incision to explore the abdomen thoroughly. The appendix is in every case carefully examined, but it is removed only if there is definite evidence of disease. If it is injected, inflamed, markedly thickened, distended, or even contains many concretions, it is taken out, but a mild degree of fibrosis or the presence of membranes and filamentous bands is not regarded as sufficient evidence of disease to warrant removal. The appendix was excised in 73 cases, approximately 4 per cent.; if it had been definitely inflamed or had been the primary cause of the upper abdominal lesion, there should have been further trouble in a considerable number of cases, yet in my total number of gastric and duodenal ulcers the incidence of gastro-jejunal ulceration was considerably under 2 per cent.; or, taking only the cases of pyloric and duodenal ulcer, which may be regarded as the only group likely to be followed by this complication, the incidence was between 2 and 3 per cent. This rate compares favourably with many of the published statistics, and I think, therefore, it can be accepted that the omission to perform routine appendicectomy does not in any way increase the possibility of the after-formation of gastro-jejunal ulceration. Of the total of over 1,700 cases only 5 have afterwards developed acute appendicitis. This is an incidence of 0.28 per cent., and is probably but very little, if indeed at all, higher than the incidence in the general population. All these cases have been most carefully watched in a follow-up department, and I feel confident that few, if any, of such complications have been overlooked. These figures show clearly that the relationship between chronic appendicitis and lesions of the upper abdomen is much less intimate than has been believed. The appendix should certainly be examined in every case of such a lesion, but it is only necessary to remove it if there is very definite evidence of disease, and it is never justifiable to inform a patient that the removal of a slightly fibrous or adherent appendix will relieve her of severe abdominal pain.

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DISCUSSION.

Mr. H. N. FLETCHER (Brighton) said that if the surgeon followed up his patients who had been operated upon for chronic appendicitis he would find many failures. In 82 cases he had investigated about one-third were failures. In 11 the diagnosis made at the operation was obviously wrong—in 4 cases glands in the mesentery or chocolate cysts in the ovary had been discovered; of the remaining failures the majority were cases of visceroptosis. A history of previous attacks was very important. The symptoms of appendicular dyspepsia were indistinguishable from those due to ulcer of the stomach, and 10 cases of the 82 had been cured by removal of the appendix. X rays were useful in diagnosis. If the appendix filled well appendicitis was not present, even though there was much delay in emptying. If the appendix did not fill, or filled irregularly, chronic appendicitis was present.

Mr. A. H. BURGESS (Manchester) thought that tenderness over the right iliac fossa was a good sign of the disease, but there should be comparison of the opposite side by symmetrical pressure. It was very important to have a history of acute attacks. The gridiron incision was only used when the diagnosis of appendicitis was practically certain, and only then when the patient was a child. In all other cases he advised thorough abdominal exploration. By following this routine he had discovered an early carcinoma of the colon on six occasions, and early carcinoma of the lower ileum associated with a well marked duodenal ulcer. If the patient was in such a condition that he could not stand this prolonged operation, it was

better, unless the case was urgent, to improve the general health medically and wait until the exploration could justifiably be undertaken. The speaker removed the appendix during the course of this examination, even if it appeared healthy.

Mr. ANDREW FULLERTON (Belfast) pleaded for the thorough examination of patients with chronic pain in the right side of the abdomen in whom chronic appendicitis was suspected. He declared that cases of hydronephrosis, cysts of the kidney, even calculus and tumours, might not give rise to any changes in the urine. In doubtful cases specimens of the urine from the two sides should be compared. In cases of calculus, cysts, or tumours the urine secreted from the affected kidney showed a diminished specific gravity. In this way a renal origin for the pain might be discovered.

Mr. G. H. COLT (Aberdeen) referred to the palpation test for chronic appendicitis demonstrated by the late Mr. Lockwood. Pressure over McBurney's point elicited a flatulent crepitation which was quite distinct from the large gurgle made by a distended caecum, and was recurrent from minute to minute. He found this test of the greatest possible use, and had only known it wrong three times in a series of 500 cases. When the sign was negative it almost certainly indicated that the appendix was not inflamed, nor were there bands of adhesions. The area of hyperaesthesia described by a previous speaker did not agree with the area he found to indicate that of appendicitis, which was, he stated, triangular in shape, higher, and more to the middle line.

