congested and vascular. The cells of the latter were well shown by virtue of their argentophil tendencies, and were seen distributed among the luteal cells. The luteal cells were vacuolated, but not to such a marked degree as in the specimen just described.

Summary.—In this corpus luteum there was no gross haemorrhage, although scattered through the cavity there were small collections of red blood cells. The luteal cells were well differentiated from the theca interna cells by the nature of the fixation. The connective tissue was well developed in contrast with the first specimen described. In the connective tissues there was congestion or a very moderate extravasation of blood.

Fourth Specimen

No. 7603, iii, 93; examined June 8th, 1932. A five-para, aged 39, menstruated with irregular periodicity, the intervals varying between twenty-six and thirty-one days. There was a prolapsed uterus, which was enlarged and retroverted. Abdominal hysterectomy was performed on June 9th, the twenty-fifth day of the cycle.

The specimen is described after the previous one, although the actual age in days is possibly younger, because the uterine mucosa showed an immediately premenstrual condition, as regards commencing blood extravasation in the stroma, the gland picture, and the appearance of the individual cells of the stroma.

I do not take this specimen in itself as very good evidence of the appearance of the corpus luteum just before the onset of menstruation, but I have another specimen, obtained on the thirtieth day of the cycle (menstruation had not yet occurred), whose appearance is very similar. The histology, however, of this specimen is very striking, and the reader can criticize the conclusions since all the facts are before him, including the important evidence that a bimanual examination was made twenty-four hours before operation.

The specimen measured 1.7 cm. by 1.4 cm. after fixation. In the photomicrograph ($\times 7$) of this specimen could be seen a central cavity occupied by a clear coagulum. The luteal tissue was somewhat more folded than in the previous specimens, and its average depth was greater—up to 4 mm. The most obvious feature in the photograph was the amount of congestion in the vessels, not only of the theca externa, but of the capillaries in the luteal tissue and in the connective tissue between the luteal tissue and the central cavity. This condition of congestion compared most interestingly with the endometrium.

Again, in this specimen the theca interna and theca externa were easily distinguishable, the cells of the latter forming characteristic wedge-shaped masses between the folds of the luteal cells. The whole structure was very well vascularized; it had a complete stroma of connective tissue, which included a well-defined layer between the luteal tissue and the central cavity.

Summary.—This corpus luteum, which I conclude had been removed just before the onset of menstrual bleeding, showed very marked congestion and commencing haemorrhage in the area between the luteal cells and the central cavity, but as yet the blood had not burst its way into the central cavity to any marked extent. The number

of luteal cells, or rather the mass of luteal tissue, appeared greater than in the previous specimens, but vacuolation of the cells was less marked than in the first specimen described.

I have, in addition to the corpus luteum, the mucous membrane of the uterus, which was typically premenstrual, with regard to both the gland picture and the capillary dilatation. This showed very well the relation between the active corpus luteum and the secreting endometrium.

Fifth Specimen

No. 7450, iii, 11; examined March 31st, 1932. A three-para, aged 39, who had been married for ten years, had had her last pregnancy in 1926. Her menstrual periodicity was twenty-eight days. An abdominal tumour reached to the ensiform process. Total hysterectomy was performed on April 4th. The tumour, though very large, was intraligamentary; it had not distorted the uterine cavity, and there had been no disturbance of the menstrual cycle. The menstrual flow started the evening before the operation; thus the operation was undertaken in the first twenty-four hours after the onset of the menstrual flow.

The uterine mucosa presented the following features. The surface epithelium was in most places intact, but there were many areas where it had become ragged and stripped. There was a well-marked compact layer of stroma wherein the individual cells were large, but there was remarkably little blood, either extravasated or in the nature of congestion. The glands presented a collapsed condition, as did the whole mucosa in comparison with the mucosa in the previously described specimen. The corpus luteum measurements of an approximately meridional section after fixation were 1.4 cm. by 1.2 cm.

The photomicrograph ($\times 7$) showed the general characteristics of the specimen. The central cavity was filled to a large extent with clear coagulum, while at the deeper end of the structure the cavity was occupied by a good deal of extravasated blood, which formed a fairly even layer around the margins of the central cavity. Its position as regards the connective tissue which separated the luteal cells from the central cavity was very definite. It lay in the cavity of the corpus luteum. The luteal cells were not well stained, and were smaller than in the previous specimens. There was a good deal of vacuolation of the luteal cells. There was no congestion of the capillaries between the luteal cells, but the vessels in the theca externa were dilated. The staining of the whole section was much less intensive than in the case of the previous specimen.

Summary.—This corpus luteum, removed on the first day of menstruation, showed an extravasation of blood into the central cavity which was not limited to any part of the periphery of the cavity. The luteal tissue was not well stained, and was anaemic. The theca externa and theca interna were both well preserved; the cells of the latter were well stained, and showed up remarkably in contrast with the luteal cells. The depth of the luteal tissue was less than in the previous specimen.

Sixth Specimen

This specimen (No. 99) was described in the account of an early ovum in the *Journal of Obstetrics and Gynaecology of the British Empire* (vol. xxxix, No. 3). It was resected on the fifth day after a missed period, and was fixed in picroformol. Its measurements were 1.2 cm. by 0.7 cm. The depth of the luteal tissue was very even, and measured 4 mm.

A photomicrograph ($\times 7$) showed a rather collapsed central cavity with no gross haemorrhage in it, but more connective tissue than in any of the previous specimens. The border of connective tissue between the luteal cells

and the central cavity was well defined. The luteal cells were well stained, and the vascular channels were shown up by the deep staining of their walls, although there was no congestion. There was much vacuolation. The theca interna cells were beautifully differentiated, while the theca externa was well marked and vascular.

