Medical Grand Rounds

USE OF ESTROGENS AFTER THE MENOPAUSE

10 July 1980

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I. GENERAL REVIEWS

1. Lauritzen, C.H. The female climacteric syndrome: significance, problems, treatment. Acta Obstet. Gynecol. Scand. Supp. 51:47-61, 1976.

2. Campbell, S., Ed. The Management of the Menopause and Post-Menopausal Years. University Park Press, Baltimore, 1976.

3. VanKeep, P.A., R.B. Greenblatt, and M. Albeaux-Ferret. Consensus on menopausal research. University Park Press, Baltimore, 1976.

4. Gambrell, R.D., Jr. Postmenopausal bleeding. Clin. Obstet. Gynecol. 4:129-143, 1977.

5. Studd, J., S. Chakravarti, and D. Oram. The climacteric. Clin. Obstet. Gynecol. 4:3-29, 1977.

6. Shoemaker, E.S., J.P. Forney, and P.C. MacDonald. Estrogen treatment of postmenopausal women, benefits and risks. J. Amer. Med. Assoc. 238:1524, 1977.

7. Utian, W.H. Current status of menopause and postmenopausal estrogen therapy. Obstet. Gynecol. Surv. 32:193-204, 1977.

8. Greenblatt, R.B. Geriatