Nov. 1979

OURNAL OF THE
merican
eriatrics
ociety

OLUME XXVII NOVEMBER 1979 NUMBER 11
 Printed in U.S.A.

Update on the Male and Female Climacteric*

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ABSTRACT: The gonadal steroids—estrogens and androgens—appear to have a mood-elevating, psychotonic effect. The improved sense of well-being and increased vigor probably is engendered by restoration of somatic efficiency and psychic equilibrium. 1. The male climacteric, as observed in a limited number of men, is associated with a low level of serum testosterone. The levels of follicle-stimulating hormone and luteinizing hormone are not elevated because estrogen concentration continues unaltered well into old age. Androgen replacement therapy often lessens fatigue, depression and headaches, and improves libidinous drives. 2. In the aging female, many climacteric symptoms other than those due to vasomotor instability were heretofore considered merely coincidental. Recent studies suggest that the metabolism of cerebral hormones is markedly influenced by endogenous and exogenous gonadal steroids. Thus, postmenopausal depression, headaches, and nervousness may be hormone-dependent symptoms. 3. The incidence of endometrial cancer is no greater and is probably less in estrogen-treated women than in women not treated with estrogen, if regular cyclic courses of an oral progestogen are added to the regimen.

An update on the male and female climacteric in order at this time. Recent developments have yielded considerable new information that enhances our understanding and treatment of the aging male and female.

Scriptural history established a bias against the existence of a climacteric in the male while suggesting its existence in the female. The Bible mentions, "It ceased to be with Sarah after the manner of women," and reveals certain changes in personality traits in this gracious matriarch. She became so cantankerous and irritable as to order her bondswoman, Hagar, from her domicile. But as to

* *The Edward Henderson Award Lecture*, presented at the h Annual Meeting of the American Geriatrics Society, May- wer Hotel, Washington, DC, April 23-24, 1979.

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the male, the Bible relates that when Moses died at 120 years of age, "His eye was not dull nor his natural forces abated." This reference to "natural forces" merely substantiates what many students of sexual behavior now believe, i.e., leadership enhances and preserves sexual prowess (1). Although attitudes in general towards the existence of a male climacteric have not changed, new studies on the subject permit greater flexibility.

THE MALE CLIMACTERIC

Clinicians deal with women manifesting a variety of menopausal complaints, but seem wholly oblivious to the fact that a much more severe crisis may be occurring in the husbands. Many a middle-aged man finds his psychologic function decreasing and his body demanding more rest. He entertains doubts about his ability to achieve his goals and about the security of his position; he begins to experience waning sexual prowess, headaches, depression, and asocial behavior. According to Jaszmann, this critical period of life is the male climacteric (2). In the average man, testosterone levels decline after the age of 50, although sometimes the values may be as high as those in young men (Fig. 1) (3). Vermeulen et al (4) found that the concentration of plasma testosterone achieved at the end of puberty is more or less maintained until the age of 50; thereafter it decreases gradually in most men, though rapidly in some instances.

Many clinicians do not believe in an entity such as the male climacteric. Three main reasons are: (a) Although the various clinical symptoms encountered in advancing age are associated with declining testicular function, testosterone levels do not differ significantly from those in control groups of asymptomatic men of similar age. (b) There is no increase in the levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), as noted in the female climacteric. (c) The response to oral androgen therapy is not nearly as pronounced as that obtained with oral estrogen therapy in the female.

To offset these arguments, one can say: (a) Many climacteric women have no hot flushes or climacteric symptoms despite a low estrogen level and high serum levels of FSH and LH. (b) Aging men may show only slight increases in FSH and LH because estrogen levels remain constant and may produce "inhibin," thus preventing the high FSH levels seen in men with primary gonadal failure, anorchia or Klinefelter's syndrome. These

