REFRESHER COURSE FOR GENERAL PRACTITIONERS

MENSTRUAL DISORDERS AND THE MENOPAUSE

I. PHYSIOLOGICAL BASIS AND DIAGNOSIS

BY

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From the menarche to the menopause the endometrium undergoes a series of changes which periodically culminate in uterine bleeding. They consist of growth, secretion, shrinkage, and shedding. This sequence of events depends on the rhythmical rise and fall of ovarian secretion, which is controlled, in its turn, by the cyclical activity of the gonadotrophic hormones of the pituitary gland.

The Menstrual Cycle

The crucial event of the ovarian cycle is ovulation; on it depend not only the release of the ovum but the formation of the corpus luteum and the secretion of progesterone. Before ovulation takes place the endometrium is solely under the influence of the oestrogenic hormone, which stimulates growth and proliferation. After ovulation the combined effect of oestrogen and progesterone leads to glycogen production and secretion of mucus by the endometrial glands, and to conversion of the stroma into the decidua that is essential for the embedding of a fertilized ovum. These changes therefore constitute the prelude to pregnancy and are described as "progestational." Thus we may refer to the pre-ovulatory phase of the endometrial cycle as "proliferative," and to the post-ovulatory phase as "secretory" or "progestational."

Unless conception sets in motion the complex chain of endocrine reactions that leads to maintenance of the corpus luteum, the latter degenerates in due course and deprives the endometrium of the sustaining influence of the ovarian hormones. The premenstrual endometrium is thick, succulent, and oedematous. It is richly supplied with elaborately coiled vessels. Withdrawal of oestrogen results in dehydration, and as the endometrium shrinks the vessels become kinked, engorged, and congested. At the same time withdrawal of both ovarian hormones leads to necrosis of the glands and stroma. This is accentuated by the subsequent ischaemia, which may last for some hours before vasodilatation finally ensues, with rupture of the vessels, haemorrhage, and piecemeal shedding of the superficial layers of the endometrium.

Effect of Oestrogen and Progesterone on Uterine Bleeding

Normal menstruation is due to deprivation of both oestrogen and progesterone. Each of these hormones, however, has a specific effect on uterine bleeding.

The effect of oestrogen is perhaps best explained by the hypothetical conception of the "bleeding threshold" (Fig. 1). Let us suppose that there are three levels of effective oestrogen concentration. (It is important to refer to "effective oestrogen concentration," for this takes into account not only the concentration of oestrogen in the blood but also the degree of endometrial responsiveness to oestrogen.) One of these levels is the bleeding threshold, and whenever the effective concentration of oestrogen lies within this range bleeding will occur. If the effective concentration is below this level, as it is in most cases of amenorrhoea due to a refractory endometrium or to ovarian or pituitary failure, "subthreshold amenorrhoea"

will be the result. Normal menstruation is due to oestrogen (and progesterone) deprivations, and consequently to a fall in the effective concentration from superthreshold to threshold levels. Similarly, the administration of oestrogen in cases of amenorrhoea usually leads to bleeding a few days after the course is completed ("oestrogen withdrawal bleeding"), and is due to the drop from superthreshold to threshold levels. On the other hand, bleeding may be arrested if

the effective concentration is raised to superthreshold levels with high doses of oestrogen, or if the effective concentration is lowered, either by opposing the action of oestrogen with androgen or by rendering the endometrium less responsive to oestrogen with progesterone.

Though the individual roles of oestrogen and progesterone in the production of uterine bleeding are not clearly understood, something is known of their characteristic bleeding patterns. Oestrogen withdrawal bleeding, for example, is nearly always brief, scanty, and painless. Bleeding can also occur while the endometrium is still under the influence of oestrogen—for instance, in the course of prolonged and continuous oestrogen therapy. Another example is metropathia haemorrhagica, in which ovulation fails to take place and the endometrium is built up, under the constant and unopposed action of oestrogen, to a polypoid, oedematous, and haemorrhagic structure. The resulting bleeding is apt to be prolonged and variable in quantity, sometimes amounting to flooding, sometimes consisting of a mere trickle. These protracted episodes of bleeding are usually associated with incomplete shedding of the endometrium. On the other hand, progesterone-deprivation bleeding from an endometrium previously primed with oestrogen has all the characteristics of a "normal" menstrual period with regard to the duration and amount of loss, and is accompanied by complete shedding of the endometrium.

