

CRITICAL REVIEW

The Internal Secretion of the Ovary.

By HENRY RUSSELL ANDREWS, M.D., B.S. (Lond.), M.R.C.P. (Lond.),
Assistant Obstetric Physician to the London Hospital.

In this review an attempt will be made to bring together the evidence which exists as to the manner in which the ovary affects the organism, and the reasons for believing that it provides an internal secretion. The transplantation experiments will be described which furnish evidence in support of this supposition. The results of treatment with ovarian extract will be reviewed, and an account will be given of the interesting work that has been done recently on the functions of the corpus luteum, and on pathological conditions of this structure which are seen in conjunction with pathological conditions of the ovum.

I. The influence exerted by the ovary upon general metabolism.

It has been known for many years that the ovary exerts in some way an influence on the organism, and that removal of the ovaries is followed by marked results. Several observers have tried to prove experimentally how the metabolism is affected by removal of the ovaries, but the exact nature of these changes is not known.

Fehling, who was instrumental in establishing the operation of removal of the ovaries as the treatment for osteomalacia, examined and found no changes in the urine of seven osteomalacic patients before and after the removal of the ovaries, from which definite conclusions could be drawn as to the nature of the change in metabolism effected by the operation.

In 1894 and 1896 Siegfried Neumann published the results of his experiments. He says that in osteomalacia not only the metabolism of the bones but that of the whole organism suffers pathological changes. In the later stages there is a destruction of proteid, not only in the bones, but in the whole organism. In the milder cases removal of the ovaries has a marked effect in diminishing the excretion of calcium, magnesium, and phosphorus, and also in diminishing the destruction of proteid.

Curatulo and Tarulli in 1895 carried out a series of experiments on bitches. They were fed on a regular diet until the average daily excretion of nitrogen and phosphorus was uniform, and then the

ovaries were removed. The operation was followed by a great diminution in the excretion of phosphorus. They conclude that "the ovaries, like the other glands, according to Brown Séquard's theory, continually pour into the blood an internal secretion whose chemical composition is as yet unknown, which favours the oxidation of phosphorus-containing organic substances which build up the bones. It follows that by removal of the ovaries a retention of organic phosphorus is brought about, which results in a greater accumulation of calcium and magnesium phosphate and the restoration of the normal firmness of the bones."

Neumann and Vas investigated the influence of ovarian preparations on metabolism by three series of experiments:—

1. Effect of ovarian preparations on normal female animals. They found that Merck's tabloids given even in excessive doses made no marked difference in the amount of nitrogen, calcium, or phosphorus in the urine. A preparation made by themselves from cows' ovaries, however, caused an increase in the amount of nitrogen, calcium, and phosphorus excreted.

2. Effect of removal of ovaries. Neither immediately nor later was there any marked change in the amount of phosphorus excreted.

3. Effect of ovarian preparations on animals whose ovaries had been removed. There was an increase in the amount of phosphorus and calcium excreted, which continued after cessation of treatment. There was a less marked increase in the amount of nitrogen excreted during treatment.

Falk in 1899 repeated Curàtulo's and Tarulli's experiments, but did not arrive at the same results. In two bitches from which he removed the ovaries he found practically no difference in the amount of phosphorus excreted before and after the operation.

From the results of these various experiments we can only draw the conclusion that we do not yet know how metabolism is affected by removal of the ovaries. In the light of modern knowledge on excretion of phosphorus, the experiments of Caràtulo and Tarulli would be of little value, as it is known that a large proportion of the phosphorus excreted in the urine is derived from nucleo-proteid taken in as food. Thus it is possible that the increased amount of phosphorus excreted after ingestion of fresh ovaries or ovarian extract is derived from the nucleotin phosphoric-acid of the nucleo-proteid. Control experiments should be performed by feeding with other glandular organs.

II. *The means by which this influence is exerted:—*(a) *Nerve influence.*(b) *Internal secretion.*

One theory, which has received very little support, is that the ovary influences the organism through the nervous system.

