REFRESHER COURSE FOR GENERAL PRACTITIONERS

MENSTRUAL DISORDERS AND THE MENOPAUSE

II. MANAGEMENT AND TREATMENT

BY

P. M. F. BISHOP, D.M.

Endocrinologist, Guy's Hospital and Chelsea Hospital for Women; Senior Lecturer in Endocrinology, Department of Obstetrics and Gynaecology, Postgraduate Medical School of London

Treatment of Menstrual Disorders

Induction of Ovulation

We have already seen that ovulation probably depends on achieving a certain ratio between the waning level of follicle-stimulating hormone and the rising level of luteinizing hormone. Moreover, in individual cases other essential conditions, such as responsiveness of the ovary to gonadotrophic stimuli, may also be absent. It is true that very large doses of chorionic gonadotrophin, such as 10,000 to 20,000 i.u. daily, will prolong the life of a normally established corpus luteum. True pituitary gonadotrophins, not yet marketed, have also been shown in isolated experiments to bring about changes in the human ovary. Nevertheless, no gonadotrophic extract at present generally available has been convincingly shown to induce ovulation in women suffering from non-ovulatory menstrual disorders.

Failure to ovulate and the consequent menstrual disturbance are often symptoms of some general metabolic, nutritional, or psychological disorder, and the ovarian failure will right itself only when the patient's normal health is restored. The empirical use of thyroid extract may be justified in such cases. Failure to ovulate *per se*, however, is serious only when it is the cause of infertility, and it is only in this connexion that attempts to induce ovulation seem worth while. Crude attempts to imitate the secretions of the ovarian cycle are sometimes successful in inducing one or two ovulatory cycles, perhaps by conditioning the pituitary in some way to restore normal gonadotrophic activity temporarily. Three courses of stilboestrol (0.5 mg. daily for 21 days) and ethisterone (30 mg. daily from the 14th to the 21st day) with a week's interval between each course, during which bleeding should take place, may occasionally be followed by one or possibly two spontaneous ovulatory cycles—as judged by the temperature records—even in patients suffering from non-ovulatory amenorrhoea. If the patient and her husband have been carefully coached in the interpretation of the temperature records and told to have intercourse immediately the temperature rises from the pre-ovulatory level, there is a chance, theoretically at any rate, of conception occurring.

Oestrogen Haemostasis

It was postulated in Part I of this paper (*Journal*, November 25, page 1214) that uterine bleeding can be arrested if the effective concentration of oestrogen is either lowered beneath or raised above the "bleeding threshold." Progesterone "neutralizes" the effect of oestrogen on the endometrium, and androgen probably acts as an anti-oestrogen. These two hormones, therefore, will lower the effective concentration of oestrogen, though it may be some days before the bleeding stops, and in many instances the treatment is ineffective. To raise the oestrogen level above the threshold is a more rapid and certain way of bringing

about haemostasis, and bleeding may abate or cease within a few hours to a day. Oestrogen should be given repeatedly and in high concentration to achieve this object, and toxic side-effects must be expected. It is therefore probably better to avoid using stilboestrol.

Not only is ethinyl oestradiol less likely to produce vomiting but it is the most potent orally active oestrogen available: 0.15 mg. should be given every two hours. If sickness occurs it may be worth while substituting 5 mg. of the conjugated equine oestrogens preparation (distributed in this country by John Wyeth and Brother, Ltd., under the trade name "strogene"), though in these high concentrations toxic effects may accompany the administration of even this "natural" oestrogen and make it necessary to resort to injections of oestradiol benzoate, 100,000 i.u. every four to six hours. This is, of course, "heroic" treatment, and it should be reserved for desperate cases, in which, as the result of prolonged flooding, the patient is becoming exsanguinated and the relatives distracted. An oestrogen withdrawal bleeding may take place two or three days after the treatment, but it is usually moderate in amount and should cause no trouble.

