GENERAL PRACTICE

The Treatment of the Menopause

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THE menopause and its management presents an ever-recurring subject for discussion. In spite of the extensive literature on the subject, opinion is still divided as to the indications for and what constitutes the most satisfactory approach to treatment. This is understandable and is due as much to the protean nature of the disturbance as it is to individual experience in the management of patients. The problem may best be examined by a consideration of the physiopathology of the menopause and its accompanying symptoms. This should provide the clue for effective management.

The menopause is the period in a woman's life when decline in balanced ovarian function is accompanied by cessation of the menstrual flow. It is a rung in the ladder in a woman's progression through life. It is the climacteric. She steps from the stage of reproductivity into the period of "middle life" free from the responsibilities, stresses, the hazards and trials associated with childbirth. Actually, declining ovarian function is a safeguard, but the loss of hormonal support may bring on a train of symptoms. These symptoms may result from autonomic nervous system imbalance (hot flashes, sweats, palpitations, spasms, formication), from psychogenic disturbances (insomnia, crying spells, depression, apprehension, nervousness), and from metabolic disorders (atrophic vulvovaginitis, urinary bladder dysfunction, osteoporosis, myalgias, and catabolic phenomena).[1a, 1b] The symptoms described may vary from the very mild to the intolerable, and management will then involve simple reassurance or the use of preparations that will provide relief with minimum hazards.

While it is true that the menopause is a physiological process and represents a period of adjustment to a new hormonal *milieu intérieur*, withholding measures that may make the transition smoother or prevent disabling pathological processes, be they psychological, neurological, or metabolic, when they are clearly amenable to treatment, is unrealistic. The fact is that many women may be restored from a chronic state of semi-invalidism to mental and physical health with the judicious use of therapy with steroid hormones.

The key word in the above statement is "judicious", and for this one must have a clear concept of what one desires to do and what means are necessary to accomplish this. Obviously, there can be no universally effective treatment. Individualization is essential. The tranquillizers, antidepressants and general supportive measures have their place, but the mainstay of treatment involves the use of hormones.

The hormones indicated are the estrogens or combinations of androgen and estrogen. These may be administered orally or parenterally. That the ideal preparation is not available is reflected in the multiplicity of preparations which are available and used. Kupperman, Wetchler and Blatt,[2] in a recent well-controlled study, have reviewed preparations currently in use, and assessed their relative merits. They point significantly to the fact that when androgen was combined with estrogen, physical vigour and *joie de vivre* became noticeable. Dull personalities seemed to become a bit less so, thus confirming the results previously reported by Greenblatt *et al.*[3] and others.

Orally administered hormone preparations are quite effective, some being better tolerated than others. They must, as a rule, be given daily and preferably for three weeks in each month. The use of conjugated equine estrogens (Premarin) has proved of value in most instances. However, many patients take these oral preparations in a haphazard fashion, with inadequate results, and both physician and the hormonal agent are blamed for the failure to alleviate the distressing symptoms. Some of these patients fare better when under closer scrutiny of the physician.

Parenteral therapy in some form is an answer to the problem, but the frequency of attendance for injections makes this burdensome to the patient and physician alike. In this communication our experience with a depot-type estrogen and androgen mixture for parenteral administration is reported. We believe that this preparation provides a distinct contribution to replacement therapy in the treatment of the menopausal patient. It is indicated in those patients who require more supervision and a more intimate patient-physician relationship.

Gleason and Parker[4] recently described an androgen derivative, testosterone enanthate benzilic acid hydrazone, with a depot type of action. This was combined with a depot-type estrogen derivative, estradiol dienanthate. The preliminary clinical trials were for orientation purposes and designed to establish the most suitable relative concentration of these compounds and the dose required. When these two depot-type compounds were used in combination, it was noted that while

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TABLE I.

