ENDOCRINES IN THEORY AND PRACTICE

This article is one of a series on Endocrinology contributed by invitation

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

BY

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The Genesis of Menstruation

The alterations in the secondary sex organs occurring during the various phases of the sex cycle are under the control of the hormones secreted by the ovaries. The changes in the ovary, as has already been explained in a previous article (*Journal*, March 6, p. 512), are in their turn controlled by hormones produced in the anterior lobe of the pituitary gland; the pituitary hormones have, however, no direct effect on the uterus or on other secondary sex organs.

The general scheme of the alterations in the uterus—follicular phase—ovulation—luteal phase leading to menstruation—has already been described. This scheme is based on numerous investigations and observations on the state of the uterus and the ovaries in primates, including the human subject, at various stages of the menstrual cycle. There is also ample evidence that the two chief phases of the cycle—the follicular and the luteal phases—are controlled essentially by the two ovarian hormones oestradiol and progesterone. Indeed, the conditions of the uterus in the follicular and luteal stages have been reproduced on numerous occasions by hormone injections in ovariectomized women and in monkeys. Administration of large doses of oestrin will produce a proliferated endometrium similar to that present at the end of the follicular stage of the menstrual cycle. If such a period of oestrin injections is followed by the administration of suitable doses of progesterone then a secretory endometrium typical of the luteal phase of the menstrual cycle is produced.

Equivalent conditions of the uterine endometrium can also be obtained in the lower animals. The exhibition of oestrin brings about a state of the uterus similar to that seen at oestrus, and injection of progesterone after a period of oestrin administration causes a state of the uterus similar to that seen during the normal luteal stage of the sex cycle. Indeed, the typical endometrial condition thus produced in the rabbit (progestational proliferation) is used extensively for the standardization of preparations of the corpus luteum hormone, though synthetic preparations of the hormone are now becoming available, the dosage of which does not depend on animal standardization, as a definite weight can be given.

Oestrin Production and Menstruation

The interrelations of oestrin and progestin in their action on the uterus require some consideration. The typical effects of progesterone on the uterine endometrium and muscle are only seen when these structures have been previously under the influence of oestrin. This latter substance therefore prepares the uterus for the action of the luteal hormone. This is, of course, what

occurs in the menstrual cycle, in which the luteal follows the follicular phase. Oestrin, however, is also produced during the luteal phase of the cycle, and acts then synergistically with progesterone in controlling the uterine changes. Indeed, examinations of the hormone content of the blood and urine during the various phases of the menstrual cycle suggest that oestrin production is at a maximum during the later stages of the cycle. Quite large quantities of the hormone are excreted in the urine of primates during both the follicular and the luteal stages, but the excretion of oestrin decreases during menstruation itself.

Peaks of oestrin excretion at ovulation and also later in the cycle have been described. The hormone content of the blood is low in the follicular phase but increases gradually and reaches a maximum a few days before the onset of menstruation. Too great a reliance cannot at present be placed on the quantitative data of oestrin production and excretion, as methods of extraction are by no means yet standardized, but the available data nevertheless demonstrate that oestrin may be found during all phases of the menstrual cycle, and suggest that the production is at least as great during the later part of the cycle as at any other time. Furthermore, they show that associated with the onset of menstruation there is a decrease in the oestrin production. Much experimental evidence also supports the view that the menstrual bleeding follows a withdrawal of oestrin. The administration of large doses of oestrin to ovariectomized primates, including women, is followed by uterine bleeding, which occurs as a rule several days after the last injection of the hormone. Occasionally, however, bleeding may take place during the period of administration of oestrin, but it appears likely that this is due to an insufficient dosage of the hormone, and that when adequate amounts of oestrin are given there is no uterine bleeding during administration but only after it.