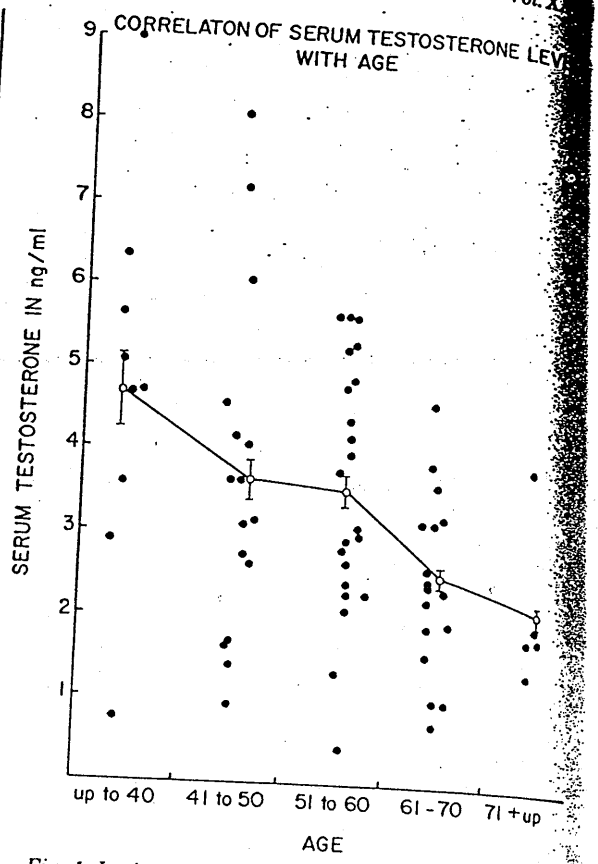
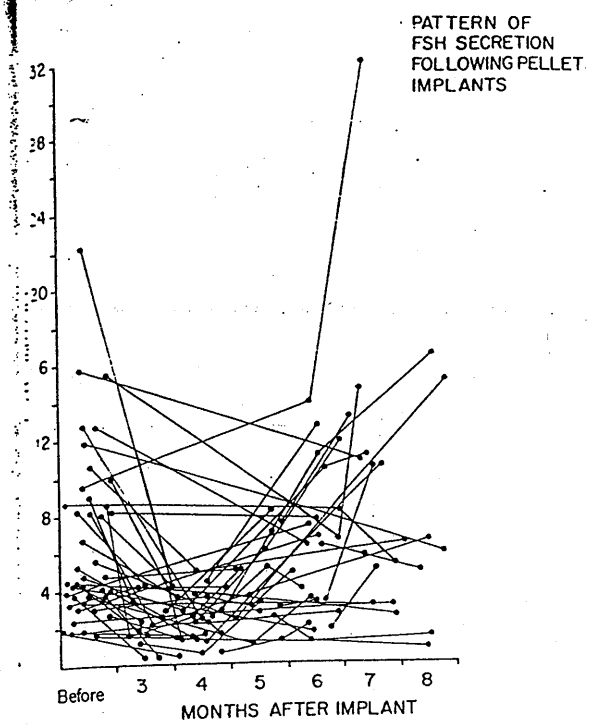


Fig. 1. In the male, serum testosterone levels begin to fall after 50 years of age.

estrogen levels, in the absence of a precipitous drop, probably prevent imbalance of the autonomic nervous system; hence the absence of vasomotor symptoms. Castration, on the other hand, often is accompanied by hot flushes.

Therapy

Orally administered androgens are poor substitutes for long-lasting injectable testosterone esters, or pellets of pure testosterone implanted subcutaneously. Injectable testosterone (100 mg at intervals of 7 to 14 days) or 75-mg pellets of pure testosterone (one of every 10–20 pounds of body weight) implanted at 6-month intervals, yield fair to excellent results in about two-thirds of the patients (5). Following administration of testosterone, FSH and LH levels fall but rebound to even higher concentrations after cessation of therapy, probably because of temporary suppression of testicular function (Fig. 2). Moreover, depression, headaches, fatigue and insomnia often are ameliorated and well-being enhanced by adequate hormonal therapy. The placebo effect of hormones has been unnecessarily exaggerated. Admittedly,



ig. 2. Implantation of testosterone pellets suppressed nd LH levels. As the pellets diminished after 4 to 5 , FSH levels began to rise, often above the baseline lues.

does exist, but double-blind studies employing placebo and androgens show a decided superiority for the hormones (3). A change of partner may be effective in cases of psychogenic impotence, as it was with Napoleon; yet it failed to help King David when put to the test. The beautiful Shunamite maiden failed to arouse him: "He gat no heat" (1, 6).

Attention should be paid to the possibility of prostatic enlargement and to a physiologic form of polycythemia. Although there is no proof that administration of testosterone will initiate development of prostatic cancer, it will stimulate the growth of one that is already present. Treatment with testosterone may reveal a latent cancer by causing a sudden irregular enlargement of the prostate which demands immediate attention and thus may prove to be a life-saving factor.

For some men there is a male climacteric that merits a trial of hormone therapy rather than benign neglect.

THE FEMALE CLIMACTERIC

The female climacteric starts from a few months to many months before the cessation of menses. For some time before the onset of the menopause, subtle changes occur in the hypothalamic-pituitary axis. The follicles of the ovary gradually lose their sensitivity to pituitary gonadotropins, resulting in normal or sometimes elevated estrogen levels (7–9). The modulating influence of estrogens no longer prevents FSH levels from rising, and irregular cycles set in. Ultimately, menses cease because of exhaustion of primary follicles or their inability to respond to pituitary stimulation. Estrogen levels fall dramatically and FSH and LH levels rise 8- to 14-fold. These phases of the premenopausal, menopausal and postmenopausal periods are part of the female climacteric and the symptomatology is a combination of many factors—hormonal, metabolic, psychogenic, and social. In women of certain personality types, the interaction between aspects of the aging process and hormonal change may cause a crisis, either temporary or prolonged.

Thus the female climacteric begins before the onset of the menopause and endures to the end of life.

Hormone-dependent neurovegetative symptoms

New information challenges the restrictive assessment of what constitutes the menopausal syndrome. The consensus has been that vasomotor instability (hot flushes, sweats) and atrophic vaginitis are the only signs and symptoms resulting from estrogen deficiency. Hitherto, mood changes and psychogenic manifestations, so frequently associated with "the change of life," have been regarded as purely coincidental and not hormone-related. Recent reports by Dennerstein et al (10), Moaz and Durst (11), Lauritzen (12) and others, employing estrogens and a placebo in double-blind studies, have shown that such manifestations as depression, anxiety and headaches are hormone-responsive, the implication being that estrogens are psychotonic agents. A scientifically based explanation has been offered by Alyward (13), who demonstrated that plasma levels of free tryptophan are low in menopausal women with depression, and that estrogens restore these levels. Serotonin is a by-product of tryptophan. In a measure, our own studies support Alyward's findings of disturbed tryptophan metabolism. We found that the ratio of total tryptophan to free tryptophan was restored to normal by the administration of estrogens (Fig. 3).

Experimental studies on mice have shown that brain norepinephrine increases and estrogen decreases following castration and that testosterone

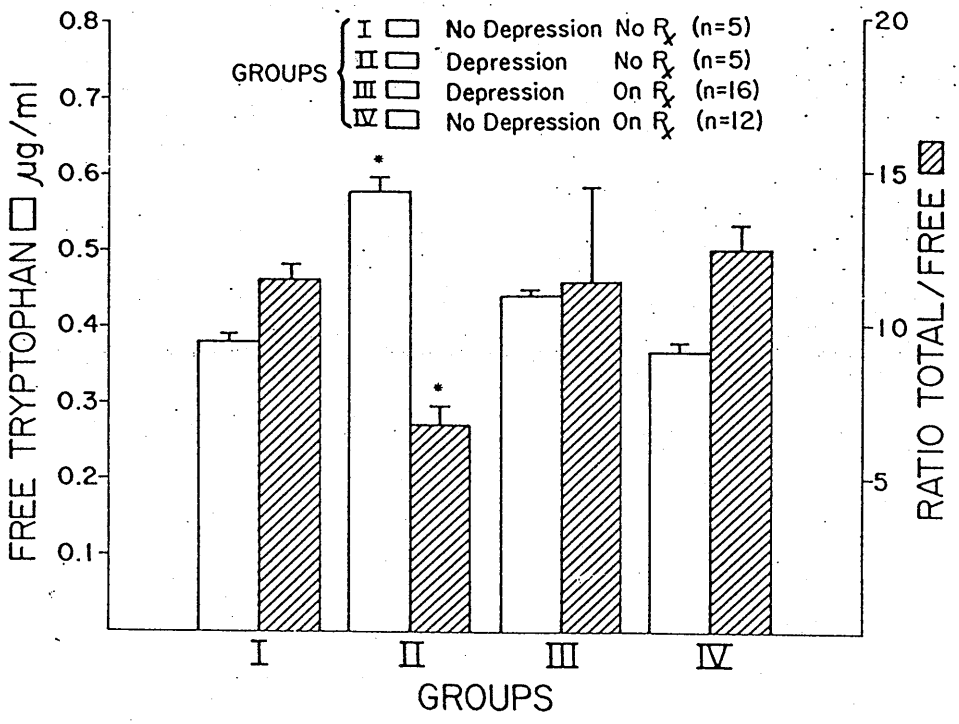


Fig. 3. Relatively elevated levels of free plasma tryptophan and low ratio of total to free tryptophan in depressed untreated menopausal patients. With estrogen therapy, values reverted to normal.

