Drug Treatment of Disease

DRUGS FOR MENOPAUSAL SYMPTOMS

BY

T. N. A. JEFFCOATE, M.D., F.R.C.S.Ed., F.R.C.O.G.*From the Department of Obstetrics and Gynaecology, the University of Liverpool*

The symptoms in question are ill-named "menopausal" and are better termed "climacteric." They result from the cessation of the endocrine function of the ovary. As ovarian activity wanes the first effect is amenorrhoea, sometimes preceded by a diminution in the amount and frequency of the flow. The first symptom of the climacteric is therefore the menopause, and any symptoms which precede amenorrhoea are never "menopausal." This, unfortunately, is often not recognized, and many women in their 40s are led to believe that their various minor discomforts and emotional disturbances are attributable to the "change of life," even five to ten years before their menstrual function ceases. Not only do general manifestations of the climacteric never appear before the menopause but their onset may be deferred for months or years after menstruation has stopped. This is because some degree of ovarian function, insufficient to cause a menstrual flow, may continue for a variable period of time.

The ill-defined physical and psychological disorders which are common in middle age, and for which the climacteric is wrongly blamed, can usually be traced to environmental causes. Children are often at an age when they can cause parental anxiety and expense. Household duties are heavy and the mother is no longer so physically fit to cope with them. The daily round is tedious, holidays and recreations are few. On the other hand, when the children mature and leave home the mother may be left without any self-satisfying interests and lives a bored and aimless existence. Again, many women live in fear of the menopause, having heard tell of its torments and possibly having already been advised that their complaints are a sign of its approach. Among other things they fear that the change of life is an end of life, especially of sexual life. They fear loss of looks and figure, and of their husband's affection. They fear cancer, insanity, and other serious illnesses which they think have some direct association with the menopause.

Such factors and fears can not only cause symptoms which may be mistaken for those of the climacteric but they make genuine manifestations worse. The climacteric is to be regarded as a physiological test of personality. Hot flushes, for example, are more troublesome when the patient is anxious, tense, or otherwise emotionally disturbed.

True climacteric symptoms are various, but the most common are hot flushes, night sweats, cold shivers, nervousness, insomnia, depression, irritability, fatigue, and palpitation. Irregular or heavy uterine bleeding, however, is *never* a manifestation of the menopause. Such a happening cannot be caused by a cessation of ovarian function and should never be treated symptomatically. It requires complete investigation, often including curettage and cervical biopsy, to find its cause before its treatment can be determined.

GENERAL TREATMENT

Although 75% of women experience climacteric symptoms of some degree, relatively few need to seek

medical advice. When they do the attendant's object should be to avoid administering drugs of any kind. Most patients require nothing more than to understand that the disturbances are physiological, temporary, and of less account if viewed philosophically, that sexual capacity need not be impaired, and that a full and active life is not at an end.

The increase in weight which is common in middle age, though not directly related to the climacteric, can always be controlled by a strict reduction of the calorific intake. Dieting to retain or restore a good figure is good for morale. The discipline is self-satisfying, and the result enables a woman to continue to dress smartly and to enjoy social engagements. She thus faces life with a confidence which helps her to discount climacteric upsets.

Many women are embarrassed not so much by their own sensation of hot flushes as by the idea that others notice the facial colour. Such patients can be assured that onlookers are not so observant as they suppose. In any case, the number and intensity of flushes can be reduced by the avoidance of hot baths, hot atmospheres, alcohol, coffee, and highly seasoned foods.

By explanation, advice, and reassurance, climacteric symptoms can be alleviated if not prevented completely. Moreover, most women prefer to have understanding than to take pills. There remains only a small minority (approximately 5%) of women, mostly those who by nature are emotional and over-anxious, for whom some form of medical treatment is necessary. The choice of drug then depends to some extent on the type of the symptoms present.