	Number	*Age range*	*Interval between injections*	*Duration of treatment*	*Results: Good*	*Unsatisfactory*	*Withdrawal bleeding*	*Hirsutism; voice change*
Spontaneous menopause.....	116	29 to 64	3 wks. to 5 mos.	6 wks. to 20 mos.	112	4	5	0
Menopause after hysterectomy.....	47	26 to 60	3 to 8 wks.	6 wks. to 20 mos.	41	6	—	0
Osteoporosis (6 after castration; 3 after spontaneous menopause)....	9	30 to 61	3 wks.	6 mos. to 20 mos.	9	0	0	0
Total.....	172				162	10	5	0

they were quite effective, it took four to seven days for optimal effects to be obtained, and this suggested the desirability of including in the mixture a more rapidly absorbed estrogen. The final product adopted for extensive clinical trial had the following formula:* testosterone enanthate benzilic acid hydrazone, 150 mg.; estradiol dienanthate, 7.5 mg.; estradiol benzoate, 1.0 mg.; corn oil, ad 1.0 c.c.

Patients selected for treatment included those with spontaneous menopause and those who had undergone hysterectomy previously and who had moderate to severe symptoms. One hundred and eighty patients were treated. Of these, eight did not present themselves for follow-up, leaving 172 for evaluation. The patients were initially given an intramuscular injection of 1 ml. Climacteron, and they were asked to return every three to four weeks for assessment and treatment. After two or three consultations they were asked to present themselves only when symptoms recurred. For some this interval was as long as five months, but for most the interval was six to eight weeks. The great majority of patients reported complete relief of symptoms; and a substantial number volunteered the information that they experienced a sense of well-being and increased libido. There were some failures, and these occurred far more frequently among the women who had had a hysterectomy. It was felt that in these the psychosomatic disturbance overshadowed the hormonal deficit, and antidepressants or tranquillizers were necessary adjuncts in management.

Vaginal cytology before and after treatment was studied in 49 patients. Maturation of the vaginal mucosa occurred in all instances as shown by a change in vaginal cytology from a hypoestrogenic or castrate type of smear to one showing a full-blown estrogenic effect. The effect on the vaginal mucosa persisted for four to eight weeks after a single injection. Bleeding occurred in five patients and was clearly related to the hormone therapy. Breast tenderness was noted in four patients. In no case were virilizing symptoms noted even after 20 months of treatment. Liver function and hematological studies were carried out on eight patients after prolonged therapy. There was no evidence of disturbance in hepatic or hematopoietic functions. The essential data are tabulated in Table I.

*Climacteron—Charles E. Frosst & Co., Montreal.

DISCUSSION

Treatment for the relief of menopausal symptoms is clearly desirable when such symptoms become burdensome and disabling. While many preparations are available for both parenteral and oral administration, and are quite effective, they do have shortcomings. In the uncooperative patient, haphazard and irregular administration of oral preparations invites inadequate control. Most of the parenteral preparations presently available are of relatively short duration of activity, and the frequency of administration required can be burdensome to patient and physician alike. Pellet implantation may overcome this to a degree, but the technique of implantation is not always acceptable to the patient and the procedure is not customarily employed by general practitioners. Climacteron in our hands has proved very useful. It is simple to administer and effective for four to eight weeks after a single dose. Untoward effects were minimal, and the occurence of bleeding is a complication that may be expected whenever estrogens are employed. The incidence of bleeding is greatly lessened when an androgen is given in association with an estrogen. Although the relationship of administered hormones and uterine cancer has never been established, it is well to investigate every patient in whom postmenopausal bleeding occurs, whether spontaneously or after hormonal therapy.

SUMMARY

The treatment of the menopause is discussed. One hundred and eighty menopausal patients, of whom 172 were available for evaluation, were treated by intramuscular injection with a new depot-type estrogen-androgen combination. A single intramuscular injection provided relief of symptoms for four to eight weeks in most patients and for as long as five months in some. There were no untoward effects.

REFERENCES

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