MEDICAL GRAND ROUNDS

October 17, 1974

THE MENOPAUSE

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Ms. [redacted] is a 50 year old woman who had a hysterectomy in 1960, at age 36, for metromenorrhagia secondary to uterine myomata. One entire ovary and part of the other were also removed at that time. About 18 months later, nervousness, irritability and hot flashes began. She was started on estrogens in 1962, including progressively increasing amounts of Premarin orally and various injections. For the past six years she had been taking 2.5 mg of Premarin b.i.d. plus 5 mgm I.M. injections of Estrone twice weekly in order to remain asymptomatic.

Her blood pressure had been normal during three pregnancies and prior to estrogen therapy. Soon after starting estrogens, it rose to the 130/90 - 145/95 range and remained there without antihypertensive therapy until [redacted], 1974, when following an undiagnosed two week illness involving headache, diarrhea and fatigue, her blood pressure was found to be 200/110. She responded poorly to various antihypertensives including diuretics, but developed hypokalemia of 2.9 mEq/L. Thereafter she was hospitalized and the following obtained:

IVP: mild rotation of the right kidney (a suspension procedure had been done on the right kidney in 1947)
Peripheral plasma renin assays: Supine = 1.0 µg/ml/hr
Upright = 5.1 µg/ml/hr
Renal venous renin assays: Right = 0.9 µg/ml/hr
Left = 3.7 µg/ml/hr
Isotopic renogram: normal
Renal arteriogram: normal
Urine aldosterone = 71 µg in a 2050 ml/24 hr specimen containing 16 mEq of sodium, 31 mEq of potassium, and 1.2 gm of creatinine.

When I first saw her on [redacted]/74 she was taking hydrodiuril, reserpine and aldactone as well as estrogens and her blood pressure was 145/90 supine, 160/100 upright. Her fundi showed only minimal arteriolar narrowing, there were no bruits and the physical was otherwise negative. Lab work included a plasma Na = 139, K = 2.9, and creatinine = 0.8. All medications were stopped. In late August and early September, her blood pressure remained around 185/110 but when she returned here for admission on [redacted]/74 it was 130/90 - 140/95. She described recurrent hot flashes, increased nervousness, paresthesias, coarsening of the skin, slight dyspareunia and loss of libido, all beginning within four weeks of stopping estrogens.

Ms. [redacted]s mother had a spontaneous menopause at age 32 after bearing eight children. Now 79, she remains active, on no therapy. No one in the family has hypertension or known cardiovascular disease. One of her sisters had a hysterectomy at age 42 and has taken estrogens for the six years since, without known complications.

1. Ryan KJ, and Gibson DC. Menopause and Aging, Department of Health, Education and Welfare Publication # (NIH) 73-319.

2. Rogers J. The menopause. New Eng J Med 254:697, 750, April 12 and 19, 1956.

3. Kistner RW. The menopause. Clinical Obst Gynec 16:106, 1973.

DEFINITIONS AND CLINICAL FEATURES

Menopause = cessation of menses due to ovarian failure of ovulation and estrogen production.

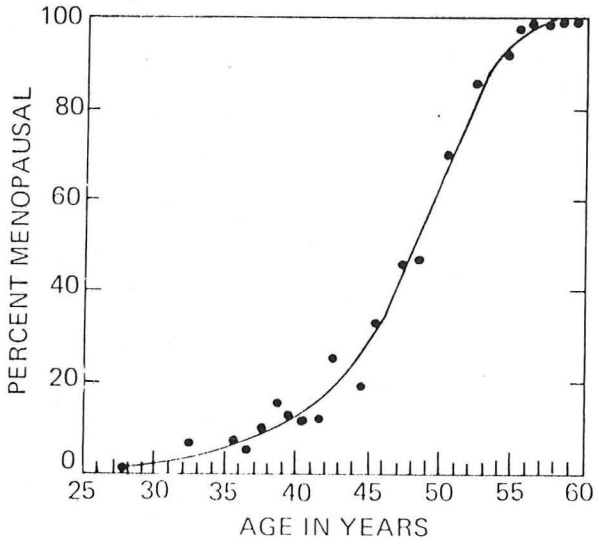
Climacteric = perimenopausal years when a syndrome of endocrine, somatic and psychic changes may occur of which the menopause is only one part; of these, only hot flashes and genital atrophy are unique.

The Time of Menopause

Women are unique in that all other species are capable of reproduction practically until death. Today in the U. S. there are 27 million women over 50 years of age with an average life expectancy of 28 years, almost seven years longer than that for men. The average age at menopause is between 48 and 50, apparently an increase of about 4 years over the last 100 years (4). The time may vary between age 40 and 55 in otherwise normal women (Figure 1). Patterns tend to be familial.

Menses may spontaneously cease in women well before the age of 40. The diagnosis of permature primary ovarian failure is based upon:

1. Failure of menses following progesterone in oil 50-100 mg I.M., or Provera, 10 mg b.i.d. per mouth for five days
2. Menses inducible by cyclic estrogen
3. Elevated plasma or urinary gonadotrophins



In two studies of secondary amenorrhea, one with 425 women below age 35 (5), the other with 425 women below age 30 (6), premature primary ovarian failure was the diagnosis in 5%.

Fig. 1. Percentage of women reporting having had a menopause, by age at time of survey. *(from Kistner RW. Clin Obstet Gynec 16:106, 1973.)*

The differential of secondary amenorrhea includes:

1. Normal ovarian function

    a. Pregnancy
    b. Galactorrhea
    c. Intrauterine synechia (Asherman's Syndrome)

2. Decreased ovarian function

    a. High gonadotrophins (primary ovarian failure)

        (1) Congenital and chromosomal defects: gonadal dysgenesis
        (2) Acquired

            (a) Iatrogenic: surgery, radiation
            (b) Auto-immune, usually with adrenal insufficiency
            (c) Idiopathic

    b. Low gonadotrophins

        (1) Hypothalamic-pituitary dysfunction

            (a) Functional: psychogenic, nutritional, debility, iatrogenic with tranquilizers or oral contraceptives
            (b) Organic: pituitary tumor or damage

        (2) Estrogen-secreting ovarian tumor

3. Increased androgen secretion

    a. Ovarian

        (1) Androgen-secreting ovarian tumor
        (2) Polycystic ovary syndrome

    b. Adrenal: Cushing's Syndrome, adrenal tumors

Clinical features of the Climacteric

Seventy-five percent of women experience climacteric symptoms and about 15% seek medical attention. This number may increase in response to widespread publicity about the benefits of estrogen therapy (e.g. Ladies Home Journal, May, 1974). The features can be divided into physical and psychological:

Physical	Psychological
Cessation of menses	Fatigue
Hot flushes	Nervousness
Cold sweats	Irritability
Paresthesias (skin crawling)	Depression
Headaches	Insomnia
Breast pains	Changes in libido

Hot flushes are usually described as a sudden feeling of heat in the face, neck and chest often but not always accompanied by flushing of the skin and sweating and occasionally followed by chilliness. They may occur infrequently or up to 30 times a day.