TREATMENT WITH DRUGS

Sedatives and Tranquillizers

These may be indicated for irritability and emotional upset. They may also help in quieting vasomotor instability and in reducing the number of hot flushes. It is doubtful whether there is now any better sedative for these purposes than phenobarbitone, $\frac{1}{2}$ gr. (32 mg.) once or twice daily. If this is combined with ascorbic acid and vitamin-B complex, its possible depressant effect is said to be reduced, though the evidence is equivocal. Of the many tranquillizers now available, promethazine, 10 to 25 mg. each night, or meprobamate, 400–800 mg. at night, are probably as good as any for climacteric symptoms.

Stimulants

When lethargy and nervous depression are dominant symptoms, sedatives are to be avoided. Instead, amphetamine or dextro-amphetamine sulphate, 5–10 mg. twice daily, may be helpful.

Sex Hormones

Climacteric symptoms are primarily caused by a persistent fall in the production of oestrogens by the ovary. This in turn releases the anterior pituitary from an inhibition so that it pours out large amounts of

gonadotrophin. It is commonly believed that it is this secondary reaction which is directly responsible for symptoms and that this explains why the administration of either oestrogen or androgen, both of which inhibit pituitary activity, gives relief.

Oestrogens

Disadvantages

Although the administration of oestrogen offers immediate and dramatic benefit to the sufferer from climacteric symptoms, it should be adopted only as a last resort because:

(i) It is a form of substitution therapy which, when withdrawn, results in the recurrence of symptoms which may be even more severe than before treatment was given.

(ii) Though this disadvantage can to some extent be overcome by careful regulation of the dose and by gradual withdrawal of the hormone, any patient who has experienced the relief which oestrogens bring is loath to abandon them. She tends therefore to continue with treatment over long periods of time and often haphazardly. This can cause tolerance to oestrogen, demands for higher dosage, and the persistence of symptoms.

(iii) Oestrogens cause hyperplasia of the endometrium and stimulate certain epithelial elements of the breast. They also induce uterine haemorrhage, sometimes during, and sometimes after, treatment. This haemorrhage can be heavy but, in any amount, always raises the question of a new and possibly unconnected development such as carcinoma of the uterus. The patient and attendant then have this worry, and it may even become necessary to carry out curettage and cervical biopsy before a cause for haemorrhage other than oestrogen therapy can be excluded.

In women previously subjected to hysterectomy this particular objection to oestrogens no longer applies. Even so, this type of hormone therapy should not be given if the indication for the hysterectomy was either pelvic endometriosis or genital cancer. The treatment may reawaken any remaining lesions of this type.

Principles of Treatment

In view of these considerations, the method of administering oestrogens is important. The object should be to give only enough to improve symptoms—to make them tolerable, not to eliminate them. The required dose varies from one woman to another and can be determined only by trial, the index being the number of hot flushes. The aim is to reduce these to an average of 4 in 24 hours. This can be achieved within a matter of a few days, and the dose is then maintained at that level for two weeks only. Thereafter it is gradually reduced during the course of the next two to three months. At the end of that time oestrogen therapy should be discontinued completely and should not be reinstated even though symptoms recur. Many authorities apply treatment intermittently, insisting on a break of seven days every three weeks, hoping thereby to avoid endometrial hyperplasia. Be this as it may, gradual weaning is essential to success. The idea is to substitute a gradual oestrogen deprivation for the sudden one which Nature, or the surgeon, may have inflicted.

At no time should the hormone be prescribed in such a form that its effects are beyond control.

Types of Oestrogen: Routes of Administration

(i) *Oral Preparations.*—The most commonly used oestrogens are the synthetic compounds stilboestrol (diethyl stilboestrol) and ethinyl oestradiol. Both are cheap and highly potent. A suitable test dose of stilboestrol is 0.1 mg. two or three times daily; it is rarely necessary to give more than a total of 0.5 mg. in 24 hours, and a daily dose of

1 mg. should never be exceeded. This last amount induces uterine bleeding in one-third of post-menopausal women. Ethinyl oestradiol is approximately 20 times more powerful than stilboestrol and not more than 0.05 mg. daily should be given. Indeed, it is best to give tablets of 0.01 mg. once, twice, or thrice daily. Synthetic oestrogens, and especially stilboestrol, sometimes cause nausea and vomiting. It may then become necessary to turn to a natural oestrogen such as oestrone and its esters. These are less potent, which is an advantage so far as climacteric symptoms are concerned, but they are expensive. The most active oral preparation is probably one of conjugated oestrogens (mostly oestrone sulphate) obtained from mare's urine. This is approximately half as potent as stilboestrol but the initial dose (as of any oestrous ester) should not exceed 1 mg. daily. This is best divided into two or three doses equally spaced.