Elisabeth Winterhalter described a sympathetic ganglion in the human ovary. She said that the ovary possessed (1) a peri-vascular plexus and (2) a ganglion in the zona vasculosa, consisting of cells of the character of sympathetic ganglion cells.

Von Herff says that the presence of ganglion cells in the ovary cannot be considered proved, although their occurrence in the sympathetic plexus in the hilum is probable. "There can, however, be no talk of a 'ganglion' in the ordinary sense of the term; no such thing is found."

The "nervous influence" theory is disproved by the transplantation experiments.

(b) *Transplantation of ovaries.*

Knauer removed both ovaries in rabbits, and implanted them either in the mesometrium or between the fascia and muscle of the belly wall. He sums up his results as follows:—

In the rabbit the ovaries can be grafted on to peritoneum or muscle. Ovaries so grafted are not only nourished but are functionally active, *i.e.*, ova develop, ripen, and, in some circumstances, can even be expelled from the follicles. Such ova are capable of being impregnated, and normal pregnancy with birth of well-developed young may result. A certain amount of the transplanted ovary always dies. If the whole ovary dies the whole genital system atrophies. The influence which the ovaries exert upon the organism, and especially upon the uterus, is intimately connected with the main function of the ovaries, the formation of ova. Ovarian tissue which has ceased to develop ova has also ceased to carry out its other functions.

The atrophy of the uterus following removal of the ovaries is due, not to cutting off blood supply, but to cutting off ovarian influence, and this influence is proved by Knauer's experiments not to be a nervous one. As long as a functionally active ovary is present in the organism it does not matter in what part of the body it is.

Grigorieff transplanted rabbits' ovaries on to the broad ligament, peritoneum of the vesico-uterine pouch, etc. He found that the transplanted ovaries differed in no way from ovaries in their normal

situation, that follicles ripened and burst, that ova could become impregnated and normal pregnancy result.

Glass transplanted a healthy ovary from a girl of 17 (removed on account of stricture of the vagina) to a patient of 29 whose ovaries had been removed two years before. The ovary was sutured in the normal situation. The patient had been much troubled by menopause symptoms. Six days after the transplantation of the ovary she had erotic dreams, 16 days later she had uterine hæmorrhage for two days, and six months later another uterine bleeding lasting three days. Eight months after the operation she was perfectly well.

Dudley, after removing a double pyosalpinx from a patient of 21, implanted the right ovary on the fundus uteri. The patient menstruated regularly afterwards.

Halban removed the ovaries of a new-born guinea-pig and transplanted them under the skin. The uterus and mammary glands developed as well as in normal animals. Corpora lutea were found in the ovaries when they were examined later. The uterus and mammary glands of control animals whose ovaries were removed but not transplanted remained in an undeveloped condition.

The results of these various transplantation experiments are best summed up in Knauer's words:—"As long as a functionally active ovary is present in the organism it does not matter in what part of the body it is situated." The deduction from this fact must be that the ovary exerts its influence over the organism by means of its connection with the blood, not through the nervous system, and this is practically the same thing as saying that the ovary exerts its influence by means of an internal secretion.

III. *Results of ovarian medication.*

Since 1889 the influence that the ovary exerts on the organism has been generally supposed to be due to the presence of an internal secretion. The ancients administered the testicles of the fox, the liver of the wolf, the lungs of the deer, etc., but apparently never used the ovary medicinally.

In 1889 Brown Séquard made his first communication on testicular extract. He admitted that a preparation from the ovary had analogous properties, but considered that the ovarian extract was much less active than the testicular, and was without special action.

In the same year Madame Brown injected 46 old women with ovarian extract, but without much success.

Villeneuve in 1892 prepared a watery solution from the ovaries

of guinea-pigs and injected it into five debilitated patients, three women and two men. It produced no effect on the men nor on one of the women, who was 90 years old. In the other two female patients, however, it was successful in increasing their strength.

In 1896 a large number of papers on the subject of treatment with ovarian extract appeared.

