CLIMACTERIC—MALE AND FEMALE

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In women the climacteric at one time referred to seven year cycles throughout life, puberal climacteric, menopausal climacteric, and at the age of 63 the grand climacteric. Nowadays when we mention the climacteric we mean the period of a woman's life in which the function of child bearing ceases; the menopause, which is an incident in this change, is the result of hormonal readjustments and genital atrophy which result. The whole process is normal and physiological and is not a disease.

In general the menopause is considered a mark of the climacteric, although climacteric symptoms frequently precede the cessation of menstruation by months and sometimes by years, and although it is rare, typical symptoms may make their appearance as late as ten years after the menstrual flow disappears. Rarely the climacteric occurs before the age of 20, and it may occur before the menarche, as in a case which I recently reported[1] in which typical hormonal changes, headaches and hot flashes were present at the age of 16 years, before the menses appeared. On the other hand menstrual periods occasionally remain regular until the age of 65. The average age for cessation of menstrual periods is 47 years, and race or the age of onset of menstruation have not been shown to have a distinct bearing on the time of the menopause.

The Physiology of the Female Climacteric

The primary change is probably in the ovary, which gradually fails to respond to stimulation from the pituitary. Failure to ovulate regularly appears to be an early part of this change, and as a consequence the corpus luteum does not form, and progesterone is not produced. The absence of progesterone may cause abnormal bleeding but produces no other symptoms. In this anovulatory state, sufficient response on the part of the follicles may remain, to bring about in turn some alternate regeneration and regression in the endometrium, with regular cycles of uterine bleeding. Eventually follicular growth and production of follicular hormone falls to such a low level that the endometrium undergoes too little growth and regression to respond with bleeding, and the periods cease. The uterus becomes smaller. The vaginal mucosa loses its cornified epithelium, and smears from the vagina, instead of showing flat, cornified cells, show smaller, rounded cells with large nuclei from the deeper layers of the vagina together with white blood cells. There is atrophy of the cervical and vulvar glands and involution of the duct system of the

breast. The sodium, nitrogen, and water metabolism, which are affected so much by androgens, are disturbed very little by estrogens. During this time the anterior lobe of the pituitary tends to enlarge, basophile elements in it increase,[2] and excessive quantities of gonadotrophic hormone appear in the urine. The titre of urinary gonadotrophins commonly rises from a normal daily average of about 25 to 50 mouse units to 200 or even 500.

The mechanism of the symptoms so commonly associated with the menopause is not clear. Albright[3] suggested that they might be caused by the heightened levels of gonadotrophins, since these substances increase as symptoms increase and decrease with estrogen therapy. However, serious objections to this explanation can be raised. For example, high titres of gonadotrophins may be present in the urine of post menopausal women who have no symptoms. It is interesting in this connection that high titres of urinary gonadotrophins can be demonstrated in postmenopausal women who have never had any climacteric symptoms. Also, menopausal symptoms are likely to be absent in the presence of pituitary tumors in patients with high gonadotrophin excretion.

Hamblen[4] has suggested that menopausal symptoms are normally controlled by an increasing adrenal production of androgens. In regard to this theory it is interesting to consider the situation which exists in women with Addison's disease and menopause. Under these circumstances climacteric symptoms may be present and the only source of androgens in the women, namely the adrenal glands, is virtually removed. According to the theory it should follow that climacteric symptoms would be more than usually severe or more difficult than usual to control. Such has not been the case, however, in our patients who have Addison's disease and menopausal hot flashes. In them small doses of estrogens have been effective. Thus if any of the normal controlling mechanism of the menopause is present in the adrenal cortex the fact is not indicated by destruction of the gland in Addison's disease. Also, postmenopausal women with myxedema may have no climacteric symptoms in spite of the fact that urinary 17-ketosteroids are very low.

Regarding the cause of climacteric symptoms, one can only say that they are intimately connected with estrogen withdrawal in an individual previously accustomed to its presence in moderate amounts and that the exact mechanism of production of symptoms is not understood.

Clinical Manifestations

Hawkinson[5] believes that distressing symptoms occur in 75 per cent of women during the climacteric. In an analysis of 1000 cases he lists symptoms in the following frequency (table 1).

