ENDOCRINES IN THEORY AND PRACTICE

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

HORMONES IN THE TREATMENT OF MENSTRUAL DISTURBANCES

BY

P. M. F. BISHOP, B.M., B.Ch.

The causes of menstrual disturbances may be organic, nervous, or endocrine. General debilitating conditions such as anaemia, tuberculosis, and wasting diseases commonly give rise to amenorrhoea; local lesions of the uterine mucosa or muscle such as chronic endometritis, polyps, fibroids, and malignant new growths may result in excessive uterine haemorrhage. Such organic causes should be excluded before endocrine therapy is considered.

Emotional disturbance, a sudden shock, or a change of environment may lead to amenorrhoea, and it has been suggested that such stimuli may induce a flow of inhibitory impulses from the hypothalamic nuclei checking the gonadotropic secretions of the anterior pituitary which control the ovarian and hence the uterine cycle. In such cases the inhibitory influence on the pituitary may be removed as suddenly as it was applied, with re-establishment of the menstrual rhythm. Should this occur while the patient is receiving hormone treatment the endocrinologist may claim a success to which he is not entitled, for it is not generally conceded that the hypothalamic nuclei are affected by the therapeutic administration of pituitary or ovarian extracts.

The menstrual cycle is disturbed in such glandular syndromes as Graves's disease and myxoedema, Simmonds's disease, acromegaly, pituitary basophilism, and the adreno-genital syndrome, but treatment of the general endocrine disorder rather than of the menstrual derangement is indicated.

Finally, the alteration of menstrual function may be the only sign of hormone deficiency, and it is with the treatment of such cases that this article is concerned.

Uterine Bleeding in Menstrual Disorders

If a course of large doses of oestrin, the ovarian follicular hormone, is administered to a castrated woman uterine haemorrhage will take place from one to two weeks after the last injection. This is known as "oestrin-withdrawal bleeding." If smaller doses are given intermittent haemorrhage may arise during the course of treatment. Such haemorrhage is due to the effect of oestrin on the endometrium being maintained at the level, or threshold, at which bleeding occurs. This may be described as "threshold bleeding." Oestrin-withdrawal bleeding therefore supervenes when the oestrin effect on the endometrium is withdrawn from a super-threshold level.

During the first half of the normal menstrual cycle oestrin is secreted by the ripening Graafian follicle and reaches a super-threshold level. Some of this oestrin probably becomes actually fixed in the uterine tissues, and under its influence the "proliferative" type of endometrium is built up. Ovulation then ensues and the secretion of oestrin by the ovary falls to a low level. The corpus luteum develops and progesterin is secreted. It renders the endometrium unresponsive to oestrin, which consequently is probably excreted from the uterine tissues.

This excretion would account for the high concentration of oestrin in the blood and in the urine which is found during the second half of the menstrual cycle, a time at which there is evidence of a comparatively low oestrin effect. Oestrin-withdrawal bleeding does not, however, take place, for in the meantime progesterin has been exerting its own specific effect on the endometrium, converting it into the "premenstrual" type. As the corpus luteum wanes the endometrium is deprived of all hormonal sustenance and begins to be shed on the twenty-eighth day of the cycle—"menstrual bleeding."

Whether menstruation occurs regularly, not at all, or irregularly and excessively, depends, therefore, on the effect of oestrin on the uterus and the subsequent presence or absence of progesterin. Amenorrhoea is usually due to a sub-threshold effect of oestrin on the uterus. The endometrium fails to reach that stage of development which must be attained before bleeding can be induced. Menorrhagia and metrorrhagia supervene when oestrin reaches and is maintained at the threshold or bleeding level. Since ovulation fails to take place and no corpus luteum is formed this constant effect of oestrin continues unopposed owing to the absence of progesterin.

Amenorrhoea, Hypomenorrhoea, Oligomenorrhoea

OVARIAN REPLACEMENT THERAPY

The sub-threshold effect on the uterus in amenorrhoea, hypomenorrhoea (scanty flow), and oligomenorrhoea (prolongation of interval), may be due to inadequate secretion of oestrin (ovarian deficiency), to failure of the uterus to react to normal quantities of oestrin (uterine deficiency), or to a combination of the two. The uterus is usually small and the endometrium atrophied.