In addition, certain post-menopausal problems, including osteoporosis, atrophy of the skin and vaginal epithelium, increasing frequency of hypertension and atherosclerotic heart disease are often included as climacteric but they should be kept separate.

Perhaps the best study of climacteric symptoms is that of Neugarten and Kraines (7), wherein 460 women were surveyed for 28 symptoms and classified by age and menstrual status (Table 1). Note that menopausal women had more of most symptoms. However, most authorities agree that only hot flushes and amenorrhea are directly related to estrogen lack and correctable by estrogen therapy. To blame the menopause as the cause for headaches, fatigue, etc. is obviously a mistake, intellectually dishonest and therapeutically meddlesome.

TABLE 1: PERCENTAGE OF WOMEN REPORTING SYMPTOMS, BY AGE
(from Neugarten and Kraines, Psychosomatic Med. 27:266, 1965)

				45 ---- 54		
Symptom	13-18	20-29	30-44	Pre- or Post-Menopausal	Menopausal	55-64
Hot flushes	29	6	24	28	68	40
Cold sweats	19	6	13	16	32	4
Paresthesias	18	14	27	37	37	17
Skin crawls	11	6	5	3	15	6
Headaches	77	80	76	47	71	45
Breast pains	20	28	31	10	37	6
Fatigue	82	96	84	71	88	65
Nervous, irritable	76	90	82	71	92	48
Depression	79	88	62	56	78	46
Insomnia	49	44	45	40	51	58
Weight gain	47	30	40	41	61	38
Rheumatic pains	7	6	33	46	49	54

4. Frommer DJ. Changing age of the menopause. Brit med J 2:349-351, 1964.

5. Keettel WC and Bradbury JT. Premature ovariam failure, permanent and temporary. Am J Obstet Gynec 89, no. 1:83-95, 1964.

6. Starup J and Sele V. Premature ovarian failure. Acta Obst & Gynec Scand 52:259, 1973.

7. Neugarten BL and Kraines RJ. Menopausal symptoms in women of various ages. Psychosomatic Med 27:266, 1965.

Sexual Function in Older Women

Kinsey's group noted that a large part of the sex drive after the menopause is related to the sexual habits established during early years (8). A woman who has had a happy and well-adjusted sex life usually progresses through the menopause with little or no interruption in the frequency of, or interest in, sexual activity. In a more recent study of sexual behavior in people aged 46 to 71, the investigators found that, for women, past sexual enjoyment and the presence of a sexually capable, socially sanctioned partner were the crucial determinants of behavior, whereas for men more variables contributed to sexual behavior.

These were negatively related: age, taking of antihypertensive medication, physical function and excessive concern over physical examination findings; these were positively related: present health status, social class and present life satisfaction (9). It appears that older men's sexual behavior is affected by many extraneous factors, whereas older women who have enjoyed sex before and who have a willing partner are able to engage in a lively and satisfying sex life.

Some women lose interest, usually not from physical inadequacy, but according to Masters and Johnson, "use the excuse of their advancing years to avoid the personal embarrassment of inadequate sexual performance or the frustrations of unresolved sexual tensions."

Other women develop an increased libido which may border on nymphomania. Obviously a variety of psychological factors, including relief from the fear of pregnancy and a desire to prove one's sexual attractiveness, may be at play. Since, on the average, women outlive men by seven years and marry men four years older, most women can expect an 11 year widowhood with little or no chance for heterosexual activity. Therefore older women masturbate more frequently.

Masters and Johnson have provided much of what is known about the sexual capacity and performance of older people. They emphasize that their studies, although based upon a small and possibly atypical sample, prove that older women are capable of enjoying sexual intercourse fully, differing from younger women only in relatively unimportant ways, such as:

1. Vaginal lubrication takes longer to develop, from 15 to 30 seconds after initiation of excitement in younger women to up to five minutes in older women.
2. The expansion potential of the vagina is reduced but not below the capacity to engage successfully in intercourse.
3. Partial atrophy of the minor labia and the mons fat pad occur, but there is no decrease in clitoral size or responsiveness.
4. Orgasms tend to be shorter in duration.
5. Uterine contractions during orgasm may be more spastic and associated with pelvic pain.

Older women who engage in sex as infrequently as once every month may experience trouble from the atrophic changes of the vaginal wall, with dyspareunia, post-coital bladder discomfort and occasional bleeding. Those women who continue to have intercourse as often as once or twice weekly, even without estrogen therapy, are generally as responsive and orgasmically satisfied as younger women. However, they point out that "Since the majority of women in the 50-70 year age group have not retained adequate ovarian function to stimulate the reproductive viscera effectively and do not experience coital connection frequently enough to accomplish the same effect by regularity of usage, sex-steroid replacement frequently is indicated in order to enable most women to continue to function effectively as interested and interesting sexual partners." More about this when therapy is discussed.

8. Kinsey AC, et al. Sexual Behavior in the Human Female. W. B. Saunders, Philadelphia, 1948.

9. Pfeiffer E and Davis GC. Determinants of sexual behavior in middle and old age. J Am Geriatrics Soc 20, No. 4: 151, 1972.

10. Masters WH and Johnson VE. Human Sexual Response. Little, Brown & Co., Boston, 1966.

11. Masters WH and Johnson VE. Human Sexual Inadequacy. Little, Brown & Co., Boston, 1970.

PATHOPHYSIOLOGY

There seems little need to detail the psychological conflicts of middle age which are responsible for most of the non-specific but oftentimes more bothersome psychosomatic complaints. Too many patients and physicians seek instant relief by an estrogen tablet without wanting to examine the true causes of the symptoms or taking the time to alleviate them by providing insight and reassurance.

Many women still look upon the menopause as evidence of the ending of their useful, active life and the starting of a progressive deterioration into senility and infirmity. Two recent movements in American society may alter this attitude: the glorification of youth aggravating the problem, the more aggressive role of women in society tending to improve their perception of worth and self-esteem. The development of psychoneurotic symptoms during the climacteric seems largely dependent upon prior responses to emotional stress. Women with a long history of difficult menses are more likely to have a difficult menopause. Anxiety and depression are related to pre-existing emotional mal-adjustments which are brought to the surface by the additional stresses of "the change of life." In one series of 110 patients with menopausal symptoms, 95% had a history of excessive psychosomatic symptoms, often preceding the menopause by decades (12).

There are obvious organic, hormonal changes occurring during the climacteric. Their relationship to the flushes and symptoms of the menopausal period and

the loss of skin, bone and muscle of the post-menopausal years is largely conjectural. Some of the best recent work in this area has been done by the Ob-Gyn Department here at UTSWMS and I wish to thank Drs. Macdonald, Madden and Edman for their help in preparing this presentation.

Ovarian Changes

Structural: Ovarian weight decreases from an average of about 14 grams at age 30 to about 5 grams after age 50. The post-menopausal ovary is yellow, lusterless and wrinkled. Few, if any, primordial follicles are seen but small follicular cysts may be found. The cortical stroma becomes hyperplastic, and this, along with the appearance of foci of lipid-containing "lutein cells" and cortical granulomas, has been noted to be more striking in ovaries from women with carcinomas of the endometrium or breast. This structural change is in keeping with the evidence that the ovarian stroma is the site of the increased androstenedione synthesis which is the source of the increased circulating estrone found in post-menopausal women with endometrial hyperplasia and carcinoma (13).