There has been much discussion about the relative importance of oestradiol and progesterone in the genesis of menstrual bleeding. It has been found experimentally that if an ovariectomized monkey is given oestrin the bleeding which usually follows cessation of the injections can be delayed by the administration of progesterone, and that uterine bleeding then occurs several days after the last injection of the luteal hormone. On the other hand, uterine bleeding during progesterone administration has been demonstrated in a monkey in which the oestrin level was decreased. This suggests that the fall in oestrin level is the essential factor in the genesis of uterine bleeding. In the normal ovular cycle this fall probably takes place about the same time as the luteal activity ceases and leads to bleeding from a secretory endometrium, while in the anovular cycle no alteration in luteal activity is involved, and the uterine bleeding following a decrease in oestradiol production occurs from a proliferated endometrium.

During the whole of the menstrual cycle (and during pregnancy) a substance is excreted in the urine of women which has certain properties ascribed to the male hormone. Whether this substance plays a part in the control of the uterine changes during the menstrual cycle and during pregnancy is at present unknown.

Sterility and Fertility During the Sex Cycle

The alterations in the ovaries and uterus during the menstrual cycle and during the corresponding phases of the sex cycle in the lower animals have now been described, and before going on to an examination of the changes which take place during pregnancy the question of the time in the menstrual cycle at which fertilization and conception can occur will be briefly discussed.

Obviously there can be fertilization only after ovulation, and the period during which coitus may lead to conception is therefore determined by three factors: (1) the actual time of ovulation during the menstrual cycle; (2) the period of time after ovulation during which the ovum can be fertilized; and (3) the period of time during which spermatozoa remain capable of fertilizing the ovum after they are introduced into the female genital tract.

Evidence derived from the study of the state of the ovaries and uterine endometrium during various phases of the sex cycle gives a satisfactory answer to the first question. It appears probable that in primates, including women, ovulation occurs at about the middle of the menstrual cycle, though the experimental data for monkeys suggest that in exceptional cases it may take place rather earlier or later. On the whole the available evidence is strongly in favour of the view that ovulation almost always occurs well within the middle third of the menstrual cycle.

No answer based on direct evidence can be given to the second and third questions in so far as the human subject is concerned; but there is good evidence that the periods during which the ovum can be fertilized after ovulation and spermatozoa retain the power of fertilization after coitus are comparatively short in a large number of species investigated. It would indeed appear that the ovum can no longer be fertilized even a few hours after its extrusion from the ripe follicle, while the spermatozoa in the female genital tract retain their power of fertilization at most for a few days after coitus. It seems most unlikely that the behaviour of the ova and spermatozoa in the human subject should be essentially different in this respect from those in the lower animals.

The conclusion from these data is that coitus can only lead to conception when the former takes place within the middle third of the menstrual cycle. Recent carefully controlled experimental work in monkeys and observations in women are in agreement with this conclusion. On the other hand, there is much previous evidence which suggests that conception can occur at all times during the menstrual cycle. Only carefully controlled clinical work by observers fully cognizant of the physiological factors involved can lead to a definite conclusive answer to the question. The general practitioner is in an especially favourable position to obtain such evidence.

Changes in the Ovaries and Uterus During Pregnancy

If the ovulated ovum is fertilized and becomes implanted then the phase of activity of the corpus luteum is markedly prolonged and extends over an appreciable part of the ensuing gestation. During the development of the implanted ovum an organ for the nutrition of the embryo is formed—the placenta—which then probably takes an important part in the production of hormones during pregnancy.

The processes of follicular maturation and ovulation which take place at regular intervals in the non-pregnant subject are inhibited during gestation. Nevertheless cyclical waves of follicular growth occur, but the follicles

do not become mature and do not ovulate, and hence no corpora lutea are formed. The duration of activity of the corpora lutea of pregnancy varies in different species. Thus in the rabbit they remain active throughout the whole of gestation and their removal is followed by abortion (or absorption of the uterine contents if they are removed early in pregnancy). In the mare the corpora lutea rapidly atrophy after the first third of gestation, but their removal at any stage after implantation does not lead to abortion. Similarly in the human subject the corpora lutea are probably not active in the later stages of pregnancy, and removal of the ovaries even early in gestation can be followed by a normal pregnancy and parturition. It appears likely that in certain species the production of the luteal hormone progesterone is partly taken over by the placenta, and that after removal of the ovaries and corpora lutea in these species the vicarious secretory activity of the placenta is sufficient to maintain a normal gestation.

