amount of urine passed affords a better index than the amount of protein in the urine, and diminution of blood pressure and oedema, and improvement generally, makes the issue favourable. A residual albuminuria is not of moment provided the blood urea and urea-concentration tests are satisfactory. So long as improvement is maintained the pregnancy can be allowed to continue, but the objections to its termination are greatly reduced once the last month is reached.

Recurrence in Subsequent Pregnancies and Permanent Renal Damage.—In this regard prognosis is guided chiefly by the duration of the illness and completeness of recovery. The severity of the attack is of little moment compared with its length, for the chronic type is more likely to be followed by recurrence or chronic nephritis than eclampsia or a shorter and sharper non-convulsive toxæmia. Hence the importance of terminating the pregnancy before permanent damage results. For this reason Arwyn Evans⁷ makes fourteen days of albuminuria the limit, and in so doing seems to me to err in his standard, for he has taken the least reliable one. His finding that young patients run less risk than the older multiparae should encourage longer trial in the former. The same factors govern advice given regarding risk of recurrence in a subsequent pregnancy. It is usual to recommend an interval of two years before the test of another pregnancy, but the time may be shortened for women of an age at which fertility is lessening fast. Husband and wife must fully appreciate the close supervision required throughout such pregnancies; also that failure on a second trial prohibits further chances being taken. If there is no return, the probability is that future pregnancies will also be unaffected.⁸ Persistent high blood pressure is unfavourable. Banister⁹ regards a systolic pressure below 150 mm. Hg as an indication that recurrent albuminuria is unlikely. Sometimes ocular symptoms arise that put the eyesight of the mother in jeopardy; rather than risk this disaster the pregnancy should be ended on this account alone.

Foetal Prognosis

Although there is a definite risk of intrauterine death of the foetus in non-convulsive toxæmia, it is much less than in the convulsive, in which the fits themselves add greatly to this risk. Danger to the foetus from toxæmic states is less than in chronic nephritis.

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A. Schwarz (*Zentralbl. f. Gynäk.*, July 13th, 1935, p. 1648) states that of 258 curettings done from 1929 to 1934 at a Vienna clinic for diagnostic purposes in cases of atypical bleeding during the pre-climacteric or post-menopausal years, no fewer than twenty-six (10.1 per cent.) showed the presence of carcinoma. Subsequent investigations done three to six years after the ensuing radical operations failed to show in any instance that the curetting had favoured extension or metastasis.

OVARIAN AND PITUITARY HORMONES*

BY

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Irregularities of menstruation are very often met with in the routine of general practice, and until recently it has been customary to diagnose excessive or irregular bleeding, exclusive of new growths, as endometritis in one of its many subdivisions—glandular, interstitial, chronic, and so on. It is now an accepted fact that endometritis, due to previous infection, is a comparatively rare disease, and should only be diagnosed when inflammatory cells are present in considerable numbers; in true chronic endometritis, the detection of plasma cells is specially significant. Although sometimes a searching inquiry is entailed, it is generally possible to place these variations from the regular cycle into one of several well-recognized groups: menorrhagia when the cycle is of normal length but the loss is excessive; epimenorrhoea when the cycle is reduced to twenty-one or even fourteen days but the rhythm remains; metrorrhagia when there is intermenstrual bleeding. On the other hand, there may be amenorrhoea for weeks, followed by continuous bleeding, not infrequently diagnosed as an early miscarriage in a woman of child-bearing age; but it is now recognized that these symptoms are often due, not to pregnancy, but to a disease in which ovulation does not take place—namely, metropathia haemorrhagica.

The discoveries of the hormones of the ovary and the anterior lobe of the pituitary gland have revolutionized many of the accepted theories as to the causes of these irregularities, and the aim of this lecture is to give a short review of the, at present, accepted opinions of the source and functions of these hormones.

Changes in Endometrium during the Menstrual Cycle

The normal menstrual cycle is regarded as being one of twenty-eight days, the first day of the bleeding being taken as the first day of the cycle. The endometrium throughout the cycle is in a constant state of change. Immediately after the period repair sets in when the epithelium grows over and covers the denuded areas, the membrane is thin, and the glands simple straight tubules. This is followed by the proliferative stage, which continues to the mid-interval. The glands become lengthened and tortuous, the membrane swollen and uneven. About the sixteenth day the endometrium begins to assume a peculiar structure, which continues to develop until shortly before the onset of menstruation. The membrane increases in thickness, and closely resembles the decidua of early pregnancy. The glands are dilated with secretion, and have a characteristic corkscrew appearance; this is the premenstrual or pre-gestational phase, and it is followed by menstruation, during which the superficial hypertrophied layers of endometrium degenerate and are shed into the cavity, and this, together with the blood which is simultaneously effused, constitutes the menstrual discharge. And then again regeneration and so on to another cycle. Thus the constant change accounts for the rather bewildering old-fashioned classification of endometritis, and when endometrium is required for diagnostic purposes it emphasizes the need for giving the pathologist the exact day of the cycle on which it was removed.