FIG. 1.—Oestrogen bleeding levels.

Mechanism of Ovulation

Rupture of the Graafian follicle and discharge of the ovum are not due simply to the mounting tension on its walls of increasing quantities of follicular fluid, but is almost certainly brought about by the activity of the gonadotrophic hormones. During the early days of the menstrual cycle the follicle-stimulating hormone (F.S.H.)

controls the development of the Graafian follicle, which in due course begins to secrete oestrogen. This, in turn, inhibits F.S.H. secretion, and its concentration wanes. Luteinizing hormone (L.H.) now begins to be elaborated by the pituitary, and ovulation probably takes place only when the falling level of F.S.H. and the rising level of L.H. reach a certain ratio.

Effect of Ovarian Hormones on Uterine Muscle

It is now generally accepted that oestrogen increases the general tone of the uterine muscle and induces relatively frequent contractions of low amplitude, whereas progesterone induces less frequent contractions, but of greater amplitude. Indeed, in some cases the strength of the contraction may exceed the blood pressure in the uterine vessels, giving rise to painful ischaemia of the uterine muscle.

Abnormal Bleeding Patterns

Ovarian failure, according to its severity, gives rise to different bleeding patterns, of which the following are characteristic.

Ovulatory Oligomenorrhoea.—The length of the cycle is increased, though ovulation does eventually take place about 14 days before the onset of bleeding. The prolonged pre-ovulatory phase may be due to inadequate F.S.H. secretion in the early days of the cycle, or failure to achieve the necessary F.S.H./L.H. ratio within the usual period of time. Bleeding is normal in amount and duration when it does appear.

Menorrhagia.—This means heavy bleeding, often prolonged, and sometimes associated with short cycles. Ovulation is usually found to be taking place, though the post-ovulatory phase of the cycle may be shorter than 14 days, and an endometrial biopsy taken on the first day of bleeding may show signs (such as persistence of undifferentiated stromal cells) of inadequate progestational development. Menorrhagia is probably due to slight deficiency of progesterone secretion, so that the endometrium tends to be incompletely shed, with increase in the duration and amount of bleeding. This condition represents the mildest type of ovarian failure.

Metropathia Haemorrhagica.—Here no semblance of a menstrual cycle remains. Episodes of irregular bleeding—sometimes amounting to alarming flooding and sometimes consisting of a mere trickle—may last from a week to several months, and alternate with phases of amenorrhoea of equally uncertain duration. Ovulation fails to take place and the endometrium is under the constant and sole influence of oestrogen. As soon as the endometrium has been built up to a thickened, oedematous, and haemorrhagic structure, irregular shedding takes place, which is incomplete, however, because of the absence of progesterone. Finally, so much endometrium is denuded that bleeding ceases, and once again, under the continuous influence of oestrogen, the endometrium is reconstructed to form an exaggeration of the normal proliferative pattern with widely dilated glands ("Swiss cheese" appearance), reduplication of glandular epithelium, and an oedematous and haemorrhagic stroma.

Amenorrhoea or Non-ovulatory Oligomenorrhoea.—This represents the severest type of ovarian failure. Not only is no progesterone secreted, not only does ovulation fail to occur, but the oestrogen level is too low (or only occasionally high enough) to lead to uterine bleeding.

Other Menstrual Patterns.—The significance of intermenstrual "spotting" is often not apparent. It may result from a fall in the effective oestrogen concentration at the time of ovulation. Though it may be a matter of inconvenience and anxiety to the patient, it is seldom of sinister significance (unless it is due to organic causes) and does not easily respond to available therapeutic measures.

Premenstrual "trickling" may be associated with mild progesterone deficiency, but endocrine therapy is equally ineffective.

Hypomenorrhoea (scanty periods) is usually of no significance. If ovulation takes place the amount of bleeding does not matter, unless it is inconveniently excessive.