One of the newer synthetic oestrogens, chlorotrianisene, is said to have a special tendency to be stored in subcutaneous fat. It is given with the object of building up a depot from which oestrogen is slowly absorbed in gradually decreasing amounts over the course of weeks or months. To this end the patient is given one capsule of 12 mg. twice daily for 30 days, it being essential to complete the full course irrespective of initial response. At the end of that time symptoms should be relieved and subsequent weaning is automatic. In fact flushes sometimes return in one or two weeks. Freedom from the need to keep the patient under observation, and to regulate the dose, makes chlorotrianisene at first appear very attractive. It is, however, expensive, and, despite claims to the contrary, is not free from the risk of inducing uterine haemorrhage. If the uterus does bleed, then, with the establishment of a depot, the situation becomes beyond control. If used at all, chlorotrianisene should be given only to women without a uterus.

In the search for an oestrogen which is relatively free from undesirable side-effects, methallenoestril has come into prominence. It is less likely than stilboestrol to cause nausea, vomiting, endometrial hyperplasia, and uterine bleeding, but is certainly not free from these disadvantages. A suitable initial dose is one tablet of 3 mg. once or twice daily. This preparation is expensive and should therefore be reserved for those women who react unfavourably to other oestrogens.

(ii) *Preparations for Intramuscular Injection.*—It is generally unnecessary and unwise to give oestrogens by injection in the treatment of climacteric symptoms. The psychological effect is such that the patient tends to return every week for another injection and it is difficult to break this habit. An adequate oestrogen intake can nearly always be established by the oral route.

(iii) *Implants.*—The subcutaneous or subfascial implantation of tablets of 50 to 100 mg. oestradiol is useful in selected cases in which relatively young women have to be subjected to total hysterectomy with removal of both ovaries. It provides a depot from which absorption takes place in a gradually decreasing amount over a period of 2 to 6 months. Progressive and slow deprivation of oestrogen is assured, and the symptoms of the surgical climacteric are avoided or mollified. Such treatment should never be applied to a woman with a uterus. The amount of stimulation of the endometrium is unpredictable and, if bleeding occurs, the pellet cannot usually be recovered.

Androgens

Because androgens inhibit the gonadotrophic function of the anterior pituitary they are sometimes used in the treatment of climacteric symptoms. Their main advantage is that they do not stimulate the female secondary sex organs and they cannot cause uterine bleeding. They also give a sense of well-being, eliminate depression, and increase libido. On the other hand, all the preparations are expensive, and in doses sufficient to relieve symptoms they are likely to cause hirsuties, acne,

voice changes, and other signs of virilism. The place for androgen therapy of climacteric symptoms is therefore very small, restricted possibly to those cases in which even small doses of oestrogen cause uterine haemorrhage, or in which a previous history of endometriosis or genital cancer contraindicates oestrogen therapy.

The administration of androgens follows the same principles as that of oestrogen. Having secured the patient some relief, the hormone is given in gradually decreasing amounts over the course of 2 months. Methyl testosterone is given sublingually, the initial dose not exceeding 5 mg. twice daily. Testosterone propionate is given intramuscularly, one injection of 25 mg. exerting its effect for approximately three days. Testosterone phenylpropionate or oenanthate is also given intramuscularly, one injection of approximately 50 mg. being effective for three weeks.

Newer synthetic androgenic preparations such as methyl androstenediol and methyl androstane are given sublingually in the same dosage as methyl testosterone. They are alleged to be less virilizing but are certainly not free from this effect.

Mixed Androgen and Oestrogen Preparations

There are several proprietary tablets containing both ethinyl oestradiol (in amounts varying from 0.002 to 0.01 mg.) and methyl testosterone (in amounts varying from 2.5 to 4 mg.). These are administered orally or sublingually, the initial dose being 3 to 6 tablets daily followed by a gradual reduction. Also available are preparations a single injection of which creates an intramuscular depot of 65 mg. testosterone oenanthate and 4 mg. oestradiol valerianate. This is said to produce an effect which lasts for two to four weeks.