Table 1

Frequency of Climacteric Symptoms

% frequency	
95+	Nervousness Menstrual disturbances Flushes or chills
85+	Excitability Fatigability—lassitude
70+	Depression Irritability Insomnia Tachycardia, etc.
60+	Vertigo Poor memory Headaches
40+	Frigidity Numbness Occipito vertical aching

(Adapted from Hawkinson)

In 1933, the subcommittee of the Medical Women's Federation in Great Britain studied women who were not under medical care and concluded from 1197 patients that 89.7 per cent were able to carry on their usual occupations; 15.8 per cent of these had no symptoms, and only 10.3 per cent of the total were incapacitated by the climacteric.[6]

Apart from abnormal bleeding the manifestations of the climacteric which require treatment are almost entirely symptomatic. It is important, therefore, that a critical analysis be made of all the features present. Hereditary traits, tendency to emotional instability, coexisting disease, poor nutrition, factors which may cause excess nervous strain, such as overwork or domestic problems, must all be carefully evaluated. It should be borne in mind that hot flashes of mild degree may occur in women with unstable vasomotor systems who do not have ovarian failure, and moderately severe flushing may occur in the presence of arterial hypertension. Under such circumstances this symptom is likely not to be amenable to estrogen therapy.

Weight gain, which is frequently associated with the menopause, shows a tendency to special distribution of fat about the pelvic girdle

and over the trochanters. Pads of fat may often be seen anterior to the lateral malleoli. In spite of the implication that such obesity is due directly to ovarian deficiency, this has never been proved, and it appears likely that most of the weight gain is due to maintenance of a good appetite in the presence of decreasing physical activity. It can be managed properly only by diet.

Arterial Hypertension

In states in which nervous tension is heightened the blood pressure is inclined to vary excessively. Such a relationship may exist in people with unstable nervous systems and climacteric symptoms. The recent studies of Taylor[7] emphasize the fact that true arterial hypertension is not related to ovarian failure. He made a careful study of 200 women three or more years after the menopause. One hundred and seventy-nine of these patients had been surgically castrated. Hypertension existed in 13 per cent of his group, almost exactly the same incidence as shown in the general population as a whole of women between 20 and 60 years of age, according to the statistics of the Metropolitan Life Insurance Company.

Menopausal arthralgia is a term applied to mild joint pains unaccompanied by objective evidence of joint disease. When it occurs it is usually found in the small joints, shoulders, elbows, and knees at the climacteric. Such pains usually disappear promptly with estrogen therapy.

Menopausal osteoporosis may reach moderately severe proportions. It affects the spine chiefly. It is associated sometimes with pain but usually not with vertebral compression. Albright[3] recommends estrogens for this condition and reports improvement in the degree of ossification of the spine following its use. We use in addition calcium lactate, 3 grams twice daily, and 50,000 units of vitamin D per day.

Mental Depression

Mild symptoms of depression are very frequently associated with climacteric. Such symptoms are usually benefited promptly by estrogen. In my own experience I have never seen true involutional melancholia benefited materially by estrogen therapy. Improvement which may occasionally be seen is difficult to evaluate because spontaneous improvement occurs in some patients.

Diagnosis

Diagnosis of the climacteric is seldom in doubt but at times peculiar problems present themselves. Because some symptoms referable to the

climacteric occur in most women after the age of 45 it is important not to assume that concurrent disease is absent. At times fatigue and hypometabolism may raise the problem of hypothyroidism, while in others in whom excitability and tachycardia are more outspoken care should be taken to exclude hyperthyroidism.

Amenorrhea may lead to a suspicion of pregnancy. If a Friedman or Aschheim-Zondek test is used it should be borne in mind that the high excretion of gonadotrophins at the climacteric causes false positive results to occur more frequently than in earlier life. Especially in younger patients when early climacteric is suspected, more complete evaluation of the problem may be indicated. In these, vaginal smear studies and endometrial biopsies make excellent means of assay for follicular function, and when low ovarian activity is present, the degree of pituitary activity can be determined by doing an assay for gonadotrophins. We employ for this the immature mouse assay described by Albright[3] and expect over 53 and usually 105 mouse units to be excreted in twenty-four hours in cases of primary ovarian failure.