Progesterone Withdrawal Bleeding ("Medical Curettage")

The nature of the bleeding after withdrawal of progesterone with its complete shedding of the endometrium has already been discussed. If the endometrium has been previously primed with endogenous oestrogen, adequate quantities of progesterone will usually induce a "medical curettage." It is possible, therefore, to forestall an episode

FIG. 3.—Prevention of metropathic flooding by rhythmic induction of medical curettage by progesterone.

of metropathic flooding, which generally begins only after some weeks of amenorrhoea, by producing a progesterone withdrawal bleeding at a relatively early stage of this non-bleeding phase. The metropathic flooding can in fact be repeatedly forestalled by performing these medical curettages regularly at four-weekly intervals using injections of 25 mg. of progesterone (dissolved in 1 ml. of oil) on alternate days for four doses (see Fig. 3), or by giving 30 mg. of ethisterone daily by mouth for a week.

By the use of oestrogen haemostasis and medical curettage the bleeding of a metropathic phase can be arrested and the next one prevented by superimposing a regular, though artificial, "normal" bleeding pattern on the unpredictable, irregular, and sometimes incapacitating metropathic pattern. One is not, however, attacking the cause of the metropathia, which is failure to ovulate. Nevertheless, this type of menstrual disorder is prone to undergo spontaneous remission. This is especially true in adolescent

girls who have their menstrual and reproductive life before them, and in whom a hysterectomy is therefore unthinkable. It is less true of women in the pre-menopausal age, when failing ovarian function is physiologically progressive until the menopause finally supervenes. At this age, hysterectomy or the induction of a radium menopause are reasonable alternatives to irksome endocrine therapy, especially if this does not go entirely according to plan.

Between these two extreme age groups there is the woman in her thirties. If she is anxious to start a family or to have more children it is obviously desirable to persist with conservative treatment in the hope of a spontaneous remission occurring (for, of course, she will not become pregnant so long as the non-ovulatory pattern lasts). If, however, she has made her family or is a spinster the fact that she is under 40, or any other arbitrarily chosen age, should not be the deciding factor in refusing her a hysterectomy if endocrine therapy fails, or is irksome, or requires to be indefinitely continued. The social, domestic, and wage-earning factors should decide the choice of treatment, and it should be emphasized that endocrine therapy does not cure, but merely prevents, the manifestations of the condition.

If it is eventually decided to embark on hysterectomy the following considerations should be borne in mind: (a) one-quarter of the patients will develop menopausal symptoms within two years of the operation if there is no operative interference with the ovaries. (b) If some ovarian tissue is resected one-half of the patients, and (c) if all ovarian tissue is removed all the patients, will develop menopausal symptoms which in the case of bilateral ovariectomy may be severe, indefinitely prolonged, and not easily controlled. (d) One-third of the patients, even if there is no operative interference with the ovaries, will suffer noticeable loss of libido after the operation. Despite this, in over 300 patients who had undergone hysterectomy and were subsequently personally interviewed, less than 10% regretted having consented to the operation.

Androgen Treatment of Menorrhagia

It has been shown that menorrhagia is probably associated with relative failure of corpus luteum development and progesterone secretion, and that this prevents adequate "neutralization" of the oestrogenic effect in the second half of the cycle. Bleeding therefore results in incomplete shedding of a poorly developed secretory endometrium and may occur early and be prolonged and excessive. It might seem logical in these cases to supplement the inadequate endogenous progesterone with exogenously administered progesterone. In practice this proves disappointing. Small doses of androgen, however, seem to diminish the amount and duration of bleeding, so that it becomes tolerable in a number of cases. How this comes about is difficult to explain: possibly the results of the disordered balance between oestrogen and progesterone caused by the relative progesterone failure are rendered less conspicuous if androgens, which may antagonize the action of both ovarian hormones, are used. Methyl testosterone, 10 mg. daily by mouth, should be given for two months.