Mainzer treated a patient who complained of heats, sweating, flushing, headache, sleeplessness, etc., after removal of both ovaries. She had previously had eighteen months' treatment with every other possible remedy with no benefit. There was rapid and very marked improvement when she was given a preparation of cows' and calves' ovaries.

Mond used two preparations, one from the whole ovary, the other from the contents of the follicles alone, in the troubles of the menopause both natural and post-operative, and in amenorrhœa due to uterine and ovarian atrophy. The results he obtained were good enough to warrant further trial of the treatment.

Mainzer in the same year published the results of further treatment with a preparation made from dried fresh ovaries. He found that the vaso-motor troubles of the natural and artificial menopause were completely removed, and saw good results in cases of primary and secondary amenorrhœa. In these cases the catamenia often made their first appearance or re-appearance during treatment. Nervous and hysterical patients in general were not at all improved. No bad results need be expected if the preparation is carefully made. The improvement did not last long after the treatment was entirely given up. Small doses should be given again from time to time.

Leopold Landau wrote that "ovarian extract is a remedy that enables us to diminish the severe troubles of the natural or artificial menopause, and usually to cure them, without any unpleasant results."

Bodon used 'ovariin' in cases of natural menopause with gradual improvement, and in a case of artificial menopause with very marked results. He also administered it to an epileptic girl with the result that the fits became much less frequent.

Jayle recorded six cases in which ovarian extract had produced good results in the treatment of the troubles of the post-operative menopause. He had also tried the treatment in three cases in which operation was indicated on account of endometritis and old salpingitis. In two of these cases there was no improvement, but the third patient felt so well at the end of a month's treatment that she would not hear of any surgical intervention.

Lissac published six successful cases. His conclusions were that

“ovarian opotherapy seems to ameliorate permanently or temporarily the majority of the troubles following oöphorectomy, particularly the flushings, insomnia, nightmares, and headaches.”

Muret employed ovarian opotherapy in 20 cases for troubles of the menopause, chlorosis, and amenorrhœa due to imperfect development of the genital organs. He found that the ovarian extract was always well borne and never gave rise to any unpleasant symptoms. In the natural and artificial menopause he found the results good. There was marked improvement in the cases of chlorosis and amenorrhœa, but the number of cases was too small for him to make any more definite statement.

Spielmann and Etienne treated six cases of chlorosis and amenorrhœa with fresh ovaries, powder of dessicated ovaries or ovarian extract. In four of the patients there was rapid improvement with re-appearance of the catamenia and a marked increase in the number of red blood corpuscles.

Fideli also obtained satisfactory results in treating cases of chlorosis with ovarian extract.

Chrobak treated three cases of post-operative menopause with ovarian extract. In the first case faintness, flushings, sweatings, etc., became less frequent under treatment, but returned when the treatment was discontinued. In the second case the attacks completely disappeared after 12 doses. The third case and one of natural menopause also improved under treatment.

In 1897 Jacobs and Touvenaint published results. Jacobs had treated 79 cases of troubles of the menopause, natural and post-operative, amenorrhœa, dysmenorrhœa, and anæmia with 75 successes. He also tried the treatment in two cases of neurasthenia with no benefit.

Touvenaint had excellent results in treating amenorrhœa and chlorosis, and good results in cases of artificial menopause. In cases of natural menopause his results were good enough to warrant further trial.

In 1898 Bestion de Camboulas published his monograph “*Le Suc Ovarien*,” which contains the best account of the subject that has yet appeared. He performed numerous injection experiments with ovarian extract on guinea-pigs, rabbits, and dogs, on males and on pregnant and non-pregnant females. He found that toxic effects were far more marked in males than in females. After large doses the males died with pyrexia, hæmaturia, sloughing of the injection wounds, convulsions, genital excitement, and in some cases paralytic phenomena. With non-toxic doses the males lost weight,

while the females gained weight. The resistance of pregnant females was much less than that of non-pregnant, and they all died with what corresponded to lethal doses for males.

The lesions found after fatal doses were congestion of viscera, most marked in the liver and kidneys, and minute hæmorrhages in the dorsal and lumbar regions of the spinal cord.

He records numerous clinical observations from his own practice and that of others. The element of suggestion was excluded; none of the patients knew what they were taking. No change in respiration or circulation was noticed.

He sums up his results as follows:—Troubles of the menopause, natural and artificial, disappeared or were much ameliorated by ovarian extract without other medication. Rapid improvement was always seen in amenorrhœa and chlorosis. The influence of the extract on the mental troubles which accompany genital lesions or follow oöphorectomy is a real one. Improvement in the general condition is marked in all cases. It must never be given to pregnant women, as it produces such grave effects on pregnant animals.

Fosbery, in 1897, reported successful treatment of climacteric flushings by ovarian extract in one case. The flushings were almost cured by the time three dozen palatinoids had been taken. After this the patient found that one palatinoid taken occasionally kept her free from flushings.

Dalché, in 1898, had seen good results in the treatment of menopause, artificial and natural, and in chlorosis. He considers that there is an antagonism between the thyroid and the ovary. In Graves' disease there is often amenorrhœa, in myxœdema often metrorrhagia, and conversely uterine bleeding is often treated successfully by thyroid extract. He considers the treatment also useful in amenorrhœa, dysmenorrhœa, melancholia, neurasthenia, hysteria, etc. He has seen no bad results, such as headache, nausea, or vomiting.

Cohn, on the other hand, writing in 1899, finds the results of all varieties of ovarian preparations disappointing, with only occasionally slight good results, although he used the same preparations as Leopold Landau, in whose hands their results were excellent.

Seeligmann, in 1900, says that his experience teaches him "that there is an internal secretion from the ovary which is necessary for the organism, and that this substance given in oöphorin tablets is most useful in the troubles of the menopause."

Baruch, writing in the same year, reports a good result in two

cases, fairly good in two others, entirely bad results in one, and in seven no result at all.

Flockemann, in 1901, reported six complete successes, four marked successes, nine partial successes, and nine failures, after double removal of the ovaries. He saw no bad results.

In analysing the observations of these various writers we find that good results were obtained in the treatment of:—

Troubles of menopause, natural or post-operative, by Mainzer, Landau, Bodon, Jayle, Lissac, Muret, Spielmann and Etienne, Chrobak, Jacobs, Touvenaint, Bestion de Camboulas, and Seeligmann.

Chlorosis and amenorrhœa, by Mainzer, Muret, Spielmann and Etienne, Fideli, Jacobs, Touvenaint and Bestion de Camboulas. Baruch, Mond, and Flockemann report a moderate degree of success.

Cohn is the only writer that I have been able to find who says that the results are nearly always disappointing. Most writers emphasise the fact that the treatment itself has no bad results. When bad results have been seen they have probably been due to faulty preparations. Many British gynæcologists have given a more or less extended trial to ovarian preparations, but have not published any results, a fact which makes it highly probable that the treatment did not meet with so much success in their hands as in those of the authors quoted above. An interesting point to be remembered is that some preparations have been made from the ovaries of heifers, sexually immature animals. It is possible that want of success has been in some cases due to the use of these inactive preparations.

The great difficulty in judging the therapeutic effects of ovarian extract in climacteric troubles is that these are mainly subjective. The objective signs—faintings, flushings, sweats, etc., are only occasional and transitory, and are too slight and too temporary to make it possible to take the patients into hospital and watch them. Hence the evidence as to the benefits conferred is derived from statements made by the patients, not from the personal observations of the physicians. The statements of patients are influenced sometimes by a desire to please their doctor. Benefit to subjective symptoms, or a belief that benefit has been conferred, is often produced by suggestion. The symptoms of the climacteric tend to diminish and disappear after a certain length of time without any treatment. This tendency to spontaneous amelioration is always present, and must be allowed for before concluding that improvement is due to treatment.

With regard to the cure of chlorosis, anæmia, and amenorrhœa by ovarian extract it must be remembered that these conditions can

be cured by other means. The practical question is, does ovarian extract cure them more quickly than anything else?