Entirely normal findings in such assays exclude ovarian deficiency. Such tests must be interpreted, however, remembering that in most instances some estrogen remains in the blood after menopausal symptoms appear.[8] Therefore, typical castrate type of smears are seldom seen, and moderately severe symptoms may exist in the presence of only slight evidence of follicular failure as judged by the smear test. In addition, smears of a deficiency type and high levels of urinary gonadotrophins continue into old age after climacteric symptoms have disappeared. However, if active estrogen therapy is given, and vaginal smears are maintained in a normal state for several weeks, any remaining symptoms can usually be rightly assumed not to result from ovarian deficiency.

In diagnosis it is essential not to overlook the possibility of malignant disease as a cause of irregular bleeding.

Treatment in Uncomplicated Cases

Symptoms may begin insidiously as increasing premenstrual tension, headache, or mastalgia. If a tendency to premenstrual edema is present, careful restriction of sodium and the use of 3 Gm. of ammonium chloride or 6 to 10 Gm. of potassium nitrate in enteric coated pills per day for ten days before the menses may be helpful. In cases in which edema is present and nervous tension is not great, small doses of benzidrine can be tried. In others mild sedation and small doses of estrogen over a similar period may give further symptomatic relief.

Many patients need no treatment.

In all uncomplicated cases confident reassurance is important, and the patient should understand the harmless nature of the condition and the lack of influence it is likely to have upon her general health and sexual life.

Attention should be given to proper rest, adequate exercise, recreation, and correct diet. Mild sedation including phenobarbital, tincture of hyoscyamus, or bromides singly or in combination is helpful.

The choice of estrogen therapy presents a problem, particularly because there are so many forms from which to choose. Stilbestrol is valuable in most cases because it is potent, orally active, and cheap. The required dose is usually about 1.0 mg. per day, but may vary from 0.25 mg. to 3.0 mg. Unfortunately it produces nausea in about 15 per cent of cases. If it does, methyl stilbestrol may be tried in approximately ten times this dose. A newer drug not likely to produce untoward symptoms is one of the hexane derivatives, which may be given in doses of 10 to 30 mg. per day. Stilbestrol dipalmitate in oil is a soap-like material which can be liquified by heat and injected intramuscularly. A single injection containing 15 or 20 mg. of stilbestrol may control climacteric symptoms for three months or more at a time. It has the disadvantage that its effects cannot be discontinued at once in the event of menorrhagia. For this reason it is admirably suited to the treatment of patients who have undergone hysterectomy. When natural estrogens are preferred or when stilbestrol disagrees, ethinyl estradiol, strongest of all estrogens, may be used. It has the advantages of potency and oral effectiveness, but may also produce nausea. Other estrogens for oral use are sodium estone sulphate (premarin), estriol glucuronide (emmenin), and estriol (theelol). They are all well borne, but weaker and more expensive than the synthetic preparations. Of the injectable natural estrogens, estradiol benzoate or propionate is the most efficient. There is a tendency to give such medicaments in inadequate doses or too infrequently, in which case the effect is unphysiologic. Estradiol benzoate in doses of 0.33 mg. (2000 rat units) three times weekly, is adequate in the majority of cases. In our hands it has shown less tendency to produce menorrhagia than has stilbestrol. Estrone (theelin) is much weaker and therefore larger doses by weight are necessary, 2.0 mg. (20,000 international units) three times weekly is sufficient in most patients and half this dose is enough in many. Few signs or symptoms of overdosage directly connected with estrogen are seen. Occasionally fullness or soreness of the breasts, a sense of fullness and discomfort in the pelvis, or an excessive vaginal discharge necessitate a lowering of the dose. Apart from these symptoms, injectable natural estrogens produce no untoward side effects, though rarely there may be seen a local allergic

type of response to the vehicle injected. There is such a variety of useful orally active estrogens available that when cost and convenience to the patient are factors to be considered the more expensive injectable estrogens are seldom indicated in the treatment of the climacteric.

A combination of small doses of androgen given with estrogen may reduce the tendency to menorrhagia, and when this tendency is not pronounced such a combination may make continued treatment possible. On the whole, androgens are much less efficient than estrogens in the control of climacteric symptoms.