Summary.—This corpus luteum showed no gross haemorrhage in the central cavity, although small collections of blood cells could be recognized. The central core was markedly fibrous, and the general appearance of the luteal tissue suggested continued activity.

Seventh Specimen

This corpus luteum (No. R 1) was removed in the course of a hysterectomy during pregnancy in a case of multiple fibroids, the size and position of which precluded continuance of pregnancy or a conservative operation. The patient was suffering from acute intestinal obstruction due to impaction at the time of operation. (I am indebted to the Master of the Rotunda Hospital for the opportunity of describing this specimen.) Pregnancy had lasted eighty-four days since the last period, so the age of the corpus luteum may be calculated as about seventy days. It was fixed in formalin, and the section measured 2 cm. by 0.7 c.cm.

Magnified by seven diameters, the picture showed the general structure very well. The central cavity was occupied by firm fibrous tissue; it had collapsed since fixation, and apparently contained a cystic centre. There was no trace of haemorrhage in this specimen. The luteal cells stained well, and vacuolation was well marked. The endothelial walls of the capillaries in the luteal tissue were also well stained, and there was no congestion. The theca interna cells were well differentiated, while the theca externa was very definite, and showed up as a well-stained and vascular area.

Summary.—This corpus luteum showed no haemorrhage either macroscopically or microscopically. The luteal tissue was bulky and well vascularized. The connective tissue was more fully developed than in any of the previous specimens, and all the constituent cells were well differentiated. Comparing it with the previously described corpus luteum of pregnancy it was larger, and its individual luteal cells were not so well stained.

Eighth Specimen

This specimen was from a pregnancy which had lasted ten weeks, and was terminated owing to the patient's general condition. In this case the corpus luteum again showed no haemorrhagic extravasation.

The Decidua in Early Pregnancy

Some lantern slides illustrated a few interesting points with regard to the decidua in early pregnancy. The first was a section of the uterus in a premenstrual condition, illustrating the condition before implantation. The second was the corresponding decidua from the last corpus luteum at the tenth week of pregnancy, which illustrated the fully developed placental attachment. During the period immediately preceding implantation and the period in which the trophoblast is actively growing there is an alteration in the mode by which the ovum obtains its pabulum. This slide was a photograph of part of the decidua of the ovum I described in the *Journal of Obstetrics and Gynaecology of the British Empire* (vol. xxxix, No. 3). It showed the surface epithelium of the uterus in a stage of active secretion, and one cannot doubt that this is a feature of early pregnancy due to

corpus luteum activity, the function of which must be to provide pabulum for the ovum before and during embedding. That the human ovum rapidly frees itself from the influence of the corpus luteum is recognized in many reported cases of removal of the corpus luteum during pregnancy without interruption of the pregnancy.

The photomicrograph showed the first stage of invasion of the maternal blood vessels by the trophoblast, and again this specimen was derived from the 15-day-old ovum. Here were seen the chorionic villus, the proliferating cells of Langhans's layer, the implantation cavity, the resorption syncytium, and the proliferating syncytium. This proliferating syncytium, so fully described by Florian, is that part of the chorionic structure which is concerned with the invasion and destruction of the maternal decidua. The next slide showed the proliferating syncytium in a higher magnification, and here could be seen the syncytial structure displacing and replacing the endothelial wall of a dilated maternal capillary.

The points I wish to stress in this discussion are only concerned with the corpus luteum. I am satisfied that the administration of luteal extracts, in the present state of our knowledge, is not of great clinical use. Whether it will ever be of much advantage to produce an artificial menstrual cycle by the administration of folliculin and progesterin is open to argument. However, the administration of progesterin may be useful in cases of repeated and threatened abortion, and my experience with it has satisfied me that results can be obtained.

The corpus luteum extract may act in one of two ways. It may produce a satisfactory condition for embedding of the ovum if its administration is commenced before the first period is missed, and it may help to maintain the early decidua in a condition suitable for development of the placenta. Another way in which it may reduce the liability to abortion is that it reduces the irritability of the uterine muscle, rendering it less likely to undergo contractions.

I think we are all agreed with Professor Novak when he says that "... the results of gynaecological organotherapy have been disappointing, while the accomplishments of gynaecological endocrinology have been numerous and brilliant." I would also call attention to the paper by T. N. A. Jeffcoate on "Sterility Due to Ovarian Dysfunction" (*British Medical Journal*, February 23rd, 1935).

Congenital absence of one kidney, though uncommon, is not extremely rare. A true unilateral kidney is usually associated with a single unilateral ureter and a single opening into the bladder; thus half of the trigone of the bladder may be atrophied, and genital abnormalities may exist. The renal vessels are usually absent or quite rudimentary. Reports by different authors vary as to the frequency of absence of the corresponding suprarenal gland. J. R. H. Turton and J. C. F. Lloyd Williamson (*Brit. Journ. Surg.*, October, 1935, p. 327) record a case of rupture of a congenital solitary kidney, and refer to four others. This phenomenon is extremely rare; it occurs most commonly in men, usually on the left side, and in young patients, the figures in the present series being: males to females, 4 to 1; left to right, 5 to 0; and average age 21 years. In cases of renal injury, where nephrectomy is contemplated, the following procedures are held by the authors to be vital. Where the patient's condition permits intravenous pyelography should be employed in order to demonstrate the presence or absence of a second functioning kidney. In the severe type, manual palpation for the contralateral kidney must be performed at the operation. If a solitary kidney is ruptured efforts should be made to arrest haemorrhage by conservative suturing or partial nephrectomy.