The moderation of the bleeding pattern may persist for some months after the course of androgens is completed. In any case it is important not to give androgens longer than for two months continuously, and at least a month's interval should elapse between successive courses. Even so, undesirable side-effects very occasionally occur, for there are undoubtedly some, though probably very few, women who are abnormally sensitive to the masculinizing effects of androgens. Mild hirsutism, especially of the upper lip,

acne, and, very rarely, hoarseness develop. If this occurs androgen therapy should be discontinued immediately. Fortunately these effects are almost always reversible. It has been suggested that side-effects are more likely to occur in brunettes than blondes, and in women who already show a tendency to hirsutism. Though it is, of course, important to dwell at some length on these undesirable side-effects, this should in no way detract from the use of androgens in menorrhagia, which is surprisingly satisfactory.

Inhibition of Ovulation as a Remedy for Dysmenorrhoea

It is generally agreed that progesterone may cause uterine contractions so strong as to lead to temporary ischaemia of the muscle, with pain similar to that experienced in angina or intermittent claudication. Furthermore, it seems certain that dysmenorrhoea—that is, the so-called spasmodic dysmenorrhoea—does not occur in non-ovulatory cycles, and that exogenous administration of progesterone may actually induce or increase the pain. It has been asserted that the effects of endogenous progesterone may be modified by giving oestrogens in the premenstrual phase of the cycle, but these claims have not been substantiated, and the underlying reasoning is not easy to understand. It seems well established, however, that if endogenous progesterone can be prevented from appearing, by inhibiting ovulation, dysmenorrhoea will not accompany the subsequent uterine bleeding. Ovulation is best inhibited by giving oestrogen early in the cycle. Stilboestrol, 3 mg. daily (or its equivalent), beginning on any day up to the fifth day of the cycle and continued for 14 days, will almost always inhibit ovulation and give rise to a scanty, painless oestrogen-withdrawal bleeding within two or three days of the end of the course.

In order to avoid more or less continuous oestrogen administration a subsequent course should not begin for at least a week after the completion of the preceding course. If the dose has not proved to be large enough to be effective the cycle will either be of normal length and the period painful or else the period will be delayed, usually by about a fortnight, and be painful when it takes place. This prolonged cycle is due to the fact that the dose of oestrogen has been sufficient to inhibit the secretion of follicle-stimulating hormone so that the events of the early part of the cycle are held in abeyance until oestrogen administration ceases, when the normal cycle will begin to unfold, culminating in ovulatory and therefore painful bleeding, which is, however, a fortnight late.

It will be seen that considerable care on the part of the doctor and co-operation on the part of the patient are required to achieve successful results. Furthermore, there is little reason to suppose that oestrogen therapy will affect any cycle other than the one during which it is administered, or that it will play any part in the permanent "cure" of the dysmenorrhoea. Nor, on the other hand, is there any likelihood of permanent harm resulting from this form of oestrogen therapy if at least a week's interval is allowed to intervene between successive courses.

At best this method of treatment can be regarded as a fairly efficient way of tiding the patient over until spontaneous remission supervenes, as it often does during the third decade or after childbirth. At worst the method will be considered an irritating and exacting exercise in "timing," which the impatient doctor and the casual patient will soon abandon by mutual, though perhaps tacit, agreement.

It is beyond the scope of this article to deal with the psychogenic element in dysmenorrhoea or with such therapeutic measures as sex hygiene, cervical dilatation, and

pelvic neurectomy. In spite of these other methods of treatment the doctor may find himself anxious on many occasions to give endocrine therapy a trial.

The Menopause

The reason why both patients and doctors hold such different views on the subject of the menopause, the severity of its symptoms, the need for treatment, and the efficacy of various therapeutic measures depends on the following considerations.

Variation in Severity of Climacteric Symptoms in Different Women.—Hot flushes, for instance, occur in 95% of menopausal women, but in some they are mild and unheeded, whereas in others they are drenching, exhausting, and so frequent that the patient is completely incapacitated.