Mr. TEMPLE MURSELL (Johannesburg) called attention to Rovsing's sign of pressure in the left iliac fossa, which caused pain in the appendix area; he had found it extremely reliable. In South African natives acute appendicitis was very rare, but chronic appendicitis was not. He did not believe a history of an acute attack was necessary to diagnose chronic appendicitis.

Professor D. P. D. WILKIE (Edinburgh) said that in the past there had been too much operating for chronic appendicitis. Removal of the appendix often failed to cure. The public would submit to operation much more easily than they could be induced to have a complete investigation in order to reach a correct diagnosis. He thought that one of the problems facing the practitioner was to educate the public to seek a thorough investigation. He pleaded for more care before operation. He thought that x rays were of value for showing an associated lesion in the stomach or duodenum, but for the diagnosis of chronic appendicitis they were useless. However, tenderness in the situation of the appendix under the screen was of some value.

Mr. TROTTER, in his reply, agreed with Professor Wilkie, and said that he regarded chronic appendicitis as important because it was frequently the beginning of a train of abdominal disease. Believing this, he thought it was often desirable to perform appendicectomy in children. Tenderness in the right iliac fossa was in 99 per cent. of cases of no importance in diagnosis, while visceroptosis might not really be a pathological entity.

THE ACTION AND USES OF OVARIAN EXTRACTS.*

BY

W. E. DIXON, M.D., F.R.S.

(From the Pharmacological Laboratory, Cambridge.)

THE endocrine function of the ovary may now be regarded as established. Knauer showed in 1900 that this organ was intimately connected with oestrus and that ovarian grafting could at least partly antagonize the effects of spaying.^{1 2} This ovarian action is evident in both sexes. If a portion of an ovary is grafted into a castrated male the mammary glands and teats hypertrophy, the glands

* The opening paper of a discussion in the Section of Therapeutics and Pharmacology at the Annual Meeting of the British Medical Association in Edinburgh, 1927.

secrete, and the animal resembles a pregnant female; a condition obtains which Steinach calls hyperfeminization. In the male the development of the mammary glands is uninterrupted, the Graafian follicles mature but do not rupture, but the implanted ovaries soon pass into cystic degeneration. In the female the development is slower and shows a rhythm which is apparently associated with the development of the Graafian follicle, and in the regressive phase with its rupture and the formation of the corpus luteum.³ Loeb has advanced evidence for believing that follicular development is governed by the corpus luteum.⁴

It is also well recognized that the ovary does not function till puberty and that the essential features of puberty are caused by some internal stimulus. A young ovary engrafted into an adult male or female will begin its secretion sooner than its age warrants, whilst an adult ovary engrafted into a young animal will not function until the animal reaches maturity. The stimulus to ovarian function can only be obtained through the mature tissues, whether male or female.⁵ This fact is of great practical importance since in cases of infantilism it is not necessarily the ovaries which are primarily at fault, and ovarian transplantation will not necessarily improve the patient, although, as no doubt will be shown in this discussion, even in these cases ovarian hormones can produce a sexual cycle.

The literature contains plenty of examples of the beneficial effect of ovarian transplantation both in men and animals. Thus a bitch aged 17 years after an endoperitoneal transplantation showed rejuvenation, sexual activity, and gave birth to five normal puppies.⁶ Bell analyses 118 cases of ovarian grafting, and states that menstruation was possible in 107 of these and occurred in 71;⁷ Sedukoff⁸ transplanted an ovary into a horn of the uterus in two sterile women and obtained normal menstruation.