Methods of administration. (The following paragraphs are taken chiefly from Bestion de Camboulas' monograph):—

1. *Fresh gland.* Jayle, Lissac, Mainzer, Spielmann and Etienne used fresh ovaries minced, in sandwiches. Against this method of administration are the facts that it is repugnant to the patients, and that fresh ovaries will not keep more than three days, even on ice.

2. *Dry gland.* Ovarian powder has been much used, usually in pastilles, under the name of ovarine, ovaraden, oöphorin, ovigenine, or ovairine. Ovarine has sometimes a rather strong odour. Some have found that it decomposed and then produced headache, vertigo, vomiting, and palpitation. These symptoms were probably due to the presence of ptomaines. Bestion de Camboulas has had none of these bad results. He uses equal parts of sugar and fresh ovary, with enough gum to enable the mixture to be made into pills.

3. *Ovarian juice* or fluid extract, either watery, glycerinated, or alcoholic has been used by Bestion de Camboulas. The last cannot be used for injections. The two former can be administered by mouth, by rectum, or hypodermically. The ovaries of the sow are the best to use. They are easily obtained, of a good size, 3—4½ grammes, and the animals are not killed until they have farrowed, therefore the ovaries are sexually active. The ovaries of heifers are not active. Cows are too liable to tubercle. Ewes' ovaries are too small. Glycerine extract contains 10 per cent. of ovary. Aqueous extract contains 16 per cent., but does not keep so well, and is less active. Bestion de Camboulas considers that glycerinated extract and dry extract are the best preparations. They are equally efficacious, except that constipation yields more rapidly to the glycerinated extract.

IV. *The functions of the corpus luteum.*

Gustav Born, of Breslau, first suggested that the corpus luteum of pregnancy was a gland with an internal secretion, the function of which was to further the embedding and development of the impregnated ovum in the uterus. Too ill himself to work out this hypothesis experimentally he asked Ludwig Fraenkel to undertake the work. Fraenkel believes from his experimental researches that the corpus luteum has a wider function. During reproductive life it maintains the raised standard of uterine nutrition; the increase in size and blood supply of the uterus during these years, and the monthly hyperæmia, are the results of the internal secretion of the

corpus luteum. If an ovum is impregnated this secretion furthers its insertion and development, and if no ovum is impregnated it brings about menstruation. When corpora lutea are absent the uterus atrophies and menstruation ceases. The condition of the uterus before puberty and after the climacteric is due to the absence of corpora lutea.

The evidence that Fraenkel brings forward in support of his views, apart from experimental evidence, may be briefly summarised as follows:—

The microscopical structure of the corpus luteum suggests that of a gland. Large epithelioid cells, the so-called lutein cells, are arranged in regular rows and columns with capillaries between the rows, in a manner much resembling a liver acinus or the cortical layer of the suprarenal body. The lutein cells are the parenchymatous or glandular cells, and the capillaries serve not only for the nutrition of the gland but also, in default of other efferent ducts, for the carrying away of its secretion. Every single cell is surrounded by blood. The structure and size of the ripe Graafian follicle suggest that it has a further function than that of simply providing a shield for the ripening ovum. The size of the corpus luteum is greater than that of the unruptured follicle. This increase in size would be unnecessary if the corpus luteum were simply a transition stage between follicle and scar. It has been asserted that the increase in size of the corpus luteum is only a part of the general hyperæmia and hyperplasia of the genital organs that occurs during pregnancy. But the increase in size of the corpus luteum is out of proportion to that of the rest of the ovary; when the corpus luteum is most hyperæmic the rest of the ovary is markedly anæmic, and at the end of pregnancy when the increase in blood supply and hypertrophy of the genital organs are at their highest the corpus luteum is only a scar. All animals in which a uterine insertion of the ovum occurs possess well-developed corpora lutea, the oviparæ have only rudimentary corpora lutea or none at all. Sobotta and others have proved that the lutein cells are derived from the cells of the membrana granulosa and not from connective-tissue cells as some had supposed. There have been many recorded cases of double ovariectomy during pregnancy without disturbance of the pregnancy. None of these, however, have been during the early weeks.