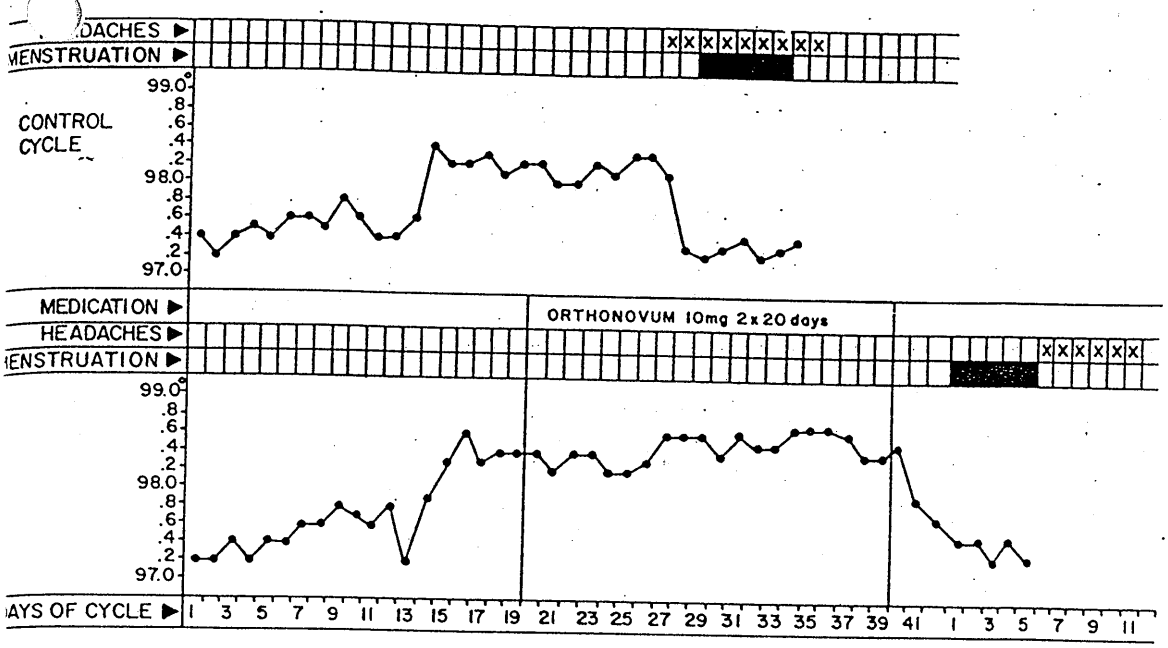
administered on day 1 prevents the normal rise in serotonin (14). Fuxe (15) found that an imbalance in cerebral neurohormones is associated with mood changes such as depression, crying spells, irascibility, nervousness, and changes in sexual behavior. Instability of adrenergic and cholinergic cerebral hormones is now believed to result from a deficiency of estrogen. The monoamino oxidase content of the brain matches the prodigious production of gonadotropins by the pituitary in estrogen-deficiency states. To argue that nonpsychotic depression and other mood changes are not hormone-dependent in the menopausal woman is to ignore the role of cerebral hormones (dopamine, norepinephrine, serotonin) in hypothalamic-pituitary physiology. Nonetheless, many excellent students of the menopause believe, as does Utian (16), that the neurovegetative symptoms such as headaches, fatigue, depressive moods, irritability, loss of libido and palpitations, are most likely part of the psycho-social-cultural phenomena and aging changes that occur in this period of life.

Menopausal headaches

Menstrual headache, held in abeyance during pregnancy, is often experienced by many women. Menstrual headache can be delayed through postponement of the menstrual period for five or six days by means of the intramuscular injection of 10 mg of estradiol valerianate one week before the expected onset of the period (17). The administration of a potent estrogen-progestogen oral contraceptive, started on day 20 of the cycle for 20 or more days, may postpone the headache by delaying menstruation, as has been shown by the delay-of-menses test (Fig. 4) (18). Menopausal women with frequent migrainoid headaches may obtain relief if estrogen concentration can be sustained at high levels for prolonged periods. Thus administration of pellets of estradiol (with and without pellets of testosterone) maintains high estrogen levels for five to six months, and has proved most efficacious in a high percentage of cases. The headaches often return as the estrogen levels fall after the fifth month (Table 1). Certain types of headaches experienced by menopausal women may be due to disturbances in the metabolism of cerebral amines such as catecholamines and histamine, which in turn disturb prostaglandin production. How estrogens and androgens influence these reactions is not clear.