The present discussion has as its object the determination of how far it is possible to substitute normal ovarian function by ovarian hormones. It should be mentioned here that menstruation is not the same as oestrus, and experiments on lower animals cannot necessarily be referred to man without qualification. Another point to which reference is necessary is the quality of the various extracts at present on the market: different manufacturing firms make their preparations often by very different methods. The ovary differs from other organs from which extracts are made in that it functions in a cyclic manner. I propose to show that its extract may exhibit different properties according to the stage of the cycle. Manufacturers, however, so far as I know, take little account of this fact. Again, the medical practitioner who uses extracts of ovary administers them in various ways—intravenously, subcutaneously, or orally. These two variables must be held responsible for some of the failures and general lack of uniformity in clinical results.

From the ovary at least three different substances can be obtained.

Oestrin.

Oestrin is the hormone which is most definite and most readily prepared; when it is injected subcutaneously into spayed rats and mice it produces typical oestrus with normal sex instincts, and when injected into immature animals it induces puberty.⁹ Like other hormones, such as adrenaline and thyroxine, oestrin is of the same nature in all animals.

The hormone is probably produced by the Graafian follicles at one stage of the ovarian cycle, the concentration in the ovary being least in the post-menstrual period and greatest just before menstruation. It is present in the wall and fluid of the ripe follicles.¹⁰ In pregnancy it is also present in large amounts in the placenta and the blood¹¹; in pregnant women it can be detected with certainty in the blood from the eighth to the tenth month. In other women it may also be detected in the blood about fifteen days before the onset of menstruation; it increases in amount till menstruation appears, when it may be detected in the menstrual blood, though not in the circulation.¹²

Oestrin is a thermo-stabile liquid soluble in all lipid solvents and also in water under certain conditions, and can be obtained free from cholesterol. The aqueous extracts

lose their power in a few days. It is recognized by physiological tests. Three of these have been used: (a) the vaginal smear test; (b) the action in virgin or spayed rabbits causing the uterus, vagina, and mammary glands to hypertrophy; (c) the action on the type of contraction of the isolated uterus. None of these tests is absolutely specific. Thus it is stated that orchitic extracts give a positive result to the vaginal smear test,¹³ and that the female willow catkins suitably extracted exert a like action on castrated rodents, though the effect is said to be more gradual in onset.¹⁴

An indication of the amount of follicular hormone in a tissue can be made by injections into spayed rodents; since this subject is being dealt with fully by Miss Coward it is only necessary to say that the unit is the least amount of lipid extract required to produce a definite effect in the spayed adult rat, and that the figure is by no means constant. For clinical purposes the extract should be put up in ampoules each containing 10 rat units per cubic centimetre. By such methods it has been demonstrated that a woman's ripe follicle contains from 3 to 5 units.

Injections of oestrin into spayed animals produce all the characteristics of a heat period. When the concentration of hormone is maintained continually and in sufficient amount a continuous oestrus results.¹⁵ The uterus enlarges and the increase in weight of the virgin rabbit's uterus within a few days of the administration of the hormone forms a qualitative test of activity. This hormone also promotes the building of endometrium. Menstruation is due to the cessation of the influence of this hormone, and, therefore, to obtain an emmenagogue effect in women the injections should be interrupted at suitable intervals.¹⁶ On the other hand, animals can be kept sterile by continuous injections.¹⁷

As oestrin exerts this remarkable action it might well be that injections into pregnant animals by bringing on oestrus would cause abortion. Margaret Smith¹⁸ found it was possible to interrupt pregnancy in rats during the first five days by injecting oestrin, but that it was not possible after the fifth day. Parkes and Bellerby,¹⁹ in mice, found that even in the later stages injections in sufficient amounts will nearly always terminate pregnancy.

Some observations have also been made on women and monkeys after ovariectomy. Oestrin promoted the growth of the uterus. In monkeys menstruation occurred when the injections ceased; in women the "subjective symptoms" of menstruation only occurred, but no bleeding approximating to that in normal menstruation.²⁰

Before leaving this hormone it should be noted that evidence exists for supposing that the production of oestrin is influenced by the anterior lobe of the pituitary gland.

Corpus Luteum Hormone.