Fraenkel would probably have modified some of his statements as to the influence of the corpus luteum on the decidua in the early weeks of pregnancy if he had been conversant with Peters' work on the embedding of the ovum. The former says:—"The corpus luteum

possesses the function of so preparing the uterus that the ovum can embed itself and develop in it. The ovum, before its insertion, is in a certain sense a foreign body not connected with the maternal organism by vessels or nerves, and so could not cause the changes which are seen in the endometrium before the ovum is embedded, viz., decidual changes." The more recent theory, as will be seen later, is that the corpus luteum is responsible for the activity of the trophoblast, and this theory can be grafted on to that of Fraenkel without any difficulty.

The following points were investigated by experiment:—

1. The influence of the ovary on the implantation of the impregnated ovum.

2. The influence of the ovary on the further development of the implanted ovum.

3. Whether this influence is exercised by the whole ovary, or by the corpus luteum alone.

Rabbits were chosen for these experiments. Their follicles burst just after parturition. They permit coitus at the same time. This coitus is fruitful, spermatozoa reach the ovary three hours later, seventy hours later the ova reach the uterus, and from four to seven days later the developing ova are embedded in the endometrium.

Fraenkel allowed numerous rabbits to copulate just after parturition. He removed the ovaries from thirteen of them, one to six days later, and killed the animals some time after and found the uterus empty in every case. The removal of the ovaries had prevented the implantation of the ova. Removal of one ovary in other rabbits had no effect on pregnancy. This was an important control experiment showing that shock, anæsthetic, etc., were not the cause of the non-implantation of the ova. When the ovaries were removed after implantation of the ova, the ova ceased to develop, but were not expelled from the uterus.

In order to show that the corpus luteum and not the whole ovary is concerned in permitting pregnancy to occur he destroyed with the galvano-cautery all the corpora lutea present in the ovaries, and did not remove the ovaries. The results were the same as when the whole ovaries were removed. There were sometimes twice as many ova as corpora lutea. He found that at least one corpus luteum must be left in order that pregnancy might continue.

Transplantation of corpora lutea delayed, but did not prevent, destruction of the ovum. He inferred from this that some secretion was carried from the transplanted corpora lutea by the blood-vessels,

and that any influence exerted by the corpus luteum could not be nervous.

Fraenkel next considers the influence of the corpus luteum on menstruation. The corpus luteum of menstruation in all animals resembles in every way that of pregnancy. Zschokke says that in the cow all corpora lutea are of the same size. Sobotta found that in the mouse the corpora lutea of follicles whose ova are unimpregnated are equal in point of size and development to those of follicles whose ova have been impregnated. Kreis compares the arrangement of the capillaries in the so-called "false" corpus luteum to that found in the liver. According to him, at the beginning of the second week the "false corpus luteum has the same appearance as that seen in the "true" in the third month.

Does the "false" corpus luteum cause the four-weekly hyperæmia? Removal of the corpus luteum causes atrophy of the uterus. Fourteen days after burning out the corpora lutea in rabbits Fraenkel found the ovaries healthy, but the uterus very much atrophied. Fraenkel has in nine cases burnt out a corpus luteum while performing laparotomy in women. In all but one of these the next period was missed, the patients having no loss of blood until three to eight weeks after the expected time.

Fraenkel sums up his deductions from his experiments thus:—
"The corpus luteum is a gland which is renewed every four weeks in women during reproductive life, and at varying intervals in animals. It controls the nutrition of the uterus in a cyclic fashion, prevents it from relapsing into its infantile or passing into its senile condition, and prepares the endometrium for the reception of the ovum. If the ovum be fertilised the corpus luteum continues to exist and to maintain the raised nutrition of the uterus during pregnancy. If the ovum be not fertilised the corpus luteum merely produces the hyperæmia of menstruation and then degenerates. There is, strictly speaking, only one corpus luteum, one real ovarian gland which regenerates itself periodically in slightly different situations and controls uterine life from puberty to the menopause. Menstruation is caused by the secretory activity of the corpus luteum, not by the pressure of the growing follicle on the ovarian nerves. This secretory activity causes the four weekly hyperæmia which leads to pregnancy or menstruation. Anomalous uterine bleeding and some cases of sterility may depend on pathological conditions of the corpus luteum. Amenorrhœa and uterine atrophy may also result from the same cause. Lactation-atrophy is a good example; during

lactation there is, as a rule, no ovulation, therefore no fresh corpora lutea are formed."