Functional: The pre-menopausal ovary produces most of the estrogen, as estradiol, that is present during various phases of the cycle with a relatively constant basal level of estrogen as estrone, derived from extra-glondular conversion of androstenedione (Figures 2 and 3).

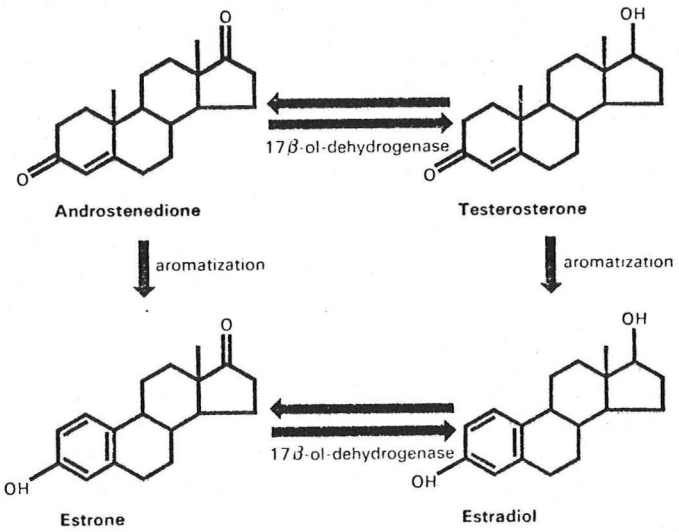


Fig. 2. The biosynthesis of estrogens.

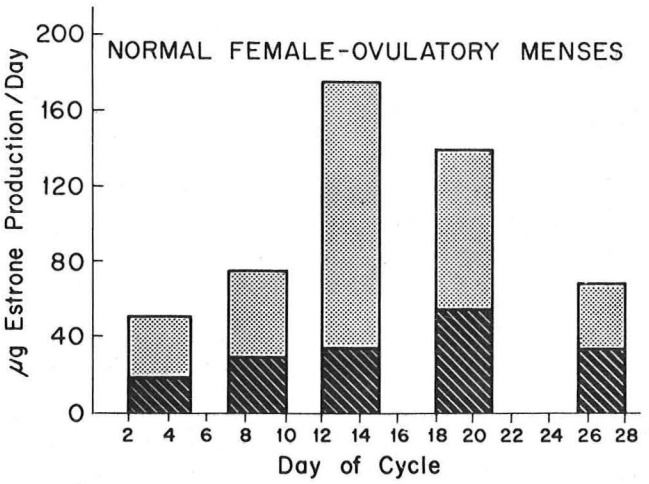


Fig. 3. Sources of estrogen production during a normal ovulatory menstrual cycle. Total height of bars represents sum of estrone and estradiol production; the *hatched portion*, that amount derived from plasma androstenedione. *(from Siiteri PK, Macdonald PC. Handbook of Physiology, Endocrinology II, Part 1, Chapter 28.*

The methods to examine the inter-conversions shown in Figure 2 and thereby to elucidate the origins of various sex hormones as shown in Figure 3 have been worked out mainly by Drs. Macdonald and Siiteri during the past seven years. Their work, described in references 14-17 and summarized in reference 18, is a fundamental contribution to our understanding of estrogen pathophysiology.

Relevant to the post-menopausal state, they have shown that endocrinologically normal post-menopausal women produce about one-half (mean = 1.75 mg/24 hr) as much androstenedione as do pre-menopausal women in the follicular phase of the menstrual cycle. But they convert twice as much of the plasma androstenedione to estrone (2.7% vs 1.3%), thereby providing about 45 µg of estrone per day, which is essentially all of the estrone produced. They thereby conclude that the major source of estrogen in the post-menopausal woman is peripheral formation of estrone from plasma androstenedione and not from either ovarian or adrenal secretion of estrogen. Both the post-menopausal ovary and the adrenal can secrete androstenedione but the levels in two oophorectomized women were essentially the same as in four women with ovaries intact (17), confirming the finding of Barlow et al. (19) that post-menopausal ovaries make no contribution to estrogen production. This strongly suggests that oophorectomy is not justified in treatment of carcinoma of the breast in post-menopausal women.

Aging and Endometrial Carcinoma

Clinicians have long recognized an association between aging, obesity, diabetes, liver disease, polycystic ovarian disease and ovarian corticostromal hyperplasia and the development of endometrial carcinoma. The UTSWMS Ob-Gyn investigators have shown that these associations may all be based on the presence of unopposed, high levels of estrone either from increased conversion of androstenedione to estrone (aging, obesity, liver disease) or increased levels of androstenedione (polycystic ovarian disease, ovarian corticostromal hyperplasia) (Figures 4 and 5).

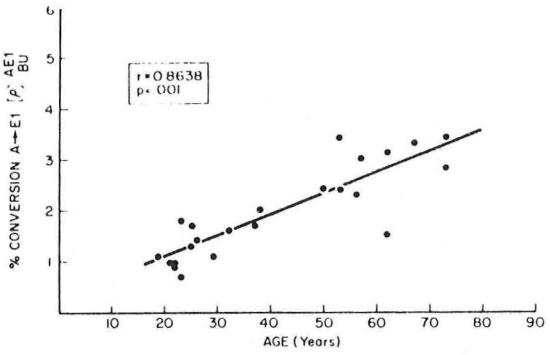


Fig. 4a. Correlation between the extent of conversion of plasma androstenedione to estrone and age in 23 women.

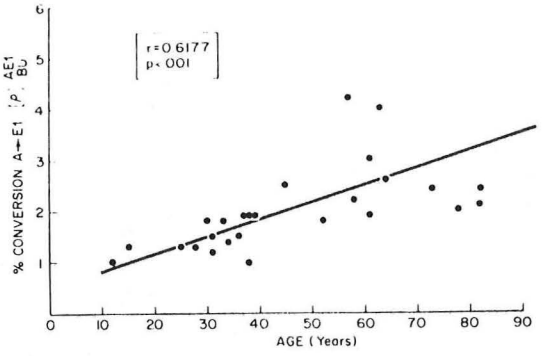


Fig. 4b. Correlation between the conversion of androstenedione to estrone and age in 26 men.