Changing Attitude of Successive Generations of Women Towards the Menopause.—The Victorian stoic resigned herself to the condition as something she just had to put up with: the mid-twentieth century cynic regards it as her right to demand all possible assistance in bearing an unfair burden practically unknown to and hardly ever appreciated by the male sex.

Variation in Attitude of Individual Doctors to Their Menopausal Patients.—Some doctors consider the condition of little consequence; others have little faith in any form of specific therapy; others believe that every woman, however mild or severe her symptoms, can receive benefit from oestrogen therapy.

Variation in Emphasis on Type of Symptom of which the Patient Complains.—"Nervousness," excitability, irritability, and disturbed sleep call for sedatives; depression, loss of confidence, and emotional instability need reassurance and common-sense psychotherapy; whereas hot flushes, sweating, headaches, and giddiness may respond to oestrogen treatment.

The Doctor's Previous Experiences with Oestrogen Therapy.—Those who have found it ineffective will be less inclined to prescribe it again.

It is clear that each case must be assessed individually, and that neither the type of treatment indicated nor the response to be expected will be the same for every case.

First, one must be sure that one is dealing with the menopausal syndrome. It may appear months or even years before the menses cease; on the other hand, it may not develop until months or even years after menstruation has ceased; moreover, it may last for many years; and, finally, the diagnosis does not depend on the patient's age but on the waning function of her ovaries. It is as wrong to regard every symptom that appears during the fifth decade as menopausal as to refuse to recognize that in a woman below the age of 30 hot flushes may be due to ovarian deficiency. The syndrome is made up of a variety of vague and bizarre complaints, such as indefinite aches and pains, numbness and tingling, and formication, though the most characteristic are hot flushes, depression, emotional instability, irritability, insomnia, palpitations, giddiness, lack of concentration, failing memory, headaches, and paraesthesiae.

Treatment of Menopausal Symptoms

(1) *Reassurance and Common-sense Psychotherapy.*—The impact upon the patient of this strange multitude of complaints may upset the poise she has developed in the course of years. She may fear cancer or some chronic and crippling illness which will make her an invalid. She may, on the other hand, recognize that this is the "change" but may have learnt to dread its consequences from the grim accounts she has received from her women friends. She may fear the effect on her husband of her "lost womanhood." She may resent this blunt reminder of her

matronly middle age. Her deteriorating memory and lack of concentration; the inconvenience, embarrassment, and loss of sleep caused by her hot flushes; the loss of confidence in herself, which may be aggravated by attacks of giddiness and palpitation; and perhaps the lack of sympathy which she detects in her own family circle, whom she suspects of resenting her increasing irritability, often send her flying to her doctor in search of that understanding which she so misses in her own home. She needs patient, sympathetic reassurance, with a careful analysis and explanation of her symptoms. She needs to be told that she is not suffering from cancer, that there is no fear of insanity, that her irritability and emotional instability are not her fault, and that something can be done to help her to weather this fleeting climacteric storm.

(2) *Sedatives.*—The climacteric is a time when the reaction of the woman to her environment becomes maladjusted. She becomes unduly sensitive to every little noise, and every afferent impulse is recorded in the sensorium with undue emphasis. She becomes "nervous," excitable, easily fatigued, and irritable, and she sleeps badly. All this clearly indicates the need for sedatives, mild enough to enable them to be prescribed more or less continuously. Phenobarbitone is an ideal preparation. In many cases a combination of patient, sympathetic handling, reassurance, and sedatives may be sufficient to overcome the effects of the syndrome, and more specific treatment is not required.

(3) *Oestrogen Therapy.*—It must always be borne in mind that, however strange and varied are its manifestations, the syndrome is primarily due to declining oestrogen secretion, and that not only are some symptoms, such as the hot flushes, directly due to this but that oestrogen therapy may lead to general beneficial effects. It is therefore probable that in most cases the maximal benefit will be derived from a combination of reassurance, sedatives, and oestrogens.