Sexual dysfunction

Sexual libido is a complex phenomenon which can be studied only in the human. State of health, psychogenic, anatomic, neurologic, and hormonal



g. 4. Headaches in relation to menstruation. Delay of menses accomplished by administration of an estrogen-progestogen oral nceptive (Ortho-Novum). Menstrual headaches postponed until after discontinuation of the hormones.

rs play important roles. Many sex therapists hat most of the problems of sexual dys- re psychogenic, and should be so ed. xual dysfunction in the postmenopausal an may be attributable to dryness of the a causing dyspareunia. Estrogens usually are ful. In women in whom estrogens are not ful, the addition of androgens to the regimen s surprisingly good results.

a double-blind study published in 1950 we d that women under treatment for severe hot es preferred a preparation that proved to be xture of estrogen and androgens (19). Re- y, John Studd (20) demonstrated in a double- l study that estradiol-testosterone pellet im- s increased the frequency and intensity of sexual climax whereas estradiol pellets and bos did little to enhance this type of response 5).

openia

ss of bone mass has been regarded by many ians as purely an aging process. Albright's ntion of some 40 years ago that demineraliza- n of bone was hastened in primary and sec- ry hypo-ovarianism has been strongly de- y Gordan (21). Gallagher et al (22) believe is unduly sensitive to the action of hyroid hormone in the absence of estrogens. ntly, a 10-year double-blind study of a se- tial estrogen-progestogen regimen and a pla-

TABLE 1

*Relief of Symptoms in Menopausal Women Receiving Estradiol Pellets**

Symptoms	No. of Patients	Relief of Symptoms
Headache	550	72%
Loss of libido	610	78%
Nervousness	515	77%
Depression	450	75%
Hot flushes	718	86%
Fatigue	544	85%
Backache	165	72%

* In addition to the pellets of estradiol, some patients received 1–2 pellets of testosterone. Usually the headaches were relieved for 5 or more months at a time, and libido increased; in a high percentage of cases, many of the neurovegetative symptoms were also alleviated.

cebo demonstrated by densometer measurements the overwhelming benefits of hormonal therapy (23). Postmenopausal osteoporosis constitutes a major health problem. Some 26 percent of all white women have osteoporotic vertebral fractures by age 50, and 50 percent by age 75. Hip fractures bear significant morbidity and mortality rates. The risk of death from the sequelae of osteoporosis is far greater than the putative risk of developing an endometrial cancer which can be detected early and treated successfully. Estrogens used prophylactically in small doses can minimize the development of osteoporosis; in larger doses, estrogens can prevent further bone decay.

Risks of estrogen therapy

Does estrogen therapy constitute a risk factor

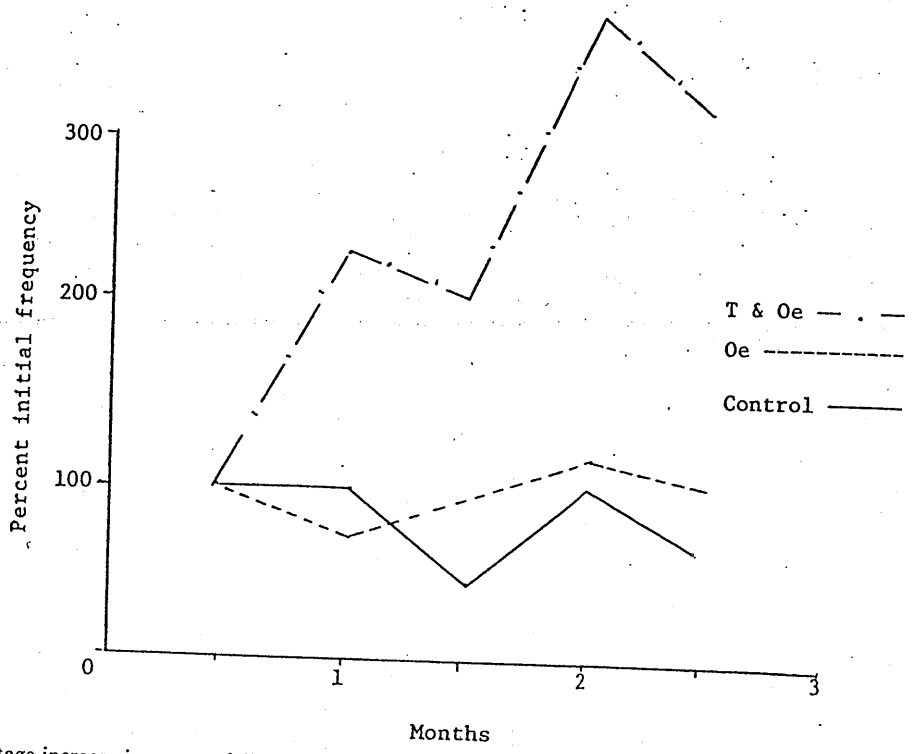


Fig. 5. Percentage increase in orgasm following implantation of testosterone 100 mg plus oestradiol 50 mg (T + Oe); oestradiol 30 mg (Oe); and placebo. (Courtesy of Studd JWW: The climacteric syndrome, *in* Female and Male Climacteric, ed. by PA van Keep, DM Serr and RB Greenblatt. Lancaster, England, MTP Press Ltd, 1979, pp 23–34.)