* Post-graduate lecture delivered at Dundee Royal Infirmary, May 9th, 1935.

A Double Ovarian Cycle

What is the factor or factors governing the changes in the endometrium? They are not present before puberty or after the menopause, but throughout the period of normal sexual activity they recur with characteristic rhythm. Turning naturally to the ovary a definite cycle is also found here, recurring with characteristic rhythm. At puberty the immature follicle containing the ovum develops and ripens and becomes the Graafian follicle, and the hormone, oestrin, is secreted by the granulosa cells of the follicle. In the few days preceding rupture this follicle rapidly increases in size, and when fully mature—it ruptures between the fourteenth and sixteenth days—the ovum escapes and passes into the Fallopian tube, where, if it has not been fertilized, it rapidly degenerates. If fertilization does occur the ovum, when it reaches the uterine cavity, proceeds to embed itself. After rupture of the Graafian follicle the cells lining its walls assume a new structure, and a convoluted yellow body, the corpus luteum, is produced. The secretion of oestrin still goes on, but another hormone, progesterin, now appears. If pregnancy has not supervened, retrogression occurs in the corpus luteum with the beginning of menstruation, and it ultimately becomes converted into a structureless hyaline body called the corpus albicans. A new Graafian follicle again assumes control, and so the cycle continues.

If pregnancy has occurred the corpus luteum goes on growing and persists, as the corpus luteum of pregnancy, and the ripening of the next Graafian follicle is arrested until some time after the termination of pregnancy.

The ovary therefore runs a double cycle: ripening of the Graafian follicle, terminating in rupture and ovulation, followed in turn by the formation of the corpus luteum. There is now no doubt that the proliferative phase of the endometrium is controlled by oestrin from the Graafian follicle, and the premenstrual or pregestational phase by progesterin from the corpus luteum. This has been demonstrated experimentally on laboratory animals by various methods, and also in the castrated woman. The uterus of an ovariectomized rabbit in time shows atrophy of the muscle and endometrium. The administration of oestrin either by mouth or subcutaneously produces renewed hypertrophy of the muscle and endometrium. This is known as the uterine growth test.

It has also been shown that progesterin from the corpus luteum produces the premenstrual or pregestational phase in the endometrium providing the proliferative stage has already been reached. This pregestational phase is absolutely essential for the embedding of the fertilized ovum, and in animals it appears that the continued influence of progesterin is necessary for the further development of the embryo, although in women cases have been recorded where after double ovariectomy, performed during pregnancy, the pregnancy has proceeded to term.

Of more clinical interest is the work of Kaufmann of Berlin. He has recently succeeded in producing menstrual discharge in a woman who five years previously had both ovaries removed, and throughout that period had amenorrhoea, so that there could be no question of ovarian remnants being left behind at the operation. By the administration of oestrin, followed by progesterin, he produced not only a period, but definite cyclical changes in the endometrium, proliferative changes during the administration of oestrin, and secretory changes following the administration of progesterin. Kaufmann has also succeeded by the use of oestrin in inducing a hypoplastic uterus to grow and develop into a normal-sized organ.

Normally the production of large quantities of oestrin in the ripening Graafian follicles is responsible for the growth of the uterus at puberty. It is also assumed that

the growth of the pregnant uterus, from a small organ weighing $1\frac{1}{2}$ to 2 ounces to a powerful muscular organ capable of housing and expelling a full-time child, is partly due to the influence of oestrin. That oestrin is not the only factor in producing the growth of the pregnant uterus is seen in extrauterine gestation, where the foetus may go on to full development, but the size of the uterus never increases beyond a two months' pregnancy, indicating that to ensure progressive growth of the pregnant uterus the mechanical stimulus of the placenta in the uterine cavity is necessary.

From the Graafian follicle where it is secreted oestrin passes to the blood, and the amount present in the blood increases from the time of rupture of the follicle until menstruation, when there is a sudden drop. Oestrin is excreted in the urine, from 1,200 to 2,000 m.u. in a normal menstrual cycle, with an enormous increase in pregnancy of over 50,000 m.u. in twenty-four hours, but it has been suggested that the placenta is responsible for a large part of the production during pregnancy.

