ENDOCRINES IN THEORY AND PRACTICE

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THE PHYSIOLOGY OF THE ENDOMETRIUM AND UTERINE MUSCLE, AND OF THE OVARIAN CYCLE

BY

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During the period of sexual maturity cyclical changes occur in the uterine endometrium and muscle. These changes are closely correlated with alterations, morphological and secretory, taking place in the ovaries, and it is now known that the gonads directly control the condition of the uterus by means of hormones released into the blood stream. The types of cycles observed in different species and the details of the changes taking place in the sex organs of these species show almost bewildering variations. In this article it is therefore intended to consider the conditions present in the primates (especially in the human subject) and to refer to experimental findings in animals only in so far as this will clarify our understanding of the problem in primates.

Broadly speaking, the sex cycle may be divided into two main phases: (1) pre-ovulatory, and (2) post-ovulatory. Obviously the extrusion of the ovum from the mature Graafian follicle (that is, ovulation) acts as the dividing point. In the pre-ovulatory period the Graafian follicles are gradually growing and maturing in the ovaries, and these organs are releasing a hormone (oestradiol*) which controls the changes taking place at that time in the uterine endometrium and muscle. Thus this phase may also be called the follicular phase of the cycle. After ovulation a corpus luteum is formed in the site of the follicle from which the ovum has been extruded. The corpus luteum also produces oestradiol, but in addition it secretes a second ovarian hormone, progesterone, which is responsible for the characteristic alterations observed in the uterus during the second phase of the cycle, which may therefore be called the luteal phase.

At ovulation one of two things may happen: (1) the ovum may not be fertilized, or (2) it may be fertilized. If it is not fertilized then the period of activity of the newly formed corpus luteum is short (about fifteen days in primates) and the cessation of its secretory function (that is, of the secretion of progesterone and oestradiol) is followed by the degenerative changes in the uterine endometrium which constitute menstruation. During the period of activity of such a corpus luteum (that is, when no developing ovum is present in the uterus) alterations are nevertheless produced in the uterine endometrium and muscle which are very similar to those observed in the early stages of a true pregnancy and represent a preparation of the uterus for the nidation and development of the embryo. This phase of luteal activity, which terminates in the degenerative process of menstruation because no ovum becomes embedded in the endometrium, has therefore being termed "pseudo-pregnancy."

When ovulation is followed by fertilization true pregnancy supervenes, and the period of activity of the corpus luteum is considerably prolonged. Moreover, an organ (the placenta) develops which acts as an additional source of the ovarian hormones. For there is now considerable evidence that in some species at least the placenta may secrete both oestradiol and progesterone. In the human subject during pregnancy the placental secretion alone may be sufficient to maintain the functional alterations produced by these two ovarian hormones, and thus removal of the ovaries from the pregnant woman may be followed by continuation of normal gestation leading to a normal parturition.

Changes in the Uterine Endometrium During the Ovarian Cycle

Let us now consider in some detail the actual changes in the uterine endometrium and muscle during the various phases of the sex cycle. The alterations in the endometrium have been studied in monkeys and in man by a number of observers, and have for the purpose of description been divided into certain stages. These are, of course, not sharply demarcated, but gradually merge into one another. The description given by Shaw and by Schroeder on the basis of their clinical studies of the human uterus will be followed. In the early stages of the cycle (that is, in the period immediately following the end of menstruation) the regeneration of the destroyed mucosa takes place, and shortly afterwards a resting stage is reached; the mucosa is lined by a low columnar epithelium, the blood supply is relatively small, and the vessels are not conspicuous. This is rapidly followed by a proliferative process. Convolutions begin to appear in the glands, and by the end of the second week after the beginning of the previous menstruation all the glands are as a rule convoluted; the epithelium is of a high cylindrical type, and a large number of mitoses may be observed.