In favour of such hormone combinations it is argued that the oestrogen prevents virilism and the androgen counteracts oestrogenic stimulation of the breasts and uterus. Both depress the overactivity of the anterior pituitary, while androgen gives a sensation of wellbeing and raises morale. Unfortunately the claims that one hormone nullifies the ill effects of the other have an insecure foundation. Preparations of this kind can certainly cause uterine bleeding on the one hand, and hirsuties on the other. They are as unsatisfactory as they are expensive. If both hormones are ever given, it is better for the medical attendant to prescribe each separately in a dose appropriate to the case.

Mixtures of Hormones and Sedatives

Certain proprietary oral preparations contain either stilboestrol or ethinyl oestradiol in combination with phenobarbitone. These, again, are to be deprecated. If both these drugs are indicated, their respective doses need to be determined and controlled independently.

Empirical Remedies

All manner of empirical remedies for climacteric symptoms have been used from time to time. Thyroid 1 gr. (65 mg.) each night has had intermittent popularity and may serve a useful purpose in certain cases. Calcium salts in doses of 30 to 60 gr. (1.9 to 3.8 g.) have their advocates; they are harmless even if their value is doubtful. More recently it was claimed that alpha-tocopherol, or dextro-alpha-tocopheryl acid succinate,

will reduce the number of flushes while having no ill effects. It has to be given in doses of 200 to 1,000 mg. daily and the results are equivocal.

CONCLUSION

The climacteric is a physiological occurrence, and, even though it calls for adaptation of the endocrine and vasomotor systems to a new situation, it does so no more than does puberty. The symptoms are more trying only because they are usually faced without the optimism and faith in the future which characterizes youth. They can, therefore, nearly always be controlled by explanation, reassurance, and correction of the physical or emotional background which is making them worse. Except in a minority of carefully selected cases, there is little more justification for giving drugs (including hormones) for the flushes and tantrums of the climacteric than there is for the blushes and waywardness of adolescence.

RADIOACTIVE MATERIALS AND THE SKELETON

[FROM A SPECIAL CORRESPONDENT]

There was a busy and successful whole-day meeting of the Bone and Tooth Society at the Royal College of Surgeons on January 13, attended by many visitors. All but the first two of the ten communications were concerned with one or other aspect of the toxicity of radioactive materials which are selectively concentrated in calcified tissue.

Microtechniques for Studying Bone

Dr. P. LACROIX (Louvain, Belgium) gave a lucid and beautifully illustrated account of his work on the micro-anatomy and histochemistry of the process of calcification in the bones of puppies. The standard methods of histology and histochemistry demand the prior decalcification of tissue before sections for microscopy can be cut, but, so far as the study of calcification is concerned, this is rather like throwing the baby out with the bath-water. Nowadays, in addition, two relatively new techniques—microradiography and autoradiography with radioactive tracers like ⁴⁵Ca—have proved indispensable. In both techniques sections of bone, without decalcification, are cut by saw and then ground down to a uniform thickness. An x-ray picture of such a section, taken with soft x rays, and on a fine-grain emulsion so that the picture may be magnified, gives the microscopic distribution of calcium in the section, the more heavily calcified areas showing up whiter than the less heavily calcified areas which allow more x rays to reach the emulsion. A radioactive tracer for calcium, however, is taken up only in those areas where calcium is being actively deposited. An autoradiograph therefore picks out the sites of active calcification, and, by varying the time interval between the administration of the isotope and the taking of the specimen, an idea may be obtained of the successive changes in the sites of active calcification. One and the same section can provide an autoradiograph, a microradiograph, and, after decalcification, a soft-tissue section which can be stained to show the whereabouts of enzymes and other histochemically demonstrable substances. The three kinds of picture can be superimposed upon each other and the histochemical stages preceding active calcification precisely defined.

Many of the new observations are not yet fully understood, and, in considering the growth in width of long bones like the tibia, there was some discussion of Dr.