A large mass of experimental observations shows that the corpus luteum is concerned with the rhythm of the oestrus cycle and with the prevention of ovulation; also it is known that a persistent corpus luteum, both in animals and women, will produce sterility, a condition which is cured by its removal. The presence of fully formed corpora lutea inhibits ovarian secretion, and this condition obtains in animals for a time between the heat periods and more particularly during pregnancy. In women there is plenty of pathological evidence to show that functional corpora lutea are not present during menstruation.

If the corpora exert this controlling action on ovarian function, then their removal should release the normal ovarian function. Removal of the corpus in animals, rabbits (Fraenkel), goats (Drummond Robinson), etc., during pregnancy is invariably followed by abortion. On the other hand, injections of properly prepared corpus luteum prevent ovulation. Pearl and Surface²¹ found this for the hen, Kennedy for the rabbit.²² Papanicolaou²³ also finds that corpus luteum inhibits and delays ovulation and oestrus in the guinea-pig. One other effect can be induced by these injections—namely, hypertrophy of the breasts, and, during pregnancy, growth of the maternal portion of the placenta. Shaw²⁴ has shown that the corpus luteum is mature in women on the nineteenth day and persists till the twenty-seventh; during menstruation it is degenerate. He also thinks that it is responsible for the

production of the premenstrual changes and of the decidua if pregnancy occurs.

Clinically treatment with extracts of corpus luteum has been disappointing, and it is easy to understand the reason. These glands are only functional at one period in their cycle; the degenerated corpus is inactive. Few manufacturers are likely to have assistants sufficiently skilled to make this distinction. Nevertheless remarkable clinical results have been claimed for this form of therapy, and many cases are on record of women who habitually aborted going to full term when treated with corpus luteum extracts.

Interstitial Hormone.

The third substance which can be prepared from ovarian extract was described by Marshall and myself. This substance is water-soluble and thermo-stable, and can be prepared from the ovary, at one stage of its cycle only, by maceration with warm saline followed by boiling and filtering. The injection of this substance into animals causes a secretion of the posterior lobe of the pituitary gland, and this in turn renders the uterus supersensitive and highly responsive to other forms of stimulation.²⁵

The pituitary secretion passes either entirely or mainly into the cerebro-spinal fluid. Histological examination has shown that the gland is suspended in a bath of the fluid and has an opening in communication with the ventricles. Since the experiments of Marshall and myself this secretion of pituitary into the cerebro-spinal fluid has been confirmed many times, more particularly by Trendelenburg,²⁶ Janassy and Horvath,²⁷ and Miura,²⁸ and there can now be little reasonable doubt of this fact. It has been suggested that the secretion of oxytocic substance is not really pituitrin, but some other substance, and to this it can only be replied that it exerts every known chemical and physiological action of posterior lobe extracts. In my Dohme lectures I gave the last piece of evidence in this respect by showing that it also exerts the melanophore dilator action on the frog, an effect which, so far as I know, is quite specific. Trendelenburg has also described this action.

The pituitary gland must be intimately connected with the phenomenon of pregnancy, because statistics show that the size and weight of the gland in men and nulliparae are about the same. In primiparae the weight has increased by about 50 per cent., and in multiparae by about 90 per cent., though most of this increased weight is due to the anterior lobe.

The posterior pituitary substance has at least three actions of importance in medicine: it inhibits the secretion of urine, it has an antagonistic action to the insulin effect, and it sensitizes and, in large doses, contracts plain muscle on the uterus. This latter action is so profound that it overshadows all the other muscular effects, and pituitrin may be said to have a true specific action on uterine muscle in rendering it supersensitive to every form of extraneous stimulus.

Our experiments showed that in only one stage of the ovarian cycle was this hormone elaborated—namely, at the stage of degeneration of the corpora lutea. So long as these corpora are functioning they govern the metabolism of the ovary, and neither the oestrin nor pituitary hormones are free to act, but when the corpora degenerate both are liberated and exert their effects—that is to say, extracts of the ovary made between the heat periods or during pregnancy are without effect on the pituitary gland, but extracts made just before the heat period or just before parturition induce secretion of the gland. As the significant action of pituitary extract is to sensitize the uterus it is difficult, if not impossible, to avoid the conclusion that these two phenomena are closely associated. It is true that insulin also causes the pituitary to secrete,²⁹ but this cannot be of importance in these experiments since the blood sugar in anaesthetized animals, into which the ovarian extracts are injected, is invariably increased as a result of the anaesthetic.