During pregnancy in primates the production of the follicular hormone oestradiol markedly increases, and large quantities of oestrogenic substances derived from it (oestrone and oestriol) are excreted in the urine. As in the second or secretory stage of the menstrual cycle, the corpus luteum probably takes part in the production of the follicular hormone during pregnancy, thus secreting both progesterone and oestradiol. After removal of the ovaries the production and excretion of oestrogenic substances is continued, and it appears likely that the placenta is the source of this hormone too; the vicarious production of oestradiol by the placenta is again sufficient to maintain normal gestation in women in whom the ovaries have been removed. It is of great interest that most of the oestradiol produced during pregnancy is rapidly converted into and excreted as inactive compounds (of glycuronic acid), and that only just before and at parturition does this hormone not become inactivated and is therefore excreted as active oestrone and oestriol.

There is considerable increase in the size of the uterus during pregnancy, necessary to accommodate the developing foetus. To some extent this growth is brought about by the large quantities of ovarian hormones produced at that time, but other factors, about which little is known, are probably also involved. Local distension is certainly one of the factors responsible for the growth of the uterus, for it has been shown that some hypertrophy will occur when the distension is brought about experimentally, apart from pregnancy.

The alterations in the uterine endometrium in the earliest stages of pregnancy are similar to those observed in the secretory stage of the menstrual cycle, and are under similar hormonal control—that is, progesterone and oestradiol secreted by the ovaries. These two hormones are necessary for the formation of the placenta, which follows implantation, and, indeed, a decidual reaction can be elicited experimentally when trauma is applied to the uterus of non-pregnant animals subjected to the action of the two ovarian hormones.

The alterations in the physiological activity of the uterine muscle during pregnancy have been especially studied in an attempt to elucidate the factors which maintain gestation and initiate parturition. Quantitative measurements of the reactivity of the muscle to the oxytocic hormone of the posterior pituitary lobe have been made in several species, and it has been found that the muscle always attains its maximum reactivity at parturition, when very small doses of oxytocin will bring about its contraction. This is true both for the organ *in situ*

and for strips of muscle suspended in physiological solution; and clinical experience with the oxytocic hormone also leads to the same conclusion as regards the human uterus. That the spontaneous rhythmic contractions of the uterine muscle gradually increase during pregnancy and attain their maximum at parturition can be concluded from clinical observation as well as from experimental data.

The alterations in the physiological activity of the uterine muscle during pregnancy are controlled by the ovarian hormones, the conditions being somewhat similar to those already discussed for the luteal phase of the menstrual cycle. To what extent progesterone plays a part in the control of the activity and reactivity of the muscle of the pregnant uterus in species other than the rabbit is rather doubtful; there exists little positive evidence on the question, and further experiments on primates are very desirable. There is a good deal of evidence, however, that the follicular hormone plays an important part in bringing about the gradual increase in the spontaneous rhythmic activity and reactivity to oxytocin which appears during the course of pregnancy, and that the culminating process of parturition may be dependent on the action of this hormone—that is, oestradiol. The sudden and marked increase in the elimination of active oestrogenic material about the time of parturition also suggests that oestradiol is a causative factor in the mechanism of parturition.