(from Hemsell, et al. J Clin Endo & Metab 38, no. 3, 478, 1974)

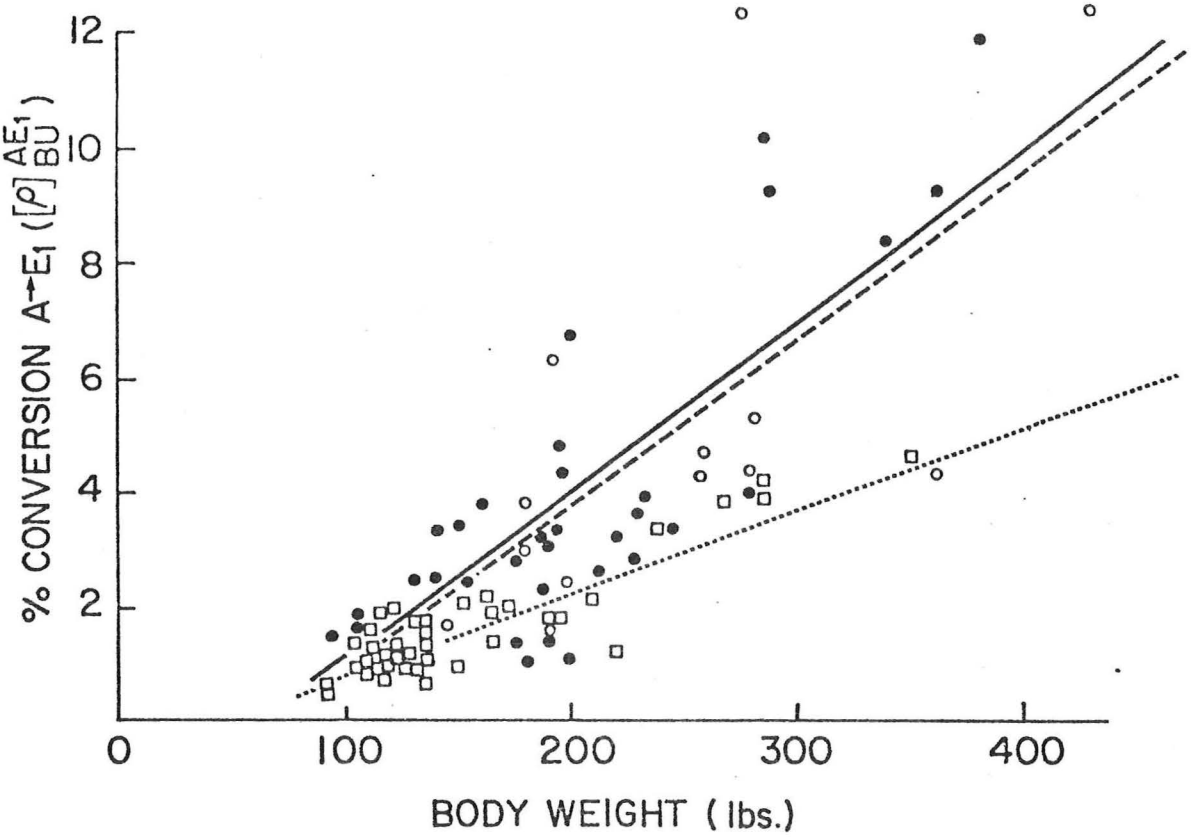


Fig. 5. Scatter diagram illustrating the extent of conversion of plasma androstenedione as a function of body weight in premenopausal women (open boxes and dotted line), postmenopausal women (closed circles and solid line), and postmenopausal women with endometrial carcinoma (15 subjects, open circles and dashed line). *(from Hemsell et al. in press)*

12. Donovan JC. Menopausal syndrome: study of case histories. Am J Obstet & Gynec 62:1281-1291, 1951.

13. Mattingly RF and Huang WY. Steroidogenesis of the menopausal and post-menopausal ovary. Am J Obstet & Gynec 103, no. 5, 679, 1969.

14. MacDonald PC, Rombaut RP and Siiteri PK. Plasma precursors of estrogen. I. Extent of conversion of plasma Δ'-androstenedione to estrone in normal males and nonpregnant normal, castrate and adrenalectomized females. J Clin Endo Metab 27:1103, August, 1967.

15. Hemsell DL, Grodin JM, Brenner PF, Siiteri PK and MacDonald PC. Plasma percursors of estrogen. II. Correlation of the extent of conversion of plasma androstenedione to estrone with age. J Clin Endo Metab 38, No. 3: 476, 1974.

16. Hemsell DF, Edman CD, Grodin JM, Brenner PF, Siiteri PK and MacDonald PC. Plasma precursors of estrogen. IV. Correlation between the extent of conversion of plasma androstenedione to estrone and body weight. In press.

17. Grodin JM, Siiteri PK and MacDonald PC. Source of estrogen production in postmenopausal women. J Clin Endo Metab 36, No. 2: 207, 1973.

18. Siiteri PK and MacDonald PC. Role of extraglandular estrogen in human endocrinology. In Handbook of Physiology ~ Endocrinology II, Part 1, RO Greep and EB Astwood eds., American Physiological Society, Washington, D. C., 1973.

19. Barlow JJ, Emerson K and Saxena BN. Estradiol production after ovariectomy for carcinoma of the breast. New Eng J Med 280, No. 12: 633, March, 1969.

Levels of Estrogen

Despite the widely held view that estrogen levels continue to fall progressively after menopause, the data using adequate techniques fail to confirm this impression, though there are relatively few data available. The ovary quits making the physiologically more active estradiol, but adrenal precursors continue to make estrone available; according to the findings of the Southwestern group, shown in Figure 4, the precent conversion rises with age so that total estrogen levels may actually rise. The data shown in Table 2, measuring plasma concentrations by radioimmunoassay, confirm the presence of respectable levels of both estrone and estradiol, with no difference in those with or without ovaries (20). These levels are about twice as high as found by Longcope using a saturation analysis technique (21).

TABLE 2: PLASMA CONCENTRATION OF ESTRONE AND ESTRADIOL IN THE FIVE CATEGORIES OF POSTMENOPAUSAL SUBJECTS
(from Rader et al. Am J Obstet Gynec 116, no. 8: 1072, Aug, 1973)

Categories	*No.*	*Mean ± S.E.*		
		Age	*Estrone (pg./ml.)*	*Estradiol*
Physiologic menopause	25	65 ± 2.0	37.7 ± 2.7	12.9 ± 0.92
Radiation menopause	13	58 ± 3.1	40.8 ± 3.2	11.7 ± 2.4
Operative menopause	12	54 ± 3.2	43.7 ± 6.8	15.8 ± 3.3
Postmenopausal with hypertension and/or diabetes	10	67 ± 2.6	43.2 ± 7.7	13.0 ± 3.1
Postmenopausal with heart disease	10	64 ± 3.0	38.6 ± 3.2	9.7 ± 1.6

It seems likely that some women, perhaps 25%, continue to secrete estrogens (or rather their precursors) from hyperplastic ovarian cortical stomal cells. These women may be protected from climacteric symptoms but they seem more susceptible to post-menopausal bleeding from endometrial hyperplasia and the progression of this process into endometrial cancer. Judd et al. (22) have found that post-menopausal women with endometrial carcinoma have falls of plasma testosterone (a precursor of estradiol) of 54% following oophorectomy, an amount larger than that secreted by the ovaries in their pre-menopausal patients.

20. Rader MD, et al. Plasma estrogens in postmenopausal women. Am J Obstet Gynec 116, No. 8: 1069, August, 1973.

21. Longcope C. Metabolic clearance and blood production rates of estrogens in postmenopausal women. Am J Obstet & Gynec 111:778-791, November 5, 1971.