The facts are, then, that the ovary just before parturition and just before the heat periods contains a hormone which causes the pituitary gland to secrete. It is well known that substances introduced into the cerebro-spinal fluid find their way almost immediately into the blood, and

hence it should be expected that extracts of blood of pregnant rabbits at the time of delivery should contract the uterus, which has been found to occur. Similarly the blood of women collected at the time of delivery contracts the guinea-pig's uterus to a considerably greater degree than normal blood.³⁰ The same effect was shown by Mayer in a different way.³¹ He collected the cerebro-spinal fluid from women during Caesarean section. This fluid he injected subsequently into ten women with deficient labour pains. In eight of the women pains were induced, which in four were followed by the birth of the child. In another case an intradural injection was made, which was followed by labour pains within twenty-four hours. Mayer states that the cerebro-spinal fluid in labour contains the active principle of the pituitary responsible for the production of uterine contraction.

All these experiments consistently support the view that in the presence of fully formed corpora lutea the normal ovarian secretion is held in abeyance, and this is the condition for a short part of the time between the heat periods, but more particularly during pregnancy. In other words, the corpus luteum may be supposed so to dominate ovarian metabolism at these periods that the ovarian secretion, which at other times activates the pituitary, is inhibited or else is neutralized by the secretion coming from the corpus luteum. At the close of pregnancy, when the corpora lutea are in an advanced stage of involution, the normal secretory activity is once more produced, and the pituitary gland is excited to secrete in greater quantity. When the threshold stimulus of the pituitary secretion upon the uterus is reached the pains of labour set in and parturition results. The well known phenomenon of the growing irritability of the uterus in the later stages of pregnancy, which is the typical effect of the pituitary action, is explained as being functionally correlated with the involution of the corpus luteum. In our experiments ovarian extract gave positive results at all times excepting when the organs contained well developed corpora lutea, but the effects produced were undoubtedly more marked in the case of the ovaries obtained at or about the time of labour. The hormone which stimulates the pituitary gland is produced in greatest abundance at these periods.

Rogers also thinks that such a hormone exists; it is stated to be of approved value in such conditions as hypovarianism and dysmenorrhoea, and is, he thinks, effective if administered by the mouth.

It is not suggested that the ovario-pituitary endocrine mechanism is the sole factor in producing labour pains. No doubt the foetus itself acts as a direct stimulus, and without the foetus the intense muscular contractions would not occur, but it seems equally clear that the onset of labour cannot easily be accounted for without postulating some further exciting cause apart from the foetus and uterus.

Oestrin, which I have examined from several sources, has not this action on the pituitary secretion. Oestrin is especially effective in bringing on abortion in the early stages of labour, and Dr. Addis will explain what the effect of ovarian extract in the later stages of pregnancy may be.

In conclusion, no romance can be more remarkable than the fact that doctors, by using pituitary extract to stimulate the uterus in pregnancy, even to the exclusion of ergot, should have adopted the method which Nature has herself employed from times immemorial.

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DISCUSSION.