in: 1) coronary heart disease; 2) thromboembolic disease and cerebrovascular accidents; 3) gallbladder disease; 4) mammary cancer; or 5) endometrial cancer?

Coronary heart disease (CHD). Reports from England showed increased CHD in women taking oral contraceptives; estrogen was believed to be at fault (24). However, natural estrogens appear to increase the levels of high-density lipoproteins (HDL), and hence should have a favorable effect (25). Samsioe (26) showed that 20 mg of ethinyl estradiol (EE) and 10 mg of norethisterone increased low-density lipoproteins (LDL) and decreased HDL, whereas 2 mg of estradiol valerianate daily decreased LDL and increased HDL. At this point, the problems are still too complex to be completely understood and no real evidence exists that administration of natural estrogens increases CHD in women. In our large series of over 1,000 women in whom natural estrogens were employed, changes in serum triglycerides and cholesterol were minor (Figs. 6 and 7).

Thromboembolic disease and cerebrovascular accidents. Natural estrogens have induced relatively little change in most of the coagulation factors studied (27). The risk of thromboembolic disease is much higher in women over 35 years of age who continue to smoke during a regimen of oral contraceptives (28).

Gallbladder disease. The incidence of gallbladder disease increases with age. Estrogens have been alleged to play a role. Steroidal compounds with a methyl grouping in the 17th position are known to be cholestatic. Hammond et al (29), using naturally occurring estrogens (Premarin), found no detrimental effect upon gastrointestinal disease, although others have suggested a relationship.

Mammary cancer. The slow rise in the incidence of mammary cancer (per 100,000 women) in the United States has been proportionate to increased longevity. Statistical studies on the relationship between estrogens and breast cancer are confusing. For instance, the report of Hoover et al (30) purported to show a slight increase; but when the same case load was reviewed by another epidemiologist (31), the outcome was a slight decrease. Gambrell et al (32) found that the incidence was far less in their hormone-treated patients than in an untreated control group. In our studies, we found the normally expected incidence (Table 2).

Endometrial cancer. There can be no doubt that estrogens play a role, for without them en-