The first stage of treatment, therefore, is to build up the uterus to adult size, which in itself may result in rendering the endometrium more sensitive to ovarian stimulation. This may be accomplished by the administration of some compound of oestrin (ovarian replacement therapy): 50,000 I.B.U.* of a reliable preparation of oestradiol† (the hormone actually secreted by the ovarian follicle) are injected intramuscularly at intervals of three to four days until five doses have been given. This course of 250,000 I.B.U., which probably represents an unnecessarily high dose, should induce an oestrin withdrawal haemorrhage ten to fifteen days after the last injection. A second course of injections should begin immediately bleeding occurs. In the absence of a haemorrhagic response an interval of three weeks should separate the two courses.

Progesterin inactivates oestrin, which is therefore more effective during the first than the second half of the menstrual cycle in cases of hypomenorrhoea. Even in amenorrhoea, where there is no apparent cycle, it is better to administer oestrin for a fortnight only because (1) if a super-threshold level is maintained continuously oestrin-withdrawal bleeding is postponed, and (2) continuous oestrin therapy may lead to endometrial hyperplasia or inhibit pituitary activity. Early evidence of response of the genital tract to oestrin may be provided by

* I.B.U. (international benzoate unit) = 0.1 γ oestradiol benzoate—that is, 1 gramme oestradiol benzoate = 10,000,000 I.B.U.

† Di-menformon (Organon), Progynon B Oleosum Forte (Schering), Oestroform B (British Drug Houses).

the appearance of the vaginal smear. Accurate information as to the uterine growth response can be obtained only by measurement of the intra-uterine length with a metal sound. The most convenient criterion of response is uterine bleeding. In cases of long-standing amenorrhoea this is produced only if relatively high doses are administered. Usually three or four courses are required to induce or restore uterine function.

If the amenorrhoea is due to uterine insensitiveness alone such replacement therapy may induce the uterus to respond to the natural secretions of the ovaries and the menstrual rhythm may be restored without further treatment.

OVARIAN STIMULATION THERAPY

If the uterine hypoplasia results not from a primary failure of uterine development but from defective ovarian activity this must now be dealt with. It may be due to an inadequate pituitary stimulus or to a failure of the ovary to respond to normal amounts of pituitary secretion.

The second stage of treatment consists, therefore, in prescribing gonadotropic extracts (ovarian stimulation therapy): 100 to 500 R.U.* of a gonadotropic extract of pregnancy urine† are injected intramuscularly three times a week for four weeks. This course may be repeated. Treatment should then be discontinued for a month, after which it may be resumed if there is no re-establishment of spontaneous menstrual rhythm.

Theoretical considerations would indicate that the ideal form of treatment is the administration of a follicle-stimulating hormone (prolan A) for a fortnight, followed by the luteinizing hormone (prolan B) during the second fortnight. Unfortunately clinically effective follicle-stimulating extracts are not yet obtainable commercially, and consequently only luteinizing extracts are used. Available experimental evidence would indicate that the adequate dose for the human female is probably higher than now employed.

Estimation of Oestrin and Prolan

Estimations of oestrin and prolan in the blood and in the urine are considered by some authorities to be useful in determining the nature of the disturbance of hormone secretion. It is found, however, by most workers in this country who are familiar with such technique that the methods of hormone assay of body fluids at present in use are not sufficiently accurate to provide valuable information. Furthermore, the finding of an excess or deficiency of any particular hormone in blood or in urine does not necessarily indicate a corresponding excess or deficiency of secretion or utilization of that hormone in the organism.

The results of hormone therapy in this group of cases are disappointing. Menstrual cycles are very seldom established in cases of primary amenorrhoea (women over the age of 18 who have never menstruated). Permanent re-establishment of menses occurs in 10 to 20 per cent. of cases of secondary amenorrhoea, and in cases of oligomenorrhoea and hypomenorrhoea regularity and normal loss are achieved and maintained in 30 to 40 per cent. Such results are not surprising when the intricacies of the problem are considered. The delicate interrelations between pituitary, ovary, and uterus are difficult to re-adjust by the use of hormone extracts of which the optimum dose is not known. The reasons for applying a particular hormone at a certain phase of the cycle are

at present based chiefly on hypothetical conjecture. Even the nature of the extract is not, in some cases, the most suitable—for example, the use only of luteinizing extracts for ovarian stimulation, which probably requires a carefully adjusted combination of follicle-stimulating and luteinizing hormone.

Menorrhagia and Metrorrhagia

This type of menstrual disturbance will be considered under three headings: menopausal, maturity, and puberty bleeding, for the treatment differs according to the age of the patient.