Aids to Diagnosis

(1) **History Taking: Menstrual Charts.**—To distinguish clinically between these various bleeding patterns an accurate menstrual history must be taken. This is not easy. The patient is often uncertain of her recent menstrual dates, and is apt to confuse the issue with misleading statements such as, "My periods come every three weeks," when she means that the interval between the end of one period and the beginning of the next is three weeks; or, "I see my periods twice in a month," when she means that one period started on the second day of the month and the next on the thirtieth. The doctor, on the other hand, can usually ill afford the time to unravel this vague and badly expressed story. Even if he succeeds he may still fail to paint a sufficiently vivid mental picture of the bleeding pattern to enable him to make a clinical diagnosis by merely entering a list of the dates of recent periods in the patient's clinical notes. The use of some form of menstrual chart

FIG. 2.—Menstrual Chart.* 1. Normal period. 2. Dysmenorrhoea denoted by blacked-in line. 3. Heavy period. 4. Scanty period. 5. Oral treatment for 14 days—stilboestrol, 1 mg. daily. 6. Injection treatment—progesterone, 25 mg., every other day for four injections. 7. Basal temperature records: (A) pre-ovulatory temperature, (B) post-ovulatory "dip," (C) post-ovulatory temperature.

(see Fig. 2) is therefore almost essential to the gynaecologist or endocrinologist constantly dealing with cases of functional menstrual disorder. Even the practitioner, conscientiously determined to understand his patient's menstrual problems, may wish to use such charts in cases of this nature. In spite of one's best endeavours, however, one may fail to make any sense out of the patient's history. In that case, she should be instructed to go home and keep an accurate note of her bleeding dates, and possibly also of her basal temperatures, and bring it back in two months. This period of observation has the added advantage that it prevents officious endocrine therapy in cases in which the menstrual disturbance is merely transient and of no serious significance. Spontaneous remission not infrequently occurs during this time, and unwarranted claims are often made for endocrine therapy administered coincidentally with the onset of a period of remission. On the other hand, if a clear-cut diagnosis of metropathia, for instance, has been made it may obviously be unwise to delay treatment.

(2) **Basal Temperature Records.**—There is evidence that the body temperature rises in the presence of progesterone. Thus, if the early morning oral temperature is recorded daily throughout a normal cycle it will show a higher level after ovulation than before (see Fig. 2). This "biphasic temperature pattern" indicates that the cycle is an ovulatory one. Furthermore, it is possible to determine when ovulation takes place—namely, on the day when the

*Menstrual charts of this type (extending over two, four, or eight years) can be supplied by Messrs. Ash and Co., Holyrood Street, London, S.E.1.

temperature rises. Sometimes there is a "pre-ovulatory dip" which heralds the ovulatory rise: indeed, in a few cases, in which the post-ovulatory temperature is not appreciably raised, this dip is the only indication of ovulation.

(3) *Endometrial Biopsy or Curettage*.—In the presence of a biphasic temperature pattern it is practically certain that the cycle is ovulatory. These temperature studies have therefore made it possible to dispense on many occasions with an endometrial biopsy. On the other hand, absence of a typical biphasic pattern does not so surely indicate that ovulation has not taken place. Furthermore, some patients are not intelligent or co-operative enough to take their temperatures accurately, and a biopsy may then be necessary. In any event, it is at least desirable, if not essential, to perform a biopsy or even a thorough diagnostic curettage, especially in cases of irregular, excessive, or intermenstrual bleeding, to exclude an organic cause before embarking upon endocrine therapy. These procedures are of course beyond the scope of the practitioner, though he should know, in explaining to his patient what is involved, that a biopsy can be taken in about 50% of cases without an anaesthetic and with little discomfort. In most cases the biopsy specimen should be obtained on the first day of bleeding.

Endocrine Preparations

Oestrogens

There are too many oestrogenic preparations on the market, and the practitioner will be well advised to select only three or four upon which he can rely. Stilboestrol is probably the least variable in effect, and has been the most widely used. We are therefore more familiar with its therapeutic performance at different levels of dosage than with any other oestrogen. Moreover, it is cheap and highly potent when given by mouth. It has the disadvantage, however, that the lower limit of its toxicity range overlaps the upper limit of its therapeutic range, and nausea and occasionally vomiting will therefore be experienced in some cases, especially if the doses are unnecessarily large. Ethinyl oestradiol is the most potent oestrogen at present available, being 20 to 25 times more effective than stilboestrol. Unless this fact is fully appreciated there is considerable danger of overdosage. It is given by mouth, and, though it is less likely to produce toxic effects, these may occur, especially if the dose is unnecessarily large.