Dr. KATHERINE A. COWARD (London) said that the standardization of ovarian extracts was based on their power to induce oestrus in ovariectomized animals, but the dose of any extract required to produce this condition in a rat varied so much that a large number of animals had to be used for the assay. A "curve of response" had been drawn up on the results of subcutaneous injections of different doses of a particular sample of ovarian extract to each of ninety ovariectomized rats; it took the form of a somewhat flat S-shaped curve. It was significant that while some rats responded to a dose of 2.5 mg. of this extract, some did not respond even to a dose of 17.5 mg. The doses of 2.5, 7.5, 12.5, 17.5 mg. respectively, were given at fortnightly intervals, then a dose of 10 mg. was given, and the number of animals responding fell exactly on the curve which had been drawn through the first four points, which indicated that the extract had not deteriorated in value, nor had the rats become less sensitive. Half the rats were then given another dose of 10 mg. subcutaneously, and half were given the same dose intraperitoneally. There was no significant difference between the results of the two methods of injection; injecting the dose in three small parts at intervals of four hours did not make the response any better than injecting the whole dose at one time. The unit of oestrin was defined as that amount which would produce oestrus in 50 per cent. of the animals tested, twenty animals being used for each test. When the response to a given dose had been found, reference to the curve would give the dose required for a 50 per cent. response, and the assay of the material could be given as 1 unit per x mg. or as x units per c.cm. A similar test was performed at the same time on 70 ovariectomized mice, using exactly the same doses of the extract as those employed in the rat experiment. It was surprising to find from the identity of the curves that the rat unit was equal to the mouse unit, and was, therefore, quite independent of the weight of the two species of animal. In the rat experiment it was also noted that the response to a given dose bore no relation to the weight of the animal.

Dr. A. S. PARKES (London) discussed the interaction of the oestrus-producing stimulus with the corpus luteum, and the function of the corpus luteum in maintaining pregnancy. There was much definite evidence that one function of the persistent corpus luteum was the inhibition of oestrus and ovulation during pregnancy, and in the last few years it had been found possible to simulate this action by inhibiting oestrus and ovulation in the normal animal by the injection of extracts of corpus luteum. Since it was possible to override the oestrus-inhibiting power of the persistent corpus luteum by the injection of the oestrus-producing hormone, the conception was suggested of an alternating dominance of oestrus producer and oestrus inhibitor, it being possible to override each in its normally dominant phase by the artificial augmentation of the other. As regards the function of the corpus luteum in maintaining pregnancy, many experiments on the elimination of the corpora lutea had shown that the corpora were necessary during at least the greater part of gestation. These experiments had, however, not been entirely conclusive. To eliminate the corpora lutea double ovariectomy or manipulation of the ovary during the operation had always been employed. The latter operation was of necessity attended by a considerable operation shock, while the former abolished all ovarian activity. To overcome these difficulties the following technique had been devised. Young mice were sterilized unilaterally by x rays, and the animals when adult thus possessed one normal ovary containing both Graafian follicles and corpora lutea, while the other ovary had neither, but was capable, as already shown, of performing all ovarian endocrine functions except those associated with the corpora lutea. The animals were then allowed to become pregnant, and at various stages of pregnancy one or other ovary was removed. Animals in which the ovary removed was that containing the corpora lutea invariably aborted or reabsorbed the foetuses, while those in which the sterile ovary was removed had in every instance an uninterrupted gestation. With any possible

operation shock thus controlled, these experiments had seemed to show definitely that in the mouse, at any rate, the presence of corpora lutea was essential for the normal progress of pregnancy. As regards the light thrown by these experiments on the mechanism of parturition, it was very doubtful whether the normal atrophy of the corpus luteum towards the end of pregnancy could be compared with its experimental elimination earlier. There was much evidence which seemed to show that an ovarian-pituitary parturition mechanism was set in motion by this normal atrophy of the corpus luteum, but in view of the relative insensitivity of the uterus to pituitrin during early pregnancy, it was probable that the abortion which followed early removal of the corpora was not dependent upon such a mechanism.

Dr. W. R. ADDIS (Manchester) described the use of ovarian extract without the corpus luteum in the induction of labour, and in dysmenorrhoea due to inadequate uterine contractions. In the first case five intramuscular injections, each of 1 c.cm. of ovarian extracts, were given at three-hourly intervals. If these failed the injections were repeated after an interval of twenty-four hours, the uterine contractions being kept under careful observation. In 50 cases so treated there were 4 failures; 31 patients were primiparae. The average duration of labour was: first stage, twenty-three hours; second stage, two and a half hours; and third stage, fifteen minutes. All the children were born alive and well. The patient hardly felt the uterine contractions during the first stage—a point of considerable interest, and comparable with intestinal and rectal muscular contractions, as well as with the freedom from pain during labour which occurred in some less civilized peoples. It appeared, therefore, that the ovary produced a hormone which acted specifically on the uterus, originating a bipolar action directly through the autonomic system.