Special Considerations

Pruritus vulvae is likely to be present when neurosis is a relatively large factor. If the tissues involved are atrophic, estrogens may be helpful in the treatment and may be used both as general therapy orally or by injection, and as local therapy in ointment or suppositories. Rest and sedation are important. Local alcohol injections may have to be used.

In *senile vaginitis* suppositories of estrone or stilbestrol are claimed to be helpful by increasing the activity and health of the local tissues. Local hygiene and simple measures of cleanliness are important. Local dermophytosis must be treated if present. Diabetes mellitus should be excluded by careful evaluation of urinalysis and of blood sugar levels, not only fasting but two and one-half to three hours after eating. If it is present meticulous control is indicated. In true kraurosis little good has been reported from estrogen therapy, and it may be dangerous since carcinoma sometimes appears in such cases and vulvectomy appears to be the only cure when the condition is severe.

Nymphomania may become a matter of serious concern at the climacteric. I have observed four patients with a moderate degree of this who were markedly improved on estrogen therapy. One eventually became seriously psychotic in spite of treatment.

Frigidity, especially when present to some degree previously, may be accentuated in the presence of severe ovarian failure. Estrogen therapy is of very little value in such a condition. Androgens in small doses may be helpful if the patient was normal previously but are not likely to be helpful otherwise. Ten to 20 milligrams per day of methyl testosterone orally daily may be tried. If it is used evidence of masculinization must be watched for.

Menorrhagia

Menorrhagia existing in patients at the age of 40 or beyond should be suspected as organic in origin. It is usually not due to malignant disease, though this possibility must always be kept in mind. Fluhmann[9] reports 53 patients of this type, none of whom had carcinoma. Hamblen[10]

mentions a study of 177 women between 40 and 55 years of age with polymenorrhea, menorrhagia, or metrorrhagia, 173 of whom had endometria showing only estrogen effects and 4 had adenocarcinoma. In such cases it is our practice when no evidence of local disease is found to give one course of injections of estrogen, usually estradiol-benzoate 2000 to 4000 rat units three times weekly, together with 3 or 4 injections of 10 mg. each of progesterone with each of the last few injections of estrogen, ending the course a few days before the menstrual period is expected. If the menorrhagia is not controlled, a diagnostic curettement is performed, and since endocrine therapy is not likely to produce a good result on further trial, radium is usually applied.

When uterine bleeding returns after the menopause has occurred malignancy should be considered present until it is proved not to be. Fluhmann[11] found carcinoma present in 75.6 per cent of 90 such cases, TeLinde[12] in 60 per cent of 179, and Geist and Matus[13] in 57.5 per cent of 182. Obviously a prompt diagnosis and adequate surgical measures are imperative under such conditions. In the immediate control of menorrhagia near the menopause androgens may be efficient. Testosterone propionate 25 mg. to 50 mg. per day for 4 or 5 doses may be used. Two hundred and fifty milligrams per month is less than the amount necessary to cause masculinization. Methyl testosterone 10 mg. orally daily for ten days before each menstrual period may be tried. In some cases 20 mg. per day may cause deepening of the voice and hirsutism.

Contraindications to the use of estrogens are few. These substances are, however, potentially carcinogenic, and although there is no proof that they have caused carcinoma in the human, certainly they should never be used in cases in which carcinoma is suspected, where it is known to be present, or where it has been present either in the genital tract or the breast.

Male Climacteric

The term male climacteric is a misnomer in that it implies a physiologic loss of power of production of sperm and internal secretion of the testes which, according to the term, should be expected to occur at a fairly regular time of life in all men. Such a condition has not been shown to exist. There are, however, some cases in which testicular failure appears in men past middle age and without evident cause—a functional hypogonadism. It is difficult to diagnose because there are no well established diagnostic criteria. In most instances where the diagnosis appears in the literature subjective symptoms have been depended upon.

Physiology

Attempts to explain the condition are based on the state which exists in extreme testicular failure.

After castration in adult life few anatomical changes are apparent. Beard and body hair are changed little if at all, the voice and genitalia remain grossly the same, sexual potence tends to diminish, though it may not be lost, the prostate and seminal vesicles shrink markedly. A mild degree of nervous instability and mild mental depression may occur, endurance is usually diminished, and in some cases hot flashes appear.