22. Judd HL, Lucas WE and Yen SSC. Effect of oophorectomy on circulating testosterone and androstenedione levels in patients with endometrial cancer. Am J Obstet & Gynec 118: 793-798, March 15, 1974.

Hypothalamic-pituitary Changes

Pituitary gonadotrophins rise as the menopause approaches. In 12 such women, urinary luteinizing hormone levels were seven times higher and follicle-stimulating hormone levels three times higher than in younger women (23). These LH and FSH levels were high despite the presence of estrogen levels within or at the upper end of the normal range, suggesting that, as the menopause approaches, the feedback mechanisms between the pituitary and ovary are disturbed.

Nonetheless, the pituitary produces more gonadotrophins as the menopause is passed. This reflects stimulation from increased levels of hypothalamic luteinizing hormone-releasing factor (24), presumably increased in response to the lower estrogen levels. The levels of luteinizing hormone-releasing factor and luteinizing hormone in the plasma vary from time to time with peaks occurring periodically at one to two hour intervals and more rapid oscillations at 10 to 20 minute intervals (24).

These high levels of gonadotrophins and not estrogen deprivation were held responsible for climacteric hot flushes by Albright (25), but many now ascribe the hot flushes to "vasomotor instability from hypothalamic dysfunction" or in the words of Greenblatt "It appears that the hypothalamus -- sensitized by years of endogenous or exogenous estrogens -- reacts dractically to withdrawal of hormonal support." The evidence concerning the involvement of high gonadotrophin levels is inconclusive. On the one hand, patients who go through menopause from hypopituitarism (with low gonadotrophins) rarely, if ever, have hot flushes and estrogen therapy both relieves hot flushes and lowers gonadotrophins. On the other hand, hot flushes continue to decrease in frequency after menopause while gonadotrophin levels continue to rise. One additional argument against the role of gonadotrophin was that relief from flushes could be achieved with doses of estrogen which failed to suppress gonadotrophins. This is probably an invalid point since, with presently available, more sensitive assays, very small amounts of estrogen (e.g. 5 µg of ethinyl estradiol) have been shown to significantly suppress gonadotrophins (27).

Whatever the fundamental cause of flushes, they reflect a peripheral vasomotor instability mainly affecting the "blush" area. Clonidine, a non-steroidal, imidazoline derivative which diminishes vascular reactivity, will significantly reduce the frequency of flushes (28). This drug, in higher dosage, will soon be introduced as an antihypertensive agent.

23. Adamopoulos DA, Loraine JA and Dove GA. Endocrinological studies in women approaching the menopause. J Obstet & Gynec 78: 62-79, 1971.

24. Seyler EL and Reichlin S. Luteinizing hormone-releasing factor (LRF) in plasma of postmenopausal women. J Clin Endo & Metab 37, No. 2: 197, 1973.

25. Albright F. Studies on ovarian dysfunction. III. Menopause. Endocrinology 20:24-39, 1936.

26. Aitken JM, et al. The relationship between menopausal vasomotor symptoms and gonadotrophin excretion in urine after oophorectomy. J Obstet & Gynec 81:150-154, 1974.

27. Wise AJ, Gross MA and Schalch DS. Quantitative relationships of the pituitary-gonadal axis in postmenopausal women. J Lab & Clin Med 81: 28, January, 1973.

28. Clayden JR, Bell JW and Pollard P. Menopausal flushing: Double-blind trial of a non-hormonal medication. Brit Med J 1:409, March, 1974.

POST-MENOPAUSAL PROBLEMS

Osteoporosis

A. Definition: reduction in the skeletal mass below some arbitrarily defined normal value, usually associated with bone pain, vertebral compression and an increased incidence of fractures in the long bones; the bone mass is decreased in amount but fully mineralized.

B. Frequency

1. Progressive loss in bone mass invariable with aging and more rapid in women (Figure 6). It begins at about 45 years and proceeds at a rate of 10% per decade in a linear fashion.

2. Twenty-five percent of white women over age 60 have spinal compression fractures; by age 90, the risk of hip fracture is at least 20% (Figure 7); fractures are 2 to 10 times more common in women.

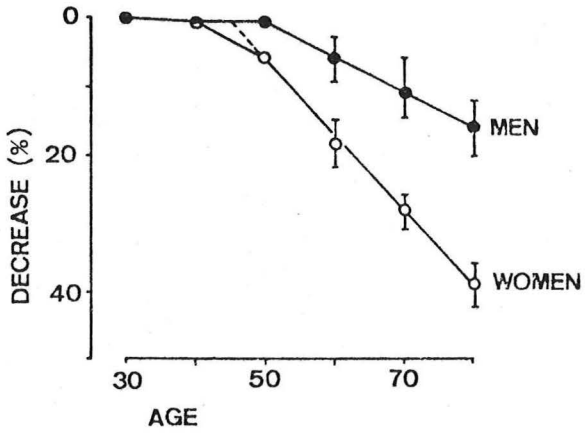


Fig. 6. The decrease in the thickness of the metacarpal cortex with age in men and women from five countries. *(from Morgan B. Clin Endo Metab 2:189, July, 1973)*

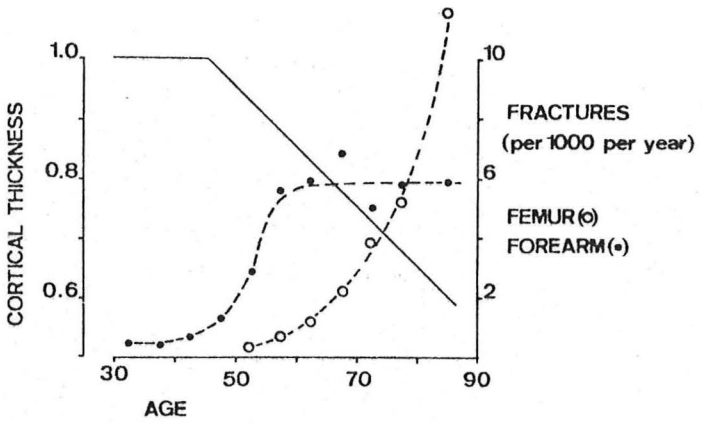


Fig. 7. The loss of bone with age (solid line) and the age-specific frequencies of fractures of the forearm and neck of femur (Alffram and Bauer, 1962; Alffram, 1964). *(from Morgan B. Clin Endo Metab 2:189, July, 1973)*

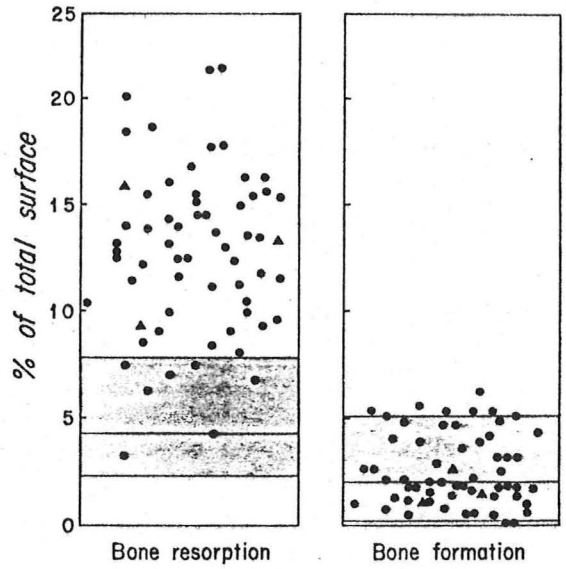


Fig. 8. Microradiographic findings from pretreatment iliac crest bone biopsy in 60 osteoporotic patients, female by circles, male by triangles. For age- and sex-matched normals, 90 per cent range is given by cross-hatched areas and means by horizontal lines. *(from Riggs, et al. Clinics Endo Metab 2:317, July, 1973)*

C. Pathogenesis

1. Newton-John and Morgan conclude that bone loss is universal and part of the aging process; there is no separate group who start with decreased bone mass who are susceptible (29); others find that some (38% of men, 22% of women) did not lose bone over an 11 year period and the rate of loss was variable (30).