MENOPAUSAL BLEEDING

The activity of the ovary is waning. It is becoming insensitive to the gonadotropic stimuli of the pituitary, even though these are now relatively excessive. Oestrin is reaching no longer super-threshold but threshold or bleeding levels. Progesterin, if secreted at all, is ineffective in lowering such levels. Attempts to prolong the life of the ovary by artificial stimulation with gonadotropic extracts are illogical. Treatment should be designed to hasten the death of the ovary by destructive doses of deep x rays or of radium, or to remove the source of the haemorrhage by hysterectomy.

MATURITY BLEEDING (METROPATHIA HAEMORRHAGICA)

Ovulation fails to take place, and the ovaries may be palpably enlarged and are studded with small cystic follicles which have not ruptured. The endometrium is submitted to continuous stimulation by oestrin, and an exaggeration of the proliferative phase ("Swiss cheese" or glandular hyperplasia) results in thickening and sometimes polypoid. The menstrual rhythm is disturbed and periods of profuse flooding or mild but continuous haemorrhage alternate with amenorrhoea. During the bleeding phase oestrin is presumably being maintained at threshold levels in the absence of progesterin. During the phases of amenorrhoea oestrin has either failed to reach the threshold level or continues to be above it.

The treatment during a bleeding phase is to administer progesterin or a luteinizing gonadotropic extract: 1 Rab. U.* of progesterin† or 500 R.U. of a gonadotropic extract, or both, should be given by intramuscular injection daily until the haemorrhage ceases. Such treatment usually succeeds in arresting the flow within three or four days. To re-establish the normal rhythm is more difficult, but an attempt may be made to do so by applying a continuous luteinizing stimulus, such as 100 R.U. of a pregnancy urine extract three times a week for a month. Such a course may be repeated as indicated in the section on amenorrhoea.

PUBERTY BLEEDING

The cause of this type of bleeding is not completely understood, but it is probably due to defective function of the corpus luteum. The menstrual rhythm is usually undisturbed and the condition is one of pure menorrhagia, though sometimes the menstrual cycle is shortened to three weeks.

Treatment consists in increasing the luteinizing stimulus: 100 R.U. of a gonadotropic extract are injected intramuscularly three times a week for four weeks. The course may be repeated as indicated in the section on

* Gonadotropic hormones have not yet been obtained in crystalline or synthetic form, and are therefore assayed biologically in rat units (R.U.) instead of international or weight units.

† Pregnyl (Organon), Antuitrin S (Parke, Davis), Prolan (Bayer), Gonan (British Drug Houses). Such extracts contain mainly prolan B, the luteinizing hormone.

* Progesterin has recently been synthesized. One I.U. (international unit) = 1 mg. of synthetic progesterone. At present the synthetic product is not generally available commercially, and natural progesterin extracted from the corpora lutea of sows is still used. This is assayed in rabbit units (Rab. U.).

† Progesterin (Organon), 1 Rab. U. = 1 I.U.; Proluton (Schering) and Progesterin (British Drug Houses), available in international units; Lutex Leo (distributed by Boots), 1 Rab. U. = 3/4 I.U.

amenorrhoea. The results of treatment are highly satisfactory and normal flow is usually established within three or four months. It is important to deal with this condition early, as it frequently leads to amenorrhoea or maturity bleeding if left untreated.

Dysmenorrhoea

When extrinsic causes of dysmenorrhoea, such as fibroid polyps, the passage of clots or pieces of membrane, or uterine congestion from pelvic inflammation, have been excluded, there remain three factors—nervous, psychological, and endocrine—the relative responsibility of which it is difficult to assess.

There is evidence to show that in a high proportion of cases of "spasmodic" dysmenorrhoea the pain is due to an inflammatory or irritative lesion of the sympathetic nerves supplying the uterus. In these cases hormone therapy is obviously of no value, and the condition should be dealt with by cervical dilatation, alcohol injection of the pelvic plexus, or pre-sacral sympathectomy. The psychological element may predominate not only in the obviously hyperaesthetic but also in the apparently "thoroughly sensible" type of woman, and the best way of determining how far it is responsible for the pain is by the administration of "dummy" tablets of oestrin (tablets of which the oestrogenic potency has been previously destroyed) or by injections of sterile olive oil. It is striking how frequently this device provides complete, if only temporary, relief.