This stage of the sex cycle—that is, approximately the first two weeks after the beginning of menstruation—represents the follicular phase, during which the Graafian follicles in the ovaries are gradually ripening preparatory to ovulation. The final maturation process involves only a limited number of follicles, and in primates usually only one; the antrum becomes enlarged, the follicle approaches the surface of the ovary and finally bursts, and the ovum is extruded. The final growth and ovulation of a single follicle (or of a group of follicles, as is usually the case in the lower animals) is accompanied by the destruction of all remaining follicles. During the phase of follicular maturation oestradiol is secreted by the ovarian substance and by the follicles, and is responsible for the proliferative processes in the endometrium which follow menstruation. A similar stage is observed in a large number of animal species in which ovulation is also preceded by proliferative changes in the uterine endometrium, produced by the hormone oestradiol secreted by the ovaries during the stage of follicular maturation. Incidentally, in certain species of monkeys marked swelling of the external genitalia is observed towards the end of the follicular phase. This swelling is presumably evidence of an intense secretion of oestradiol, as it can be induced in the ovariectomized animal by the injection of the hormone.

* The general term oestrin is used for a number of substances which have oestrogenic properties—that is, produce alterations in the secondary sex organs of the ovariectomized lower rodents, similar to those seen at heat or oestrus. There is evidence that the substance actually secreted by the ovary is oestradiol, and this term will be used when referring to that particular hormone.

Immediately after ovulation there is haemorrhage within the cavity of the follicle. The follicular epithelial cells are, however, nearly all retained, and, indeed, the essential part of the corpus luteum is formed chiefly from these cells, which begin to hypertrophy immediately after ovulation; there is no evidence, though, of cell division. Very soon the clot organizes and there is growth of connective tissue from the theca. The hypertrophy of the epithelial cells continues, and the mass is penetrated by connective tissue. The corpus luteum then becomes fully organized and the follicular epithelial cells contain the characteristic lutein of the fully formed corpus luteum. The cavity in the organ also gradually disappears.

After ovulation certain well-defined changes occur in the uterine endometrium. The glands become fuller, wider, and richly convoluted. Translucent areas are to be seen behind the nuclei of the gland cells, which shortly begin to secrete. About a week after ovulation additional changes appear and three layers can now be distinguished in the endometrium:

1. A layer immediately below the surface epithelium, in which the cells are tightly packed round the gland ducts.
2. An oedematous layer, which surrounds the glands and in which dilatation of the capillaries has occurred.
3. A basal layer, in which the oedema and hypertrophy are absent.

The hypertrophy continues up to the twenty-eighth day after the beginning of the previous menstruation, and degeneration then sets in in the form of disorganization and disintegration of the glands of the superficial and middle zones. Following this, and apparently as a secondary phenomenon, blood is extravasated and haematoma form. The blood and epithelium are then shed (menstruation) and regeneration of the epithelium subsequently takes place, thus starting again the follicular part of the cycle.

The period between ovulation and menstruation represents the luteal phase of the cycle for the non-pregnant subject. During this period both progesterone, the specific luteal hormone, and oestradiol are produced; in the primates the corpus luteum secretes both these hormones, and degeneration of the corpus luteum is followed by menstruation. In lower species, too, ovulation is succeeded by the formation of corpora lutea which, even in the absence of pregnancy, usually have a definite period of secretory activity. In many animals specific changes are induced in the uterine endometrium by the luteal secretion homologous to the secretory phase in the primates and constituting a preparation for the nidation of the ovum; but the cessation of the luteal function at the end of pseudo-pregnancy is not, in the lower animals, accompanied by the marked degeneration of the endometrium observed in the primates at menstruation.

Changes in the Uterine Muscle During the Ovarian Cycle

In addition to the well-known changes in the endometrium certain alterations have also been described in the uterine muscle during the various phases of the sex cycle, though there is much difference of opinion as to the changes occurring in primates. For this reason the experimental data in some animals which led to the investigations in Man will first be given.

Two main and antagonistic actions have been extensively investigated in the rabbit: (1) an increase in physiological activity, and (2) a decrease in physiological activity. Certain criteria have been elaborated for the measurement of the physiological activity of the uterine muscle. These are: (a) the reactivity of the muscle to oxytocin—that is,

the dose of oxytocic hormone of the posterior pituitary lobe necessary to cause contraction of the muscle either *in situ* or suspended (in strips) in some oxygenated physiological solution; and (b) the spontaneous rhythmic contractions exhibited by the muscle *in situ*, a method of measurement being used which will disturb the uterus as little as possible and not stimulate the contractions.