2. Bone resorption increased (31) (Figure 8).

3. Bone formation normal, though not as high as expected to compensate for increased bone resorption (32).

4. Calcium balance negative but probably secondary to increased bone resorption.

5. Disruption of normal hormonal regulation of bone turnover by parathormone (32).

   a. Small number have increased parathormone levels, either primary or secondary to imparied intestinal absorption of calcium.

   b. In majority, parathormone decreased, probably compensatory to increased rate of calcium release from bone; the decreased parathormone levels may explain the subnormal intestinal absorption of calcium; despite low levels, parathormone probably still plays a role in bone resorption.

6. Estrogen-androgen deficiency

   a. Blood concentrations of estrogen, testosterone and gonadotrophins no lower in women with vertebral compression fractures than age-matched controls (33).

   b. Short-term estrogen treatment decreases bone resorption which lowers serum calcium and this, in turn, raises parathormone levels. In the presence of estrogens, these increased parathormone levels do not increase bone resorption, suggesting that estrogen acts to decrease the responsiveness of bone to endogenous parathormone, as proposed by Heaney in 1965 (35). The basic defect may be within the osteolytic cells, rendering them abnormally responsive to parathormone when gonadal sex hormones are deficient (32).

   c. Long-term estrogen treatment decreases bone formation to very low levels, suggesting an intrinsic abnormality of osteoblastic function that is masked, in the untreated state, by an increase in bone resorption but becomes apparent when resorption is decreased by estrogen treatment.

D. Treatment: Long-term, controlled data not available. Goal is to increase skeletal mass to a point that would prevent fractures, achievable only by a sustained increase in bone formation beyond that of bone resorption (Figure 9).

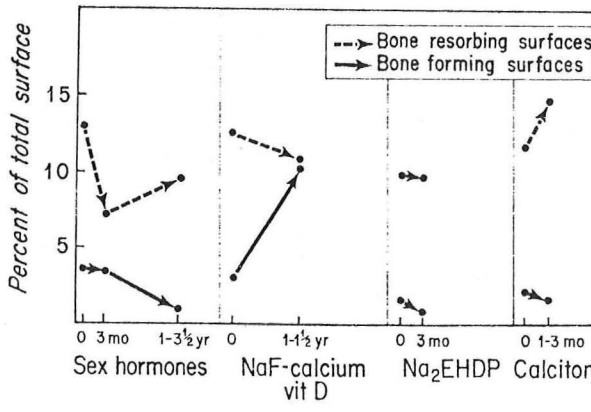


Fig. 9. Effects of various forms of therapy on bone-forming (*solid arrows*) and bone-resorbing (*broken arrows*) surfaces in osteoporosis. *(from Riggs, et al. Clinics Endo & Metab 2:317, 1973)*

1. Estrogens-androgens decrease resorption but later also decrease formation, thereby only arresting or slowing progression of bone loss.

2. Gordan found estrogens to be more effective in preventing fractures than androgens (36).

3. Calcitonin alone did not decrease bone resorption probably due to hypocalcemia → increased parathormone secretion. If oral calcium is administered simultaneously, calcitonin may be effective.

4. Calcium per mouth or by infusions (37) may suppress parathormone and stimulate calcitonin. Pak, et al. found sustained beneficial effects.

5. Flouride stimulates new bone formation; with supplemental calcium and vitamin D, the newly formed bone is mineralized (38). The Mayo Clinic group advocate this therapy:

   (1) Sodium flouride, 50 mg/day
   (2) Calcium carbonate, 1 g/day
   (3) Vitamin D, 50,000 units twice weekly
   (4) Premarin, 1.25 mg/day for 25 of each 30 days

E. Prevention: Aitken, et al. found protection from bone loss, measured by photon absorption, in a controlled trial of 114 middle-aged women given estrogens (mestranol 40 µg daily) either two months or three years, but not six years after oophorectomy (39)(Figure 10).

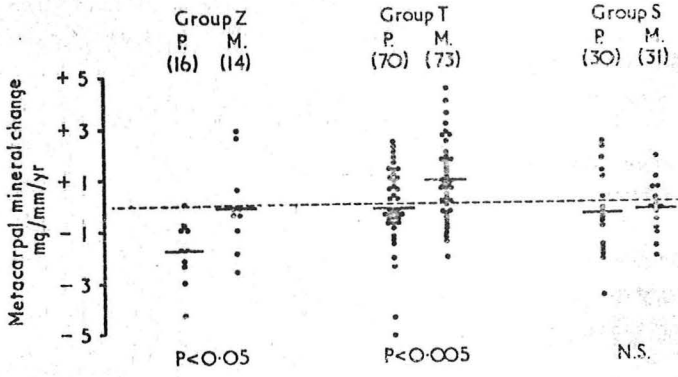


Fig. 10. Mean yearly change in metacarpal mineral in women receiving mestranol (M.) or placebo (P.) starting two months (group Z), three years (group T), or six years (group S) after oophorectomy. Numbers of patient-treatment-years are given in parenthesis. N.S. = Not significant. *(from Aitken et al. Brit Med J 3:515, 1973)*

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Cardiovascular Disease

In the late 1950's and early 1960's, a large number of papers appeared indicating 1) excessive cardiovascular disease in women castrated at an early age 2) protection from this accelerated course by estrogen replacement and 3) protection of man from heart attacks and stroke by administration of estrogens. Critical analysis of these largely uncontrolled data shows that all three conclusions are probably wrong (40), and that estrogen therapy is possibly associated with an increased rate of cardiovascular complications perhaps by deleterious effects on blood lipids and induction of hypertension.