The amount of oestrin is generally estimated in mouse units, and therapeutic preparations are standardized in terms of mouse units. In mice certain characteristic features are found in vaginal smears at the height of oestrus, which of course are absent in an ovariectomized animal. If such an animal is treated with injections of oestrin the changes reappear in the vagina, and the least amount of oestrin necessary to produce oestrous symptoms is called a mouse unit.

Source and Functions of Ovarian Hormones

The source and functions of the ovarian hormones would now appear to be in an undisputed position. To recapitulate, the Graafian follicle with oestrin dominates the hypertrophic phase of the endometrium, the corpus luteum with progesterin dominates the premenstrual phase; but progesterin produces this phase only if the endometrium has been previously sensitized by oestrin. If pregnancy occurs progesterin is responsible for the formation of the decidua, and also prevents the ripening of fresh Graafian follicles. Periodicity and rhythm prevails in both uterus and ovaries throughout normal sexual life, and the obvious question arises, Is there a mechanism controlling this rhythm, and, if so, where is it to be found?

Clinical evidence of the relationship between the ovary and pituitary gland has long been recognized in Fröhlich's syndrome as being due to hypopituitarism, but American research workers were the first to approach the question from the opposite angle, and they demonstrated by means of a fresh implant from the anterior pituitary, and repeated injections of the extract, that the animals showed gigantism, and that there was enormous activity in the follicular system of the ovary.

Interaction between Pituitary and Ovaries

A single implant of anterior pituitary lobe into an immature mouse produces five days later full maturity, seen in the oestrous changes in the vaginal smear, and complete development of the uterus, and also abnormal activity in the ovaries. Therefore it would appear that there is a hormone in the anterior pituitary lobe which stimulates the Graafian follicle to the production of oestrin, which, in turn, stimulates the immature uterus to grow, and to produce oestrous changes in the vagina. The characteristic changes in the ovaries are haemorrhage into the unruptured Graafian follicles (blood spots) and the formation of corpora lutea containing imprisoned ova. These changes indicate the presence of a hormone in the anterior lobe of the pituitary gland, which leads to the production of progesterin in the corpora lutea. And further, if these experiments are carried out on an ovariectomized animal, no effect whatever is produced

on the uterus or vagina, showing that the pituitary acts only through the agency of the ovary, and it is now regarded as the "starting mechanism or motor of the ovary."

This interaction between the pituitary and ovaries has been demonstrated in ovariectomized animals where what are known as castration cells appear in the anterior pituitary. The appearance of these cells can be prevented by the administration of oestrin, and they reappear with its withdrawal, so that it would seem that, while the anterior pituitary has a profound action on the ovary, the products of the reaction also affect the pituitary. In other words, the anterior pituitary stimulates the production of oestrin, and oestrin in turn affects the anterior lobe.

Prolan A and Prolan B

This hormone of the anterior lobe is called prolان, and because of its dual action it is thought there are two—prolan A responsible for oestrin, prolan B for progestin, the Rho I and Rho II factors of Crew and Wiesner. The Aschheim-Zondek test for pregnancy depends on the presence in the urine of prolان, which is produced in excess due to the hypertrophy which normally occurs in the pituitary gland during pregnancy. The experiments already referred to also show that there is a growth-producing factor in the pituitary which is seen in gigantism.

Prolan A is thus responsible for the development of the Graafian follicle, prolan B for the corpus luteum; but what is responsible for the rupture of the Graafian follicle and ovulation? It is now accepted that, generally speaking, ovulation occurs between the fourteenth and sixteenth days of the cycle, and a convincing proof is the recovery of ova by reverse irrigation of the Fallopian tubes at operation between these dates. Examination of these recovered ova also showed that they have a very short span of life, signs of degeneration being apparent in twenty-four hours or, according to Knaus, even less, which is contrary to the popular opinion that an ovum may survive for two or three days. Other methods of establishing the date of ovulation are by histological examination of the endometrium, showing early secretory changes, indicating recent ovulation, or of a young corpus luteum removed at operation; but the results of these examinations give a wider margin. It has also been stated that there is a sudden rise in the excretion of prolان A in the urine about the middle of the menstrual cycle, which may be the stimulus to ovulation, and the recognition of this rise would indicate the time of ovulation.