"If the corpus luteum is the ovarian gland there is no object in using the whole ovary for purposes of organo-therapeutics. Cows' corpora lutea can be obtained easily, a corpus luteum as big as a walnut being found in every fourth ovary. Fraenkel used a preparation of "lutein" made from cows' corpora lutea in sixteen cases of troubles of the menopause, and was satisfied with the results. As regards ovariectomy during pregnancy he advises that the operation be put off if possible until after the fourth month, and that resection leaving the corpus luteum be performed. When the ovaries are removed during pregnancy "lutein" should be administered."

Fraenkel's view that the corpus luteum is responsible for the early development of the ovum receives support from the number of cases recorded in which pathological conditions of the ovum have been found with pathological conditions of the corpus luteum.

Many cases have been recorded of double ovarian tumour with hydatidiform mole. In 1880 Max Runge described a case in which, together with a vesicular mole were found bilateral ovarian tumours the size of hen's eggs containing numerous cysts filled with clear fluid. Marchand, in 1895, notes the frequency of cystic change in the ovaries in cases of hydatidiform mole, but does not describe a case. Matwejew and Sykow recorded a case in which a cystic right ovary was found, containing a corpus luteum, with a vesicular mole in the right tube. Albert saw a case in which, at the time of expulsion of a hydatidiform mole, bilateral ovarian tumours, each as large as a fist, were found. Two months later the ovaries were found to be once more of normal size. Runge, in 1903, found that in 28 recorded cases of vesicular mole the presence of bilateral ovarian tumours was noted 12 times. In the other 16 cases no note was made as to the condition of the ovaries. Pfannenstiel, Kaltenbach, Baumgart, Mrs. Scharlieb, Malcolm, Bell, Cuthbert Lockyer, and Deseniss have also recorded cases of bilateral ovarian tumours with hydatidiform mole. In spite of these cases Findley says that there is no proof that cystic degeneration of the ovaries has any influence upon the cystic degeneration of the ovum.

In 1895 Marchand recorded the presence of a cystic ovary in a case of chorio-epithelioma. Ludwig Fraenkel found bilateral ovarian tumours in a case of "carcinoma of the uterus growing from the epithelium of chorionic villi."

In many cases microscopical examination of the ovaries has

proved that they contain *corpus luteum cysts*. In 1896 Neumann found both ovaries in a case of "deciduoma malignum" full of small cysts and permeated by lutein cells. Poten and Vassmer found bilateral corpus luteum cysts with a vesicular mole. In 1903 three important papers appeared by Pick, Runge and Jaffé, showing that in cases of vesicular mole and chorio-epithelioma there is an excessive production of lutein cells in the ovaries.

Pick gave a very full description of the microscopical appearances of an ovary from a case of hydatidiform mole. The "corpus luteum verum" itself was not cystic. Not only were the "corpora lutea spuria" cystic, but even unruptured follicles had undergone abnormally rapid development and formed corpus luteum cysts. Pick gave the name "degeneratio polycystica luteinalis" to this variety of ovarian tumours. Stoeckel had found widespread dissemination of the lutein cells throughout the ovarian parenchyma. Pick considers that the most important point is not the formation of corpus luteum cysts but the overproduction of lutein tissue. He regards this overproduction of lutein tissue as the cause of excessive chorio-epithelial action in the uterus or the tube, and the conversion of the ovum thereby into a hydatidiform mole. Whether this overproduction always occurs in cases of vesicular mole and chorio-epithelioma or not Pick says it has always been found when looked for.