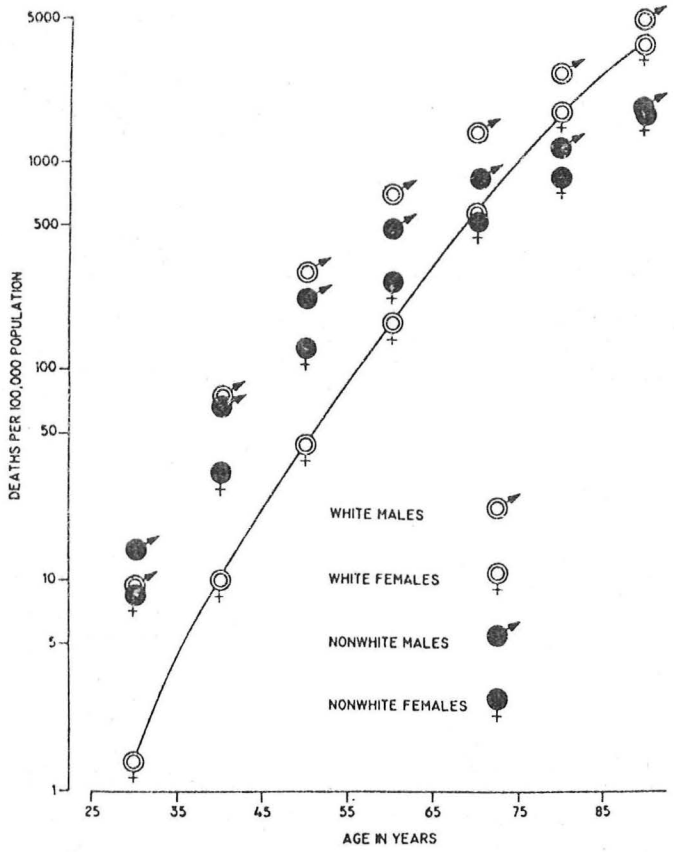
Coronary Heart Disease

Men die more commonly than do women from coronary disease, the difference being most striking in the 30 to 50 age groups. Since the male-to-female ratio declines steadily after age 45, the assumption was widely held that coronary heart disease increased markedly in women after the menopause. But as Furman noted, the explanation is a slower acceleration of coronary deaths in men with increasing age, probably by the early deaths of those

men vulnerable to coronary disease (Figure 11). The curve for women shows no skewing at or after the menopause.

In the Framingham study, coronary disease was manifested in women mainly by angina pectoris but in men mainly by acute myocardial infarction and sudden death. In 16 years, the incidence of coronary heart disease was only about 50% as high in women as in men, aged 30 to 62, but rose from 58/1000 among the 40-49 age group to 159/1000 in those over 50 (41). Mean serum cholesterol levels rose sharply in women from 190 at age 30 to 225 at age 45 to 250 at age 55; the levels in men ages 30 through 62 were quite similar, averaging 220; as in men, the risk of coronary disease was strikingly related to the level of serum cholesterol. As in other populations, hypertension was less common in women than in men before age 50; thereafter progressively more women have hypertension. It seems likely that the increased prevalence of these two known risk factors, hypercholesterolemia and hypertension, could explain the increasing likelihood of women developing coronary disease after the menopause.

Death rates for coronary heart disease
White and non-white population, by age and sex: United States 1955.



(from Furman RH. in Menopause and Aging, DHEW Publication # 73-319 (NIH).

Figure 11

The possibility that this greater likelihood is related to estrogen lack seems unlikely. The best data are those of Ritterband et al (42) who compared the prevalence of coronary disease between 267 castrated women and 385 women who had had a hysterectomy but whose ovaries were intact. The groups were quite similar in all regards and they were carefully observed 10 to 25 years after operation. Coronary disease was found in 8% of both groups. The postoperative use of estrogens (in 18% of the oophorectomized, 10% of the hysterectomized) did not alter the incidence.

On the other hand, estrogen intake in the form of oral contraceptives appears to be a risk factor for myocardial infarction. Radford and Oliver (43) found that 6 of 22 women aged 31-45 with acute myocardial infarction were taking oral contraceptives. This 27% figure is about three times the percentage of women in the general population taking the pill. All of these women had other risk factors for premature coronary disease and they conclude that oral contraceptives probably enhance the chance of developing myocardial infarction in women whose risk is increased for other reasons.

Estrogens may be causing trouble by increasing serum triglyceride levels, as detailed in my 1973 rounds. Stokes and Wynn (44) found a rise in serum triglycerides from 70 mg% to 100 mg% in women taking 50 µg of estrogen in oral contraceptives. Occasionally massive hyperlipemia (45) and pancreatitis (46) occurs in women with previously covert, asymptomatic hyperlipemia.

Cerebral Vascular Disease

Subsequent to the interest in preventing coronary disease with estrogens, trials in patients with cerebral vascular disease were undertaken. Despite wildly enthusiastic claims by some (47), carefully controlled studies clearly showed no benefit and probable harm in the use of 1.25 to 2.5 mg of Premarin in such patients (48,49). Significantly increased incidence of strokes has also been reported in younger women given oral contraceptives (50).

Hypertension

The problem of estrogen-induced hypertension was considered in last year's rounds. Despite some negative reports (51) the best evidence is that estrogens given to young women as oral contraceptives will induce hypertension in a small but significant number. In an ongoing, massive study in England, the figures suggest that 5% of women receiving oral contraceptives for five years may become hypertensive (52).

Post-menopausal women given "replacement" estrogens do not appear to be susceptible to venous thromboembolic disease as are younger women given estrogens for contraception (53). Evidence concerning the relative risk for hypertension in post-menopausal estrogen takers is unavailable.

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GUIDES FOR THERAPY

There are a few therapeutic nihilists and a number of therapeutic enthusiasts, the latter seemingly winning increasing support from both physicians and patients. It is hard to deny the appeal and the logic of those such as Greenblatt who writes:

> The difficulties of the postmenopausal period -- the imbalance of the autonomic nervous system, the psychogenic disorders, the metabolic disturbances -- continue, in mild to severe form, to the end of life. Many women cannot adjust to them. Although their hormonal environment can be improved, they envision goals that must remain inaccessible. Inner illuminations fade, and moments of exultation give way to hours of melancholic gloom. In those who have staked everything on femininity, the pathetic urge to turn back the flight of time contributes to the crisis. Hormones will not stay the aging process, but they can help a woman to grow old with grace and dignity. It is unrealistic to withhold measures that may prevent disabling pathologic processes or help a woman to make the transition smoother during these difficult years.(54)

There does seem to be a middle ground. My own attitude has become considerably more liberal about the indications for estrogen usage during the preparation of this presentation. Basically I believe that most postmenopausal women should receive estrogens but in the lowest effective doses and only for limited periods. The belief is based upon the premise that the advantages outweigh the disadvantages.

Advantages of Estrogen Therapy

1. Hot flushes can be controlled. These are bothersome enough for about half of women during the climacteric to require relief. Tranquilizers and reassurance won't provide it.

2. Genital atrophy can be ameliorated and sexual capacity improved.

3. Some of the emotional trauma can be relieved. Don't neglect reassurance and tranquilizers and don't expect too much. Some find no effect from estrogens (55) but most do.

4. Osteoporosis may be blunted but estrogens alone are probably not enough.

5. For most women, the dosage can be kept so low that uterine bleeding will not occur and few side effects should be encountered. There is no evidence that post-menopausal estrogens are carcinogenic and some even claim they may offer protection against cancer (56).