The Time of Ovulation

In a recent publication Knaus limits the time of ovulation to an exact day—the fifteenth day before the onset of the period in women with a normal reproductive physiology of ovulation—and gives convincing proof. It has been shown experimentally in rabbits that during the corpus luteum phase the uterine muscle becomes flaccid, and gives a negative reaction to the extract of the posterior lobe of the pituitary gland, and that this change begins at exactly the same time as the corpus luteum begins to form. The return of the muscle to normal activity occurs when the activity of the corpus luteum ceases. By means of an apparatus for recording the rhythmical contractions in the human uterus *in situ*, Knaus has shown that during the first fourteen days of the cycle the reaction to pituitrin is positive; on the sixteenth day there is a striking change with a negative reaction to pituitrin, which continues until at least three days before the onset of the period, but during the twenty-

four hours immediately preceding the period it has reverted to the positive reaction which characterizes it during the first fourteen days of the cycle. From these observations Knaus concluded that ovulation in women with a normal twenty-eight-day cycle must take place during the two days which precede the time at which loss of reactivity to pituitrin is detected—that is, between the fourteenth and sixteenth days after the beginning of the last period. As a result of further clinical investigations he limits the time of ovulation to the fifteenth day before the onset of the period. The time of ovulation is therefore now generally regarded as occurring between the fourteenth and sixteenth days; but the factor causing actual rupture of the follicle is not yet known, and the problem as to why the endometrium should bleed every month is still unsolved.

Clinical Applications of New Knowledge

Of what value are these discoveries to the general practitioner, and how is their importance to be assessed in relation to diagnosis and treatment? The pregnancy diagnosis test of Aschheim-Zondek is regarded as a most brilliant scientific discovery. This test shows an accuracy of about 99 per cent. some few days after a period has been missed. It depends on the presence of an excess of prolان in the urine of a pregnant woman, which when injected into immature mice produces enormous activity in the follicular system of the ovaries. Not only pregnancy, but by a special quantitative analysis hydatidiform mole and chorion epithelioma are successfully diagnosed.

Metropathia Haemorrhagica

It is only by a recognition of the constant rhythmical changes going on in the normal endometrium, secondary to rhythmical changes in the ovary, that the pathology of metropathia haemorrhagica has been clearly understood. There is a period of amenorrhoea of some weeks' duration, followed by almost continuous haemorrhage, persisting for weeks, or it may be months. It is rare to find excessive loss or large clots, which is an important clinical factor in the differential diagnosis from an early miscarriage, and the bleeding resembles an ordinary period which will not stop. Most frequently it occurs from the age of 40 onwards, but it is also seen in the years succeeding puberty, and in fact it may occur at any age between puberty and the menopause. The uterus may be slightly enlarged; a cystic ovary is often palpable due to a persistent follicular cyst. There is no corpus luteum. The endometrium is much thickened, and is generally removed in ribbon-like fragments with the curette. Microscopically, it always shows the hypertrophic phase, but in excess and of a pathological nature, with cystic dilatation of the glands, and, in addition, areas of necrosis in the superficial layers of the membrane. There are no secretory changes, as there is no corpus luteum. During the period of amenorrhoea the endometrium is under the constant stimulation of oestrin, which persists in the unruptured follicle. What actually precipitates the bleeding is not yet known, because the periods of amenorrhoea vary considerably; neither is it known why the bleeding should persist so long, even allowing for the much-thickened endometrium. That the hyperplasia of the endometrium is produced by prolonged and excessive stimulation by oestrin from the persistent Graafian follicle has been demonstrated by Kaufmann, who was able to produce the same cystic dilatation in the glands, and hypertrophy of the stroma in a castrated woman, by the administration of large doses of oestrin spread over several weeks.

In the treatment of metropathia haemorrhagica the administration of oestrin in any of its forms is therefore

definitely contraindicated. Curettage is necessary for diagnosis, and removal of thickened endometrium sometimes gives relief. Proluton (corpus luteum hormone) is now giving encouraging results. It is said that resection of the cystic ovary may lead to cystic formation in the other; but, nevertheless, this operation is often followed by definite relief, and should be performed before hysterectomy is resorted to in young subjects. Patients over 40 present no difficulty, as they are most successfully treated by the intrauterine application of radium. It is well to warn the patient of the possibility of irregular haemorrhage up to six or eight weeks after the treatment.

Epimenorrhoea: Sterility

In epimenorrhoea the cycle remains regular, but it is reduced to twenty-one or fourteen days. Ovulation still occurs normally, but there is a speeding up of the cycle. This condition not infrequently follows parturition, and as it is known that the anterior lobe of the pituitary gland hypertrophies during pregnancy, Shaw suggests that the acceleration of the ovarian cycle may be explained by assuming that the activity of the anterior lobe persists, with the result that follicles ripen and ovulate more frequently. The treatment is unsatisfactory. In patients over 40, after a preliminary curettage, radium is again most satisfactory. In younger patients the treatment resolves itself into rest at the periods, curettage, and full doses of iron to combat the anaemia, if present, with hysterectomy as a last resource.