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SURGERY OF THE THYROID GLAND

LECTURES BY SIR THOMAS DUNHILL *

LECTURE III

In his third and last Lettsomian Lecture before the Medical Society of London on March 1 Sir THOMAS DUNHILL dismissed the consideration of surgical technique by saying that it was best studied in the operating theatre. Each surgeon varied in the details of his procedure. He described and illustrated the operation table he favoured, drawing attention to the neck rest. He added that his death rate had remained at about 2.6 per cent.; it had never been below 2.5 or above 3. To his actual knowledge forty-one patients had died without operation after having made an appointment for consultation, or while awaiting admission, or during the first few days after admission. Post-operative management should be easy, but was often neglected. The new tranquillity, the low pulse rate and regular rhythm, the increasing strength were sometimes liable to induce carelessness. The regained health was worth guarding.

Malignant Disease

Sir Thomas Dunhill said that he did not propose to cover the entire field of malignant disease of the thyroid gland, but only to make such observations as seemed to him of interest and importance. Metastases might occur in malignancy of such a low grade that for a long time it might be regarded as innocent. In no other organ did malignant change work slowly enough for its operation to be watched. It had been seen how responsive was the

thyroid epithelium to stimulation. The morphological appearance of the epithelium might vary greatly in simple tumours. To be of service to their patients they must recognize the very beginnings of malignancy, and for this they were dependent on histology. If they who had the care of patients were to save the lives of some of them they must learn what changes were suspicious enough to justify their belief and line of action, show clinical evidence of such weight that it could not be ignored, and re-examine the histological conclusions in the light of such knowledge.

"Malignant adenoma" was not a perfect term, but in the present state of knowledge it might be the most satisfactory. It was intended to convey a malignant transformation, while the tumour yet maintained in some respects the morphological characters of an adenoma. This type of carcinoma constituted a high percentage of the total number—the average in very large clinics was 85 to 90 per cent. Benign adenomata differed from one another. Some were composed of anastomosing columns of cells; in others differentiation had occurred, and the tumour consisted of follicles. When malignant transformation took place these ancestral characteristics were maintained to a considerable extent, though ultimately the differentiation was lost and the cells grew in disorderly fashion, presenting the appearance conveniently called medullary, and many authors had given that name to a type of carcinoma.

Often some degree of papilliferous activity occurred. One could not say with certainty where normal tissue ended and tumour tissue began. The incidence of papilliferous adenocarcinoma constituted about 24 per cent. of his total, but apparently this was not the case in some other countries. One authority in Switzerland had mentioned its rarity there. This type, unlike malignant adenoma, spread to neighbouring glands. It was very slow in its evolution. He mentioned four cases in which this change had been shown. Of two he had lost trace, although he had kept in touch with both of them for over seven years. One other had died in St. Bartholomew's Hospital, and in one the condition was causing extreme discomfort. It was interesting that out of forty-five cases collected from literature, including his own, the condition in twenty-five became obvious before the age of 30, and in fifteen before the age of 20. A third type was scirrhus, which was infrequent; it originated in the same manner as scirrhus in the breast.

Illustrative Cases

Turning to illustrations of cases the lecturer mentioned one woman, seen in 1930, in whom the histological examination showed at least three types of fibroid epithelium. This case illustrated how the morphological types of epithelium might overlap. He removed the tumour, x-ray treatment was given at St. Bartholomew's, and she was well for five years. In 1935 the breathing became laboured on slight exertion and several quite severe haemorrhages occurred. Examination showed a projection into the trachea, just below the larynx. After she had been given an appropriate amount of x-ray treatment it flattened out.

Speaking with regard to lymphadenoid goitre, Sir Thomas Dunhill said that when those who had as frequent opportunities as many of them had of seeing cases differed in their views he thought it meant that all cases did not run along parallel lines. He quoted some cases which showed that lymphadenoid goitre could clear up and need not go on to myxoedema, though it did so in certain instances. He thought it could be taken that lymphocytic infiltration to a very high degree could occur whenever there was exhaustion of epithelial tissues. Lymphadenoma might sometimes disappear, sometimes continue, sometimes go on to myxoedema or fibrosis. Rarely in these patients was any past history to be found. No surgeon saw enough of them to generalize about them. He had seen cases in which he had thought that focal

* Concluded from page 516.