Disadvantages of Estrogen Therapy

1. Too much may be expected if the claims made by Ayerst and some of the therapeutic enthusiasts are accepted. Estrogens will neither provide eternal youth nor prevent atherosclerosis nor overcome serious psychoneurosis.

2. Uterine bleeding may be induced, requiring careful gynecological evaluation to exclude malignancy.

3. Side effects may occur, including

   a. breast tenderness
   b. hypertension
   c. gall-bladder disease. The risk is increased two and one-half-fold according to the Boston Drug Program (53).
   d. hyperlipemia

4. Laboratory tests may be influenced, interferring with their use in clinical diagnosis. Table 3 is taken from a useful summary of the alterations produced by oral contraceptives (57). The same can be expected with estrogens alone.

5. Once estrogen usage has been accepted, a therapeutic frenzy may be unleashed, involving massive doses of estrogen and androgens which may be harmful to the patient.

Table 3.—Altered Clinical Laboratory Measurements With Most Clinical Significance

Substances Measured*	Change in Level
Albumin	Decreased
Glucose	Elevated glucose level at 1 hr
Triglycerides (S)	Elevated
Thyroid-binding globulin (S)	Elevated
Thyroxine (S)	Elevated (free thyroxine normal)
Triiodothyronine resin uptake	Decreased (FTI† normal)
Cortisol-binding globulin (S)	Elevated
Cortisol (P)	Elevated
17-OH-corticosteroids (U)	Decreased
17-ketogenic steroids (U)	Decreased
Metyrapone test	Impaired responsiveness
Sulfobromophthalein test	Impaired excretion
Platelets (B)	Elevated, mild
Blood procoagulants (B)	Elevated‡
Iron (S)	Elevated
Iron-binding capacity (S)	Elevated

*S indicates serum; P, plasma; U, urine; B, blood.
†FTI indicates free thyroxine index.
‡Not evident on routine testing.

(from Weindling H and Henry JB. JAMA 229:1762, 1974)

Specific Guidelines

1. Women who probably should not be given estrogens:

   a. history of thromboembolic disease
   b. history of breast or uterine cancer. Obese patients with a family history of endometrial carcinoma or a personal history of endometrial hyperplasia probably should be excluded.
   c. active liver disease
   d. hyperlipemia

If climacteric hot flushes need relief, use medroxyprogesterone acetate (Depo-Provera), 150 mg I.M. monthly (58) or Catapres (Clonidine) (28).

2. The choice of estrogen: Most favor conjugated equine estrogens (Premarin) because of fewer side effects (and an effective advertising campaign) but synthetic estrogens may be used, with these equilavencies:

    0.625 mg Premarin
    0.2 mg diethylstilbesterol
    10 µg mestranol
    10 µg ethinyl estradiol

3. The dosage should be the least needed to relieve climacteric symptoms. The above dosages are reasonable to start with. There is no reason to monitor therapy with vaginal cytology (maturation index) since it does not correlate with plasma concentrations of estrogen nor symptomatology (59). The medication should probably be started within a year after menopause if the findings of Aitken (39) are valid.

    Women without a uterus can be given daily estrogen without pause or additional hormones. Women with a uterus may be purposely caused to continue monthly menstrual bleeding with cyclic therapy including progestogens (60) but that seems unnecessary and meddlesome. It seems preferable to use such small doses of estrogen so as not to induce endometrial hyperplasia. Some advocate the use of progestogen, either initially to exclude those with a tendency toward endometrial hyperplasia, or intermittently during therapy to prevent hyperplasia (61).

4. Vaginal creams of estrogens and corticosteroids may be needed to manage atrophic vaginitis and vulvar pruritis.

5. Those women who do not have climacteric hot flushes presumably have enough endogenous estrogen so as not to need exogenous supplements. Some would give estrogens to all women, hoping to prevent esteoporosis and atherosclerosis but I believe discretion is indicated.

6. The proper duration of therapy is unknown. Some advocate one to two years by which time the climacteric symptoms should be passed. Others advocate life-long therapy. I favor the shorter duration.

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THE MALE CLIMACTERIC

Men don't have climacteric hot flushes nor the other sudden changes of the perimenopausal years. But there is a gradual loss of testicular function, usually after age 50 (Figure 12). The studies of Vermeulen et al have shown:

1. Plasma testosterone levels tend to fall progressively after age 50 (62).

2. The decreased testicular function is testicular in origin since the response to exogenous gonadotropins is decreased, whereas the pituitary secretes high levels of gonadotropin spontaneously and in response to luteinizing hormone-releasing factor (63).

3. The plasma free testosterone levels are diminished, whereas plasma estrone and estradiol levels are slightly increased (63), suggesting an increased peripheral conversion of androstenedione and testosterone to estrone and estradiol in aged men as shown by the Southwestern group to occur in aged women.

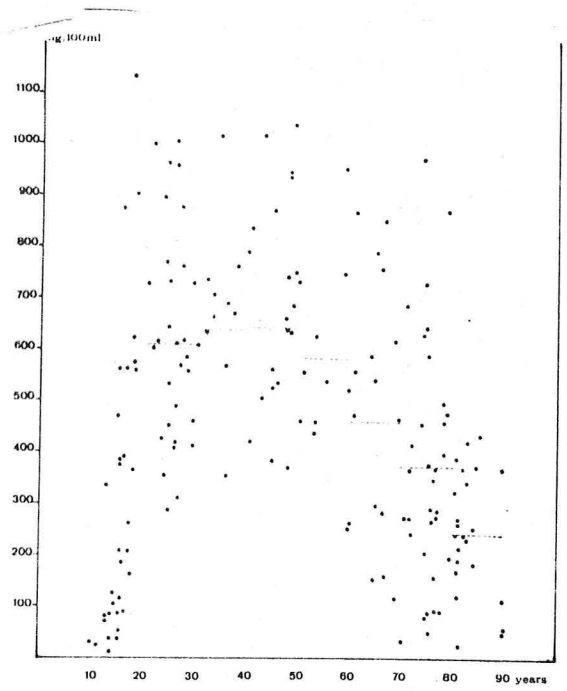

FIG. 12. Plasma testosterone levels in normal males in function of age.

(from J Clin Endo 34:730, 1972)

Men may have problems in sexual performance secondary to these decreased androgen levels but these are much more likely to be psychogenic in origin and not truly responsive to exogenous testosterone. Men of 70 are certainly capable of full sexual responses, including production of fertile semen. But as detailed by Masters and Johnson (11), many older men have a delay in the onset and a shortening of the maintenance of penile erection and a slower ejaculatory response. They repeatedly emphasize, however, that "loss of erective prowess is <u>not</u> a natural component of aging."

Most of the cases of impotence seen by Masters and Johnson were secondary to physical problems (alcoholism, diabetes, drugs) or psychological

hang-ups (premature ejaculation, religious orthodoxy, homosexual influences). They were successful in treating 74% of these cases by "1) removing the man's fear for sexual performance 2) reorienting his involuntary behavior patterning so that he becomes an active participant, far removed from his accustomed spectator's role and 3) relieving the wife's fears for her husband's sexual performance."

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