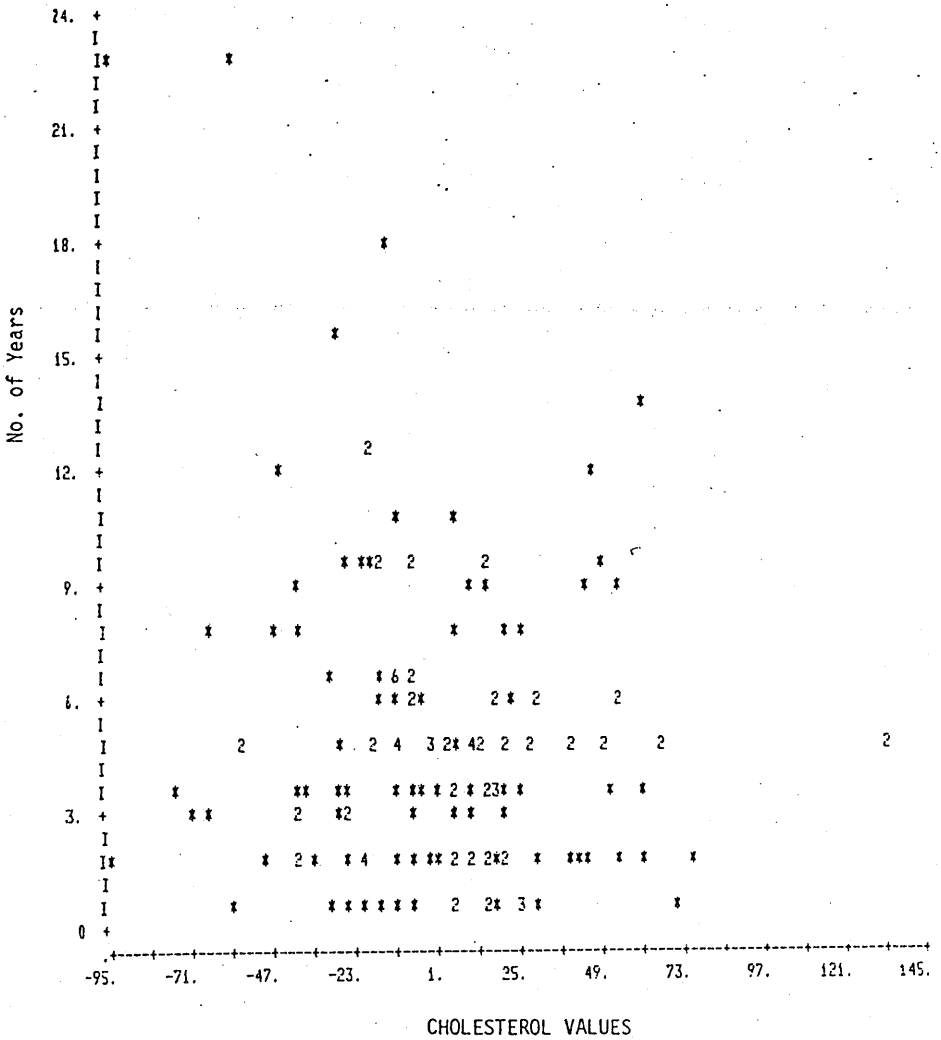


Fig. 6. Computerized statistical scattergram showing change in cholesterol values for 841 postmenopausal women following implantation of estradiol pellets: mean change, 1.774.

metrial cancer would not occur. Unopposed estrogen, whether endogenous or exogenous, increases the incidence of hyperplasia, atypical adenomatous hyperplasia, and cancer. Preliminary data from a descriptive study by Shanklin (1976) on the age distribution of patients with various types of hyperplasia and cancer suggest that progression from hyperplasia to malignancy usually requires many years (33). Since 1945, we have advocated the addition of cyclic courses of an oral progestogen whenever estrogens are administered (34). The recent reports by Gambrell (1978) and Hammond et al (1979) in the United States, and Campbell and Whitehead (1978) and Paterson (1978) in the United Kingdom, indicate that the cyclic use of progestogens exerts a protective action (35–38). Neither Hammond et al nor Paterson reported any cases of endometrial carcinoma among 72 and 133 patients, respectively, who were given a progestogen for 10 or more days during the cycle. Gambrell (35) found an incidence rate of 3.8 per 1,000 women-years in patients receiving unopposed estrogens and only 0.3 per 1,000 women-years in those receiving sequential oral estrogen-progestogen therapy. In untreated women, the incidence was 2.0 per 1,000 women-years.

We have reviewed the data on 1,058 women aged 45 or older who have been receiving estradiol pellet implants for 1 to 21 years, for a total of 9,175 women-years (5,402 of which were with the uterus intact). The patients were advised to take a 5-day to 7-day course of an oral progestogen at monthly intervals. Endometrial biopsy specimens were obtained frequently during the course of therapy, either before or at the end of courses of progestogen. Specimens were also obtained whenever spotting, breakthrough bleeding or excessive flow occurred (Table 3). The expected occurrence of en-