Conjugated equine oestrogens (an extract of oestrogenic material, mainly in the form of oestrone sulphate, from the urine of pregnant mares) constitute a highly active natural oestrogenic preparation (half as potent as stilboestrol) with minimal tendency to produce unpleasant side-effects. Finally, if it should be necessary to use oestrogens in very large doses without any risk of toxic effects, oestradiol benzoate may be administered by intramuscular injection (50,000 i.u. given twice a week is probably equivalent to 2 mg. of stilboestrol daily by mouth).

Progestogens

Progesterone is usually given by intramuscular injection, whereas ethisterone has progestogenic properties when administered orally. No direct comparison of their potencies has been made, but it is usual to give 30 mg. of ethisterone daily by mouth in those cases in which 20–25 mg. of progesterone would be injected on alternate days.

Androgens

It is seldom necessary to use testosterone propionate by intramuscular injection, and methyl testosterone in oral tablets of 10 mg. daily is usually effective for therapeutic purposes.

Gonadotrophins

These compounds have led to disappointing results. Until more potent or effective preparations are available for clinical use the practitioner would be wise to avoid them.

BRITISH ORTHOPAEDIC ASSOCIATION

ANNUAL MEETING, 1950

The annual meeting of the British Orthopaedic Association was held in London on October 26, 27, and 28, under the presidency of Mr. S. L. HIGGS.

Femoral Lengthening in Leg Equalization.—Mr. D. WAINWRIGHT (Newcastle) discussed the problem of leg equalization in such conditions as poliomyelitis, congenital short femur, and premature epiphysal fusion. He considered that femoral lengthening had a definite place in treatment. Twenty-five patients had been operated upon. The average gain in length was two inches. Complications included: delayed union, one case; stiffness of the knee, two cases; and temporary nerve paralysis, two cases. There were no vascular complications. Mr. F. G. ALLAN (Birmingham) agreed that knee stiffness presented a real problem.

Immobilization Osteoporosis.—Dr. HARWOOD STEVENSON (Stanmore) had studied the radiographs of 100 patients submitted to prolonged immobilization for various diseases and had found that the process of osteoporosis followed a typical pattern irrespective of the nature of the primary disease. Osteoporosis developed rapidly and might be obvious within six weeks, but if mobility was maintained disease might be present in a limb for many months without leading to marked osteoporosis. These observations suggested that osteoporosis was a consequence of immobilization as such rather than of disease. Dr. H. A. SISSONS (London) had studied the gross and microscopic structure of bone obtained from osteoporotic limbs and from the site of prematurely fused epiphyses. Examination of trabecular structure was aided by radiographs of thin bone sections. In areas of bone atrophy osteoclasts and osteoblastic new bone formation proceeded concurrently. Hyperaemia was not evident. In sections from areas of premature epiphysal fusion there was disruption of the epiphysis into the diaphysis and bony bridging of the epiphysal line. The evidence suggested that the process of atrophy occurring during immobilization was one of osteoporosis in the strict sense of the word, and was not simply a halisteresis. The process was not due to hyperaemia alone. Mr. H. JACKSON BURROWS (London), discussing the two preceding papers, said that in normal bone there was a continual and balanced process of absorption and laying down of bone. In disuse atrophy there was diminished replacement of bone and increased absorption. The stimulus responsible was unknown. Vascularity had little to do with it. It was noteworthy that a general stimulus might affect only local areas of bone.

Curve Patterns in Idiopathic Structural Scoliosis.—Mr. J. I. P. JAMES (London) recalled that recent work in America had shown that the pattern of the curve in idiopathic scoliosis was the key to the prognosis. He reported a study of the typical features and prognosis in two curve patterns—infantile idiopathic scoliosis and primary lumbar idiopathic scoliosis. In the former the prognosis had been assessed from an analysis of 33 cases. Exceptionally a curve that was initially slight might disappear; a few might remain stationary; but most curves progressed and led to severe deformity. Treatment was very unsatisfactory. Primary lumbar idiopathic scoliosis had a benign course; correction was not required. But pain, developing in middle life from osteoarthritis, was much more common in this than in other patterns of scoliosis. If not relieved by a suitable corset, fusion (without correction) might be required. Mr. H. OSMOND-CLARKE (London) said that although a study of the curve patterns simplified prognosis it did not simplify treatment. Infantile scoliosis was a problem to which no solution was known. All such patients should be segregated in specially equipped clinics.