Now in the rabbit an increase in physiological activity is witnessed during the follicular phase of the cycle, and it can also be brought about by the injection of oestrin into the ovariectomized animal. Hence during this phase of the cycle the muscle will contract when quite small doses of the oxytocic hormone are injected intravenously into the animal, or are added to the bath of physiological solution in which the muscle is suspended. On the other hand, a decrease in physiological activity of the uterine muscle is seen, after ovulation, during the luteal phase of the cycle, and this decrease can also be produced by the injection of progesterone in animals which have passed through a (natural or experimental) follicular phase. In the luteal phase the uterine muscle does not respond to large doses of oxytocin injected into the animal or added to the solution in which it is suspended, and its rhythmic contractions *in situ* are small or absent.

Preliminary investigations of the uterine muscle in Man suggested that alterations occur similar to those obtained in the rabbit. It was apparently found that during the follicular part of the cycle—that is, for about a fortnight after the beginning of menstruation—the uterine muscle would contract after the injection of an extract of the posterior pituitary lobe and that it showed quite appreciable spontaneous rhythmic contractions. On the other hand, after ovulation and the formation of a corpus luteum (that is, during the luteal phase of the menstrual cycle) the reactivity of the uterine muscle to the posterior pituitary extract was abolished and the contractility of the muscle was depressed. The onset of menstruation after the degeneration of the corpus luteum was again accompanied by a return of the reactivity and activity of the uterine muscle. Hence, as in the rabbit, the follicular phase of the human cycle was apparently accompanied by an increase in the activity of the uterine muscle, while in the ensuing luteal phase there was a decrease in this activity.

Later observers, however, have been unable to confirm these results, and there is strong evidence now that, under certain conditions of registration, the uterine muscle may show rhythmic contractions and a response to an extract of the posterior pituitary lobe during the luteal phase of the cycle too. This evidence also agrees with experimental data which have been obtained on other animals. For it has been demonstrated that the luteal hormone, progesterone, does not inhibit the physiological activity of the uterine muscle in any species so far investigated other than the rabbit, which, it would appear, is exceptional in so far as the specific action of progesterone on the uterine muscle is concerned.

On the other hand, there is stronger support for the view that the follicular hormone, oestradiol, increases the activity of the uterine muscle in several species and that it may be a factor in controlling the activity of the muscle in primates. Further investigations of these questions are, however, necessary, and in the meantime it appears desirable to reserve final judgement.

The Anovular Cycle in Primates

The general description so far given for the alterations in the uterine endometrium during the various stages of

the menstrual cycle probably applies to the great majority of cases where the cycle is divided into two stages (that is, follicular and luteal) separated by ovulation. There is, however, no doubt that occasionally menstrual discharges may arise in the absence of ovulation. This phenomenon was first noted in monkeys, which were kept under experimental conditions and at times showed regular cyclic discharges of blood which could not be differentiated from normal menstruation (apart from an examination of the uterine endometrium or of the ovaries), although there had been no ovulation and no formation of corpora lutea. There is now evidence that such anovular cycles also occasionally appear in women, though there is some difference of opinion as to the frequency of these.

It seems likely that the sequence of events in such cycles is somewhat as follows. The follicular stage is normal and the follicles gradually mature to the usual pre-ovular condition. But the final ovulation does not take place (possibly because of a deficient pituitary stimulation) and atresia of the follicles then supervenes. The secretion of oestradiol is, however, continued by the ovaries and decreases at the usual time, leading to uterine bleeding. In those circumstances there is bleeding from a proliferated endometrium subjected to the action of oestradiol only, and not, as is usually the case, from a secretory endometrium subjected to the action of progesterone and oestradiol.

There has been some discussion as to whether the term "menstruation" should be applied to the bleeding in such anovular cycles, and it has been suggested that the nomenclature should be reserved for bleeding from an endometrium brought to the secretory stages under the influence of the hormone produced by the corpus luteum. As it is difficult to differentiate between the two types it seems probable that cyclical uterine bleeding in primates will be called menstruation, even when there is no ovulation. It is important, however, to realize the functional difference between ovular and non-ovular menstruation, since in the latter there can be no fertilization and no implantation. Indeed, there is some suggestion that certain cases of sterility in women are due to the occurrence of non-ovular menstrual cycles.