Dr. W. F. T. HAULTAIN (Edinburgh) said that it had been his practice for at least five years in cases where both ovaries had been removed, either with or without the uterus, to give such patients a course of ovarian extract, beginning on the fifth day following operation by giving 5 grains three times a day and continuing it for two months. For the next two months 5 grains were taken twice a day, and for the fifth and six months following operation 5 grains were given once a day—the idea being to minimize the menopausal symptoms by decreasing doses of ovarian extract. If the symptoms became more severe the dose was increased. Out of 31 patients so treated, 24 took ovarian extract for one month or more, and there were 7 who did not, the latter including principally hysterectomy and salpingo-oophorectomy cases. The general health was improved in 19, 12 patients became stouter, and of these 6 were cases of salpingo-oophorectomy and under 40 years of age; 9 had periods of depression. In 14 cases flushings were severe, in 7 slight, while three had practically no flushings at all. After a period of twelve months flushings were only present in 8; of these 6 were cases of salpingo-oophorectomy under the age of 40, in whom the uterus had been left. This result compared very favourably with the patients who had not taken ovarian extract, for in 6 of the 7 who had not received it flushings were still present at the end of twelve months, headaches occurred in 8, while nervous symptoms were manifested in 5. Flushings were very much improved by the treatment. The ovarian extract seemed to have helped the patients with regard to adiposity, headache, and nervous symptoms, but most of all in regard to flushings. Dr. Haultain thought that when both ovaries had to be removed then the uterus should be taken out also, especially in cases of chronic or purulent salpingitis. The ovarian extract had been administered orally, and Dr. Haultain concluded that if it were given hypodermically once or twice a week following operation the results would be even better.

Dr. W. KENNEDY (Edinburgh) believed that the disappointing nature of ovarian medication was due to the very diverse and sometimes uncritical methods adopted. The

species and oestrous period of the animal from which the gland was derived, the methods of extraction and of exhibition, and the diseases for which the substances had been used were all of prime importance. Dr. J. C. Hirst had shown that the intravenous administration of corpus luteum in the pernicious vomiting of pregnancy was effective. The speaker had also found that the corpus luteum would inhibit ovulation, and indeed in continued dosage would produce extreme degeneration of the follicular apparatus. The evidence was not plentiful, but it was very probable that there was a direct relationship between ovarian function and the blood sugar level. The speaker was surprised that Miss Coward had found mouse and rat units identical in oestrin standardization, as this was contrary to the usual finding. Further, it was undoubted that the lutein cells arose from the theca interna in some animals, the membrana granulosa in others, and possibly from both in some others. It was, therefore, necessary to specify the species in any assertion as to the endocrine function of these cells.

Dr. DAVID CAMPBELL (Glasgow) raised the question whether the injection of ovarian extract into animals had any inhibiting effect on the activity of insulin. With Dr. Scott he was investigating this point, and up to that time their results were as follows: (1) Subcutaneous injection of oestrin or the lipo-soluble ovarian hormone and of watery extracts of the ovary had no effect on the blood sugar of a normal animal. (2) Subcutaneous injection of oestrin twenty-four hours before, and again simultaneously with, insulin injection had no inhibiting effect on the action of insulin when compared with control experiments. (3) Subcutaneous injection of watery extracts of ovary given at the same time as insulin had no inhibiting effect on the action of insulin when compared with control experiments. Dr. Dixon, however, in his experiments, had used the intravenous route, and had showed that the apparent effect on the pituitary gland was transitory, lasting only ten to twelve minutes. Dr. Campbell had tried to determine whether the intravenous injection of watery extracts would have any effect on the blood sugar of an animal in the state of insulin hypoglycaemia. These experiments had not progressed very far, but up to the present there was no evidence to suggest that it did inhibit insulin activity; occasionally the reverse effect had been observed. It might be that they had used extracts of ovaries taken at a time when there was no hormone present, and it was necessary to investigate this point further before they could say definitely that ovarian extracts had no inhibiting effect on insulin activity through the medium of the pituitary gland.