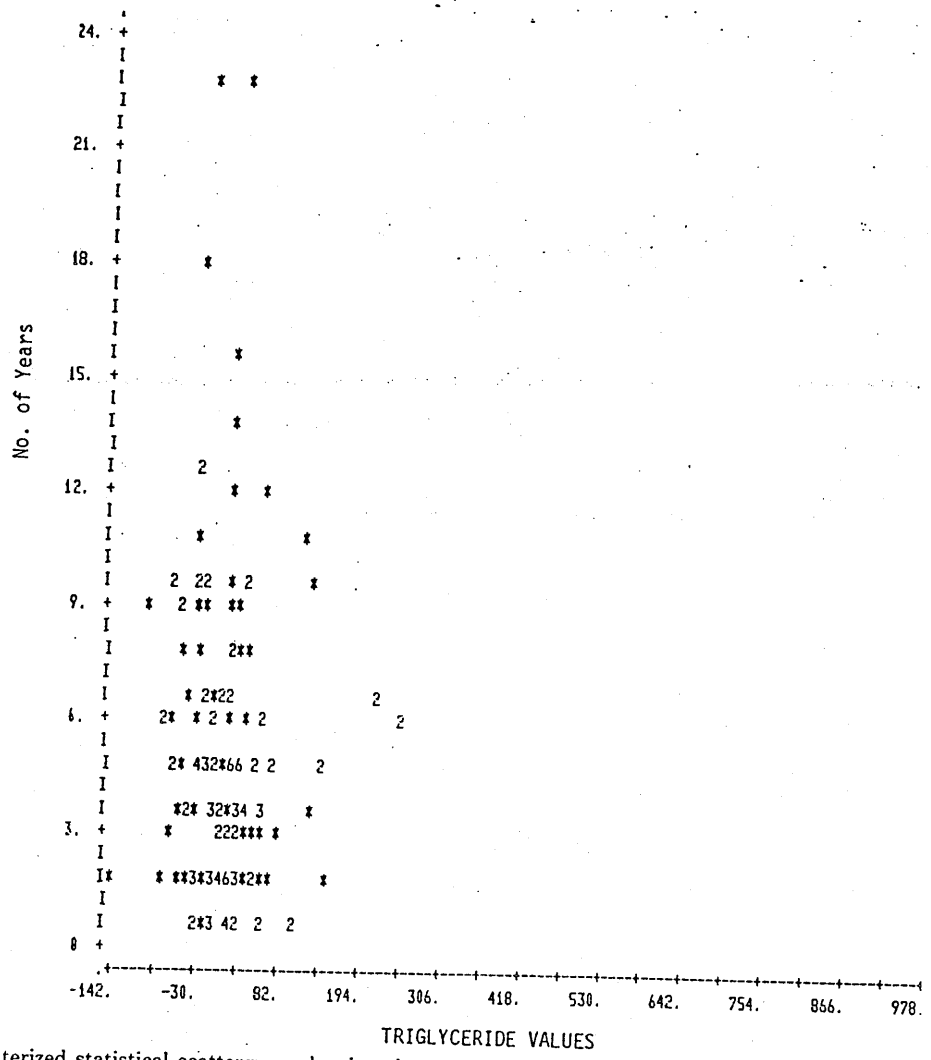


Fig. 7. Computerized statistical scattergram showing change in triglyceride values for 841 postmenopausal women following implantation of estradiol pellets: mean change, 1.7951.

TABLE 2

Breast Status after Pellet Implantation (9,175 Women-Years of Estrogen Therapy)

No. of Patients	Benign Breast Disease	Cancer of Breast
1,058	197	11

dometrial cancer would be somewhere between 6 and 11 cases. In this series, we found 5 cases of endometrial cancer (well differentiated, noninvasive, and cured by hysterectomy). However, because of breakthrough bleeding, carcinoma was discovered in 4 other patients within the first few months of therapy. It may be that these 4 women had endometrial cancer before coming under our care, and estrogen therapy merely unmasked it. Our findings demonstrate that the incidence of endometrial cancer was no greater than that expected in menopausal women not treated with estrogens. We are in total agreement with Campbell and Whitehead's conclusion that "the epidemiologic evidence suggests a true link between unopposed estrogens and early, less invasive forms of endometrial adenocarcinoma," and that "progestogens appear capable of protecting against development of cancer and hyperplasia, although complete protection is still to be achieved."

CONCLUSIONS

The concept of a male climacteric occurring in an unestimated, but probably small, number of men is receiving more and more attention. At any rate, adequate androgen therapy in such men is often helpful in lessening depression, headaches and asocial behavior, and improving libidinous drives.

Heretofore, the restrictive assessment of what

TABLE 3

Endometrial Status after Estradiol Pellet Implantation, with Oral Progestogen at Monthly Intervals

Endometrial Biopsy	No. of Patients	Proliferative	Secretory	Simple and/or Cystic Hyperplasia	Atypical Adenomatous Hyperplasia	Cancer of Endometrium	
						Present at start	Developed later
1st	279	174	56	42	8	3*	
2nd	72	46	11	14	1	1**	
3rd	24	14	6	3	1		
4th	12	5	0	1	3		3
5th	9	2	2	1	3		1
6th	6	3	2	—	—		1
Total	402	224	77	61	16	4	5

* Diagnosis was made either at time of first implantation or within a few months thereafter—hence, should not be linked to pellet therapy.

** Diagnosis was atypical adenomatous hyperplasia but another biopsy one month later showed endometrial cancer, evidently missed on first biopsy.

constitutes the female climacteric did not take into consideration that mood changes and psychogenic manifestations may be hormone-dependent. Estrogens have proved to be psychotonic agents. The appropriate use of gonadal steroids can help to maintain physical and mental health. There are some hazards associated with hormone replacement therapy, but the benefits far outweigh the [illegible].

Acknowledgment

The authors thank Paul Blankenship for his technical assistance.

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