Runge found that in 144 reported cases of syncytial tumours there was no note as to the condition of the ovaries in 81. Out of the remaining 63 the ovaries were more or less markedly cystic in 24. He examined the ovaries in seven cases of chorio-epithelioma and one case of vesicular mole. The ovaries were full of corpus luteum cysts and also contained in the ovarian stroma collections of cells exactly like the lutein cells, with no apparent connection with any corpus luteum cyst. He considers it probable that this change is never found except in cases of vesicular mole or chorio-epithelioma.

Jaffé examined the ovaries from a case of hydatidiform mole, followed by chorio-epithelioma. He found corpus luteum cysts in both ovaries and lutein cells disseminated throughout the stroma. He says this change is sometimes seen in ordinary pregnancy, but appears to be constant in cases of hydatidiform mole. He considers that the corpus luteum presides over the activity of the trophoblast.

Corpus luteum cysts and tubal pregnancy. Fraenkel has seen three cases of tubal pregnancy in which the corpus luteum was cystic. Matwejew and Sykow, as mentioned above, record a case in which the right tube contained a vesicular mole and the right ovary a corpus

luteum cyst. Opitz found the corpora lutea to be cystic in seven out of 18 cases of tubal pregnancy. In another case no corpus luteum could be found, and each ovary was converted into a unilocular cyst of the size of a goose's egg.

We do not know at present, and it is unlikely that we shall ever know in what proportion of cases of normal pregnancy corpus luteum cysts and "degeneratio polycystica lutinealis" occur. Jaffé says that the latter condition is sometimes seen in normal pregnancy. I have found no recorded cases. An observation on the condition of the ovaries in a case of one normal placenta and one hydatidiform mole in a twin pregnancy would be of great interest.*

Ludwig Fraenkel found, experimentally, that damage to corpora lutea short of destruction produced death or no effect on the impregnated ova, never pathological insertion or development.

Although there seems to be no doubt that the vital relations between the ovary and the uterus are to be looked on chiefly as the effect produced by the former on the latter, there is some evidence that there may possibly be action in the other direction, viz., influence exerted by the uterus on the ovary. It has been suggested, although I do not know that the idea has appeared in print, that there may be an internal secretion of the uterus, possibly from the whole organ, possibly only from the cervix.

It was hoped that menopause troubles could be avoided by leaving behind one or both ovaries after hysterectomy. Abel, however, noticed a gradual shrinking of the ovaries after hysterectomy, so that in many cases after three years he could hardly recognise the ovaries by bimanual examination. Menopause troubles appeared in these cases.

Burkhardt found troubles of the menopause in 33 per cent. of cases in which one ovary had been left after supravaginal amputation, in 50 per cent. after leaving one ovary after total hysterectomy, and in 50 per cent. after leaving both ovaries after total hysterectomy.

Werth found troubles of the menopause in 24 out of 35 cases in

* Since this paper was written such a case has been recorded by Birnbaum (*Monats. für Geburts. und Gynäkol.*, Bd. xix., Ht. 2), in which a patient was delivered of a fœtus 30cm. in length with a normal placenta and also a vesicular mole. She died 6 weeks later from morbus cordis. The right ovary showed nothing of interest. In the left ovary were two corpora lutea. One of these was normal; the other was markedly abnormal. The tunica propria and lutein sheet could not be properly differentiated, and there was irregular extension of lutein cells into the ovarian stroma.

which one or both ovaries had been left behind after supravaginal amputation. In some of these cases they appeared so soon that they could hardly be explained as due to secondary atrophy of the ovaries, and Werth considered that they were due to the operation itself.

Leopold and Ehrenfreund saw menopause troubles come on soon after the operation in 22 out of 43 cases in which one or both ovaries were left behind in vaginal hysterectomy for fibroids. More than half of these 22 patients had not reached the age at which the menopause is expected.

In view of the marked difference in structure of the corporeal and cervical endometrium it would be interesting to have further evidence as to whether troubles of the menopause appear more commonly after total hysterectomy than after supravaginal amputation, the ovaries being left behind in both cases. For such evidence to be of any value it would be necessary to have records only of cases operated on several years before the natural menopause would be expected.

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