Professor C. W. GREENE (United States of America) called attention to work by Professor Edgar Allen of the University of Missouri, who was a pioneer in the discovery and scientific testing of oestrin. Professor Allen had recently been testing the reactions of ovariectomized monkeys. His publications on this new work had not yet crossed the Atlantic. Allen first established the sexual cycle of individual monkeys and then removed the ovaries. Follicular extracts were then given in repeated doses. The animals reacted with all the phenomena of the normal oestrus—reddening and swelling of the skin of the vulva, reddening of the ischia and adjacent skin, and growth of the mammary glands. The uterine-vaginal growth changes occurred as in the normal, and menstrual bleeding actually occurred in these test monkeys.

Dr. DIXON, in reply, briefly referred to the work of Dr. Addis, and laid stress on the fact that the action of pituitary extract was essentially to render the uterus super-sensitive to any form of stimulus. Dr. Addis and he were in entire agreement regarding facts, but Dr. Addis thought that the ovary acted directly; all previous investigators were agreed that it exerted no such action. In reply to Dr. Campbell, he referred to a paper written by Dr. Wadia and himself, and published in the *BRITISH MEDICAL JOURNAL*, showing that insulin also excited the pituitary gland to secrete as it did other endocrine glands. He referred

finally to the primary work of Allen and Doisy, and explained to Professor Greene that if the names of these two investigators had not been mentioned in the discussion, it was not that their pioneer efforts had not been appreciated, but rather because their conclusions were generally known and accepted.

THE CLINICAL FEATURES OF ECTOPIC PREGNANCY.*

BY

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THERE is an extensive and very complete literature on the subject of ectopic pregnancy, and I cannot hope to add anything new to what has already been written. In the early part of this year, however, I reviewed a hundred cases operated upon by myself, and it may be of interest to refer to some of the main clinical features in the light of the results obtained from an analysis of that series.

Pregnancy in one or other Fallopian tube is by far the most common variety, and as all my cases come under that heading I propose to leave out of account the other and rarer forms. I will also say very little about the pathological anatomy of ectopic pregnancy, except to mention the frequency of the various terminations found at the time of operation in my own cases.

Tubal abortion occurred in 52 per cent., tubal rupture in 37 per cent., and the tubes were unruptured and unaborting in 12 per cent. A tubal mole was present in nearly 80 per cent. of the cases.

ETIOLOGY.

Most authorities agree that the chief predisposing cause of ectopic pregnancy is a preceding pelvic infection which so damages the Fallopian tubes as to obstruct or delay the passage of the fertilized ovum to the uterine cavity. The results of pelvic infection may be visible to the naked eye at the time of operation in the form of adhesions, especially about the non-gravid tube, and the frequency of this factor can therefore be determined with some accuracy. It has to be remembered, however, that gonococcal infection may be limited in its results to the tubal mucosa, and be incapable of demonstration except by careful histological examination.

In my own series old-standing adhesions about the non-gravid tube were observed in 50 per cent. of the cases, but as this leaves out of account those in which the gravid tube only was affected or the mucous membrane alone damaged, it will be realized that the percentage is probably much higher.

Gonorrhoea and puerperal septic infections are undoubtedly mainly responsible for the pelvic inflammatory lesions, but appendicitis and abdominal tuberculosis are also important. There were four patients who had had previous operations for appendicitis, and in the course of my own operations I found the appendix adherent in twelve cases, in ten of which it was found necessary to remove it. The appendix was not always examined, however, so the incidence of this source of infection is probably greater than I have indicated. In this connexion it is interesting to note that tubal pregnancy is somewhat more common on the right side—59 per cent. as against 41 per cent. in my own series.

Developmental abnormalities, such as tubal diverticula and distortion of the tubes by tumours, also play a part, though I think it must be a very subsidiary one. I found only one example of developmental abnormality, a double uterus, and the malformation was probably in no way responsible for the extrauterine pregnancy. Fibroid tumours were observed in two cases (about 2 per cent.), but in both instances the tumours were small and not situated near the uterine cornua.

There are certain other factors which have a bearing on

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