Under certain pathological conditions the follicular phase, which generally ends at about the middle of the menstrual cycle, is continued. Ovulation and corpus luteum formation do not occur, but the secretion of oestradiol goes on beyond the normal duration of the cycle. The uterine endometrium is thus acted upon by the follicular hormone for long periods, and pathological changes take place in it which result in the prolonged bleeding which constitutes metropathia haemorrhagica. Since this condition is due to the continued action of the oestrous hormone without any luteal secretion whatever, treatment with progesterone appears to be indicated, and has indeed been used successfully. Incidentally, gonadotropic hormone preparations have also been used successfully in the treatment of metropathia, but their mode of action is at present unknown.

(To be continued)

The Trustees of the Rockefeller Foundation have given a further research scholarship for a year to the Institute of Medical Psychology (Tavistock Clinic), London. The fellowship is held by Dr. A. T. Macbeth Wilson, who is engaged on the study of certain diseases—peptic ulcer, essential hypertension, diabetes mellitus, and Graves's disease—whose onset has often been related to emotional disturbances in the lives of patients.

SURGERY OF THE THYROID GLAND

LECTURES BY SIR THOMAS DUNHILL*

LECTURE II

In his second lecture, delivered at the Medical Society of London on February 24, Sir THOMAS DUNHILL dealt with the complications of toxic goitre. Those affecting the cardiovascular system were the most common. It was not so much the intensity of the intoxication as the age or quality of the heart muscle which determined its breakdown. Considering the prevalence of the disease up to early adult life the proportion of cases of heart failure during that period was small. In elderly patients, on the other hand, the incidence of cardiac complications was high, despite the well-known fact that symptoms might be mild. His impression was that the number of patients gravely ill with congestive heart failure who came for operation was tending to decrease, but the number coming with auricular fibrillation before a severe grade of heart failure had arisen was large and increasing, the reason being that when a patient was found to have auricular fibrillation a goitre was now looked for as a possible cause. It was becoming recognized that a long-standing goitre, frequently regarded as innocuous, might lead to this trouble. Some of his cardiologist friends maintained that thyrotoxicosis did not actually damage the heart muscle; in the majority of cases when the toxicity had been eliminated recovery appeared to be complete. But it must be remembered that thyroid toxæmia often continued into the period of life when arteriosclerosis or other degenerative processes were commonly seen.

Heart Risk

When the operation began to be practised it was quickly realized that the attendant heart risk could not be ignored. The first question was, and still remained, whether the heart was strong enough to stand the operation. Lists of contraindications were published, and prominent on those lists was enlargement of the heart, irregular rhythm, and congestive heart failure. It was also thought that even though thyroid intoxication had caused breakdown and the toxic goitre had burnt itself out the damage to the heart was permanent and nothing could be achieved by operation. He was speaking of views current from thirty to twenty years ago, but it might surprise his hearers as it had surprised him to know that he had been met recently with the same objection by two men occupying high positions in the profession in London.

The total number of cases with fibrillation and congestive heart failure on which he himself had operated was 305; the number that had regained normal rhythm was 248, or 81.3 per cent. Among these the rhythm returned spontaneously in 147, and quinidine had to be used to bring it about in 101. It was expedient to give quinidine if the rhythm did not become regular seven or eight days after the operation. A very few patients had proved intractable to this while in the surgical wards, but some or most had regained normal rhythm when later admitted to the medical wards. Other factors, such as arteriosclerosis or endocarditis, might be present and account for failure in some cases.

Following operation and with adequate time given for recuperation, many patients appeared to regain normal health. Others lived happy and tranquil lives so long as they kept within the limits of their strength. Some felt so well that it was difficult to keep within those limits, and they paid the penalty.

High Blood Pressure

The association of high blood pressure with toxic goitre concerned the physicians primarily, but it was of importance to surgeons also. Any surgeon who saw many cases

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