Urinary androgens as measured by the capon comb growth test fall, urinary 17-ketosteroids fall as a rule to about half their normal level, but not infrequently remain within normal range, and urinary gonadotrophins rise. Testosterone injections 25 mg. intramuscularly three times a week promptly remove such symptoms. In castrate men such treatment brings about a return of sexual potence, a return of ejaculate, growth of the prostate, disappearance of nervous and vasomotor symptoms and an increase in energy together with a growth of the skeletal muscles. The latter is associated with increased retention in the body of certain electrolytes, including sodium and potassium, water is retained, nitrogen is stored, and the basal metabolic rate rises.

Diagnosis

When symptoms similar to these seen after castration appear spontaneously in a man of 50 or above, and when careful examination fails to reveal the cause, testicular failure may be considered a possible explanation. Too frequently impotence is the only presenting symptom, and judging from experience, impotence is seldom due to testicular failure.

In many patients a final analysis makes it clear that the symptoms suspected of being due to male climacteric can be explained more rationally on the basis of the increasing pressure of social and business responsibilities and the concurrent increase in nervous fatigue in an aging man.

Angina pectoris has been considered an evidence of male climacteric.[14] Symptomatic improvement has been reported following the use of testosterone propionate in cases of angina pectoris and patients with peripheral occlusive vascular disease. I have seen some patients with angina pectoris who appear to obtain some symptomatic benefit from testosterone. On the whole, the results are not very impressive. Considerable symptomatic improvement may follow testosterone therapy in patients who have urinary retention, especially in those patients who have no severe mechanical obstruction. It is unlikely that testosterone ever causes any prostatic shrinkage, though it may increase the strength of the bladder and other musculature and in this way aid in bladder emptying.

In treatment of any case with testosterone one must remember that marked depression of sperm production may be brought about.

My opinion in the matter of male climacteric can be best expressed by a few facts taken from the investigation of 60 patients whom I suspected of having the condition as judged purely on the basis of history and physical examination. The chief symptoms were nervousness, emotional instability, mental depression, fatigue, decreased libido and potency, and in about one-quarter of the group, mild hot flashes.

Seven assays were done for androgens by the capon method in 6 cases. The results in brief were: in 2 of the 6, androgen excretion was subnormal; in 2, borderline; and in 2 normal.

Assays for urinary 17-ketosteroids as an index of testicular function were done 38 times in 33 cases—only 6 were within normal range and only 1 reached average normal. The mean was 5.0 mg. per twenty-four hours. The normal average lies between 7 and 14 mg. (table 2).

Table 2

Male Climacteric ?

17-ketosteroids—38 assays—33 cases		
mg./24 hr.	cases	
1—2	2	
2.1—3	1	
3.1—4	7	Improved cases assayed measured 3.1, 1.1, 4.0, 8.0.
4.1—5	9	
5.1—6	4	
6.1—7	9	
7.1—8	1	
8	1	
10.9	1	

The question mark refers to the fact that these were individuals in whom this diagnosis was originally suspected on clinical grounds alone.

Gonadotrophin assays were done on twenty-four-hour specimens of urine. Thirty-two assays by the mouse method showed 17 to be above normal, nine assays done by the rat uterine weight method showed 6 to be above normal (table 3).

These objective studies appear in the majority of the cases to bear out a pattern quite in keeping with the idea that some degree of testicular failure together with a tendency to pituitary hyperfunction exists.

In this group of 60, so far as we know at present, only 10 showed what we choose to call good clinical results from treatment with testosterone propionate. These results ranged from moderate to excellent.

Due to the symptomatic nature of the improvement its degree cannot be more accurately evaluated.

Eighty-four per cent of this group remained with little or no improvement after several weeks of therapy known to improve the symptoms which follow castration. For this reason it appears that the method of diagnosis requires improvement, and further critical evaluation of the subject is necessary before a dependable conclusion can be reached as to the position in which the term, male climacteric, should be placed in clinical medicine.

Table 3
Male Climacteric?
Gonadotrophin Assays

	Mouse Test	Rat Test	10 Improved Cases
High	17	6	6
Normal	15	3	2
Total	32	9	

10 improved cases refers to all of the cases showing distinct symptomatic improvement. Six of the improved group were known to have a high titre of urinary gonadotrophins.

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