The cases of endocrine origin fall into two groups: those due to deficiency of oestrin, and those due to lack of progesterin. Dysmenorrhoea often accompanies uterine hypoplasia. Menstruation, which is usually scanty, is taking place in an organ inadequately developed for such a function. There may be lack of co-ordination between the contraction of the uterine muscle and the evacuation of the blood from the narrow os. The dysmenorrhoea may disappear if the uterine hypoplasia is corrected. This may be accomplished by the oral administration of a compound of oestrin: 1 tablet of oestrone,* the strength of which varies from 1,000 to 50,000 I.U. according to the requirements of the case, should be administered daily by mouth. Such comparatively small doses affect only the development of the uterine muscle and do not interfere with the menstrual rhythm. They may therefore be given continuously throughout the cycle without fear of inhibiting menstruation. If higher doses are required they may be injected intramuscularly, as in the course outlined in the section on amenorrhoea.

There is evidence to suggest that progesterin inhibits uterine motility. Observations obtained by introducing a balloon into the uterus and recording the uterine movements on a kymograph show that during the second half of the menstrual cycle uterine contractions are in abeyance, though they begin to reappear during the premenstrual twenty-four to forty-eight hours and reach maximum intensity during menstruation, this period corresponding with the regression of the corpus luteum and the absence of progesterin.† The administration of progesterin therefore alleviates the symptom in some cases of dysmenorrhoea, particularly when the pain begins a day or two before the onset of the menstrual flow, and is most intense on the first day of menstruation: 1 Rab. U.‡ of progesterin is administered daily, commencing one or

two days before the expected onset of the menstrual flow,* and continuing up to the third day of the period.

Conclusions

During the past four or five years the pendulum of opinion has swung from unreasonable scepticism to unscientific optimism, and it is important to consider critically the present possibilities and limitations of endocrine therapy in menstrual disorders. The subject is still in its infancy, and it will probably take another five years for sufficient data to be collected to enable sound principles of treatment to be laid down and clinical results to be evaluated.

At present there are two main principles of treatment: replacement therapy and stimulation therapy. Replacement therapy yields comparatively good results, for its purpose is simple and direct. By administering oestrin, for example, it is possible to induce uterine growth. By injecting progesterin the level of oestrin utilization, which, in a case of maturity bleeding, has reached and is being maintained at the bleeding threshold, may be lowered, and the bleeding is immediately checked. The knowledge that progesterin or prolan can effectively control the sometimes alarming haemorrhage of menorrhagia should save many a young woman from the tragedy of hysterectomy or the futility of a curettage. Replacement therapy, however, is only temporary in its effect. Discontinue the administration of oestrin in a case of ovarian deficiency and the uterine muscle will atrophy. The progesterin which checked a bout of bleeding in a case of menorrhagia will not prevent the repetition of such a flooding.

Stimulation therapy yields comparatively poor results, except in cases of puberty bleeding. Re-establishment of menstrual rhythm in a long-standing case of amenorrhoea or menorrhagia demands readjustment of a delicate endocrine balance whereby the ovary is subjected to hormonal stimuli of varying nature and intensity throughout the cycle.

Finally, some of the preparations in use are substances of considerable potency, the remote effects of which are even yet not fully recognized. They should therefore be employed cautiously and with respect, lest they cause permanent damage to the uterus, ovaries, or pituitary.

The Laboratories La Biotherapie of Paris have instituted an annual Besredka prize, subject to the following regulations: (1) The prize will be awarded for an original manuscript or printed work on local immunity in its therapeutic applications. (2) MSS. or printed works must reach *La Biotherapie*, 5, Rue Paul Barruel, Paris 15e, before December 31 of each year, either in typewritten or printed form in five copies. Printed works must not be of earlier date than November 30 of the preceding year. (3) For manuscript work anonymity is optional; in such case the MS. must bear a motto reproduced on an envelope containing inside the name and address of the author. (4) The competition is open to scientists without distinction of nationality, but MSS. or printed works must be presented in French. (5) The prize is of 15,000 francs. If the jury decides that no one of the presented works is worth a prize the amount is to be added to that of the next year, but cumulation cannot exceed the sum of 30,000 francs. (6) The jury is composed of Professor Ch. Achard, member of the institute; Professor A. Lisbonne of the Faculty of Medicine of Montpellier; Professor Ach. Urbain of the Museum of Natural History; and Professor Devraigne, hospital obstetrician. (7) The results of the competition will be made known each year in June.

* Oestrone (keto-hydroxy-oestrin), a degradation product of oestradiol (dihydro-oestrin), is extracted from pregnancy urine. Reliable products available include Menformon (Organon), Progynon (Schering), Oestroform (British Drug Houses).

† These observations are disputed by certain English authorities.

‡ The dose is empirical. Some American authorities have obtained satisfactory results using 3/25 Rab. U.

* If progesterin is applied too early in the cycle it may inhibit menstruation.