By the discovery that menstruation may occur without ovulation, a new factor has arisen as to the possible cause of sterility. It is now considered that an essential part of the investigation in a sterile woman is examination of the endometrium one or two days before the period is due. Secretory changes denote a recent corpus luteum, and therefore ovulation; absence of such changes denotes a non-ovulating woman.

Other Applications

Interest in the value of hormone therapy was unquestionably stimulated by the publication of Kaufmann's results of the administration of ovarian hormones in a castrated woman. He was able to produce menstruation by the use of progynon (oestrin), in doses far in excess of any that had been previously employed, over a period corresponding to the follicular phase in the cycle, followed by the administration of proluton (progestin) during the period normally governed by the corpus luteum. As previously stated, he was also able to demonstrate the normal cyclical changes in the endometrium. Primary amenorrhoea is frequently accompanied by an infantile uterus, conical cervix, and a narrow short vagina. It is known that at puberty the uterus develops steadily under the prolonged and constant influence of oestrin. By the administration of large doses of oestrin over a period of three to six months Kaufmann has succeeded in stimulating an infantile uterus to grow to an advanced stage of development, although actual menstruation has not yet been produced.

Kaufmann next turned his attention to the treatment of secondary amenorrhoea. In these cases examination will usually reveal a perfectly normal uterus and ovaries, and often there is a history of a normal menstrual cycle for some years succeeding puberty. He again administers large doses of progynon at intervals of three days over a period representing the first half of the cycle, then, after an interval of three days, during which ovulation and the formation of the corpus luteum is taking place in a normally menstruating woman, he administers proluton on five consecutive days. He found that on the second day after the last proluton injection menstruation

begins. This treatment is carried out for three consecutive months. Whether or not this apparent return to normal which occurred in his series of cases will be of a permanent nature after withdrawal of the hormones has not been firmly established.

Scanty menstruation with dysmenorrhoea is undoubtedly benefited by the administration of progynon alone given intramuscularly during the first half of the interval, and also by the mouth. There is definite increase in the menstrual flow, and alleviation of the dysmenorrhoea. Menopausal symptoms are successfully dealt with by progynon, given by mouth in mild cases, or by injection once or twice a week if the symptoms are distressing.

Conclusion

As a result of the brilliant investigations carried out in Britain, America, and the Continent, opinion as to the source and functions of the ovarian hormones is firmly established, and attention is now directed towards elucidating the problems of the anterior and posterior lobes of the pituitary gland. Until the results of these researches are forthcoming, clinicians should refrain from the indiscriminate use of hormones. Hormone stimulation may be associated with epithelial activity, but it is comforting to learn that in laboratory experiments malignant formation as a result of such stimulation appears to be confined to immature animals.

THE FALLACY OF THE SUGAR TOLERANCE TEST IN THE DIAGNOSIS OF DIABETES MELLITUS

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The methods adopted in different countries to diagnose diabetes mellitus are not identical. In England the majority of practitioners ask the consultant to make the diagnosis at a single consultation, whilst in the U.S.A., Germany, and several other countries they expect their patients to be admitted to a clinic for the investigations which will permit a definite diagnosis. This may be the explanation of the popularity of the sugar tolerance test in this country. There is much to be said in its favour, because if it be carried out after a fast of fourteen hours on an individual who has had a generous diet, rich in carbohydrates, for the preceding week, a normal curve excludes diabetes mellitus. Until recently I was of the opinion that the sugar content of the blood rising above 0.25 per cent., and remaining high for two hours, indicated diabetes mellitus. The five cases which I record prove that a so-called positive sugar tolerance test does not necessarily mean that the patient is suffering from diabetes mellitus.

I have reason to believe that hyperglycaemia following the ingestion of 50 grams of glucose in individuals who possess metabolisms which allow them to utilize large quantities of starch has been described previously, but I have not succeeded in finding the paper upon the subject, which most certainly has not received the attention it merits. It might be argued that because it has not received attention it must be rare and only of academic interest, but a condition cannot be recognized by those unacquainted with its existence. It would not be surprising if among the patients of those physicians who treat diabetes by restricted diet a percentage of the most successful cases which have never complained of thirst or polyuria proved to belong to the category of those recorded here.