It might seem reasonable to argue that, if one wants to be sure of overcoming the results of oestrogen lack, it will be wise to give large doses of oestrogen. In fact, however, this is not the case, and high-dosage oestrogen therapy is probably responsible for most of the failures of this form of treatment. The woman whose ovaries are failing or who has recently undergone oestrogen deprivation is exceedingly sensitive to exogenous oestrogen and will nearly always react favourably to small doses. For instance, it is practically never necessary to give more than 1 mg. of stilboestrol (or its equivalent) daily, and results can often be obtained with as small a dose as 0.1 mg. daily. A useful dosage scheme is to give 0.1 mg. thrice daily for three weeks: if improvement occurs the optimal dose between 0.1 and 0.3 mg. daily is determined; if there is no improvement the dose is raised to 0.5 mg. daily for another three weeks, and if necessary to 0.75 mg. daily for a further three weeks. Once the optimal daily dose has been found, repeated attempts should be made to lower it so that the patient is "weaned" as soon as possible. In order to assess the results more easily the patient may be instructed to keep a daily record of the number of her hot flushes. Decrease in the number will provide semi-objective evidence of progress.

Initial large doses raise the threshold of response to oestrogens, so that larger and larger doses will be required; even then the patient may "escape" from the oestrogen control and begin to experience hot flushes again.

Side-effects are more likely to occur with large doses than with the minimal effective dose.

(a) *Nausea and Vomiting*.—Menopausal women are specially sensitive to oestrogens and therefore particularly liable to exhibit "toxic" effects. For instance, 1 mg. of stilboestrol (or its equivalent) daily will induce nausea in most menopausal women. If the patient shows intolerance, even to minimal effective doses, some other oestrogen should be employed, preferably a natural oestrogen such as "strogene."

(b) *Uterine Bleeding*.—Although this is almost certain to take place if large doses are employed, it not infrequently occurs if small doses (even as low as 0.1 mg. of stilboestrol daily) are used continuously for a prolonged period. If this happens, treatment should be discontinued until the bleeding ceases, and then readministered in courses of three weeks with a week's interval between successive courses, during which a withdrawal bleeding may appear.

(c) *Other Side-effects*.—Water and salt retention is a feature of intensive oestrogen therapy. It gives rise to increase in weight, often accompanied by a bloated feeling. Pain, tenderness, and swelling of the breasts may also develop during continued oestrogen treatment, especially if unnecessarily large doses are used.

There is no convincing evidence that exogenously administered oestrogens are carcinogenic. Nevertheless, it is obviously undesirable to submit a menopausal woman, who is specially sensitive, to excessive doses of oestrogens for prolonged periods.

Artificial Menopause

Experience has shown that any interference with, or resection of, ovarian tissue increases the likelihood of precipitating the climacteric syndrome, whereas removal of all ovarian tissues renders this practically certain. Furthermore, the severity of the symptoms of the artificial menopause at whatever age it is performed is likely to be considerably greater than that of the natural menopause. Not only are the hot flushes apt to be very frequent but also so severe that the patient is repeatedly drenched in sweat and quite unable to obtain any continued sleep at nights. In addition to this it is not unusual for the symptoms of depression to be especially marked, leading in many cases to severe depressive psychoses and in some instances to involutional melancholia. Every effort should therefore be made by gynaecologists to conserve all possible ovarian tissue, and, if it is decided to abandon the conservative treatment of metropathia, hysterectomy may be preferable to a radium menopause.

THE CHEMOTHERAPY OF CANCER

EXPERIMENTS WITH NEW COMPOUNDS

A lecture on "The Chemotherapy of Cancer" was delivered to the Fine Chemicals Group of the Society of Chemical Industry at the Royal Institution on November 13 by Professor ALEXANDER HADDOW, director of the Chester Beatty Institute, the Royal Cancer Hospital.

The great majority of cases of cancer at present, said Professor Haddow, were treated either by surgery in an attempt to extirpate and remove the tumour cells, or by radiotherapy to destroy the cells *in situ*. Each of these methods had its limitations, and in any case it would clearly be advantageous, particularly as widespread dissemination was an outstanding feature of the disease, if a less local and more general control of malignancy, such as could presumably be brought about by chemical means, were possible.

This had been well recognized from the earliest beginnings of the study of cancer. Ventures in chemotherapy, of a kind, long antedated the modern developments of surgery. Thus at different times in the past there had been applied such agents as belladonna, aconite, mercury, antimony, and arsenic. Many

of these chemical applications had a merely caustic action, as, for instance, in the local use of concentrated acids and alkalis and various metals and metalloids. Arsenic had an action which, though not specific, was less indifferent than the others, and the effects of arsenic in the treatment of cancer had been studied more continuously than those of any other agent.

The chemotherapy of cancer was thus of ancient date; interest in it was by no means a recent development. Nevertheless, there had been during the last few years a new burst of activity, arising very largely from a similar increase of interest in more fundamental work in the cancer field as a whole. In fact, more had been accomplished during the last 10 years than in any other period, though the greater part still remained to be achieved.

The Cancer Cell

Cancer, Professor Haddow continued, was perhaps the most difficult of all biological problems. The cancer cell was simply a modification of the normal cell. Conversion to malignancy of the normal cell might possibly be brought about by a subtle and elusive change of enzyme constitution quite unaccompanied by any grosser alterations affecting protein structure. On this account there was little or no protective reaction on the part of the body or host, such as occurred in parasitic infections. The malignant cell also appeared to be highly stable in its properties, as was shown by the manner in which its newly acquired characters were transmitted and maintained quite indefinitely. In many ways the processes of cell division were reminiscent of a self-propagating mechanism varying in the degree of control to which it was subject.

It had been suggested that the new configuration of the properties which distinguished the cancer cell from its predecessor might be expressed in terms of energy level or level of organization. The transition from normal to malignant appeared to be by way of intermediate cell types. Undoubtedly the normal cell was highly controlled in contrast to the cancer cell, in which the process of cell division might be regarded as almost autonomous. Nutritionally the normal cell might be regarded as highly dependent, and the malignant cell much less so, if not possibly in many ways autotrophic.

The cancer cell was a unique development of a specific cell type in an adaptive response to unfavourable conditions, and this was only one of the inherent difficulties which confronted any attempt at chemotherapy. Chemotherapy was expected to undo what could almost be regarded as a natural process.

Sex Hormones

In face of these difficulties it was perhaps not surprising that such developments in this field as had taken place in recent years had been accomplished without much thought of practical application, mostly as by-products of more important work. This was certainly so in the endocrine control of cancer of the prostate, which was of great importance as the first indication that the autonomy of the cancer cell was not necessarily complete and that it was in fact open to attack by chemotherapy. This development was very largely due to Huggins and his co-workers at the University of Chicago, and followed preliminary studies on normal and hyperplastic prostate glands of dogs. It was very greatly influenced, as Huggins had told him many times, by Huggins's studies at the Lister Institute in London on phosphatase.

In the special case of cancer of the prostate pronounced therapeutic effects were produced by the administration of a natural or synthetic oestrogen, stilboestrol being the synthetic substance most frequently used. In favourable circumstances improvement consisted of a decrease in size of the primary tumour, possibly regression of metastases in bone, improvement in the blood picture, gain in weight, and relief of pain. All these changes were accompanied by an increase in the sense of well-being, and not a few patients, from being confined to bed, became ambulatory and resumed an active life.

This therapy had now been employed for a sufficiently long time to make it clear that, while cancer of the prostate certainly could not be cured by this means, there was equally no doubt that the foci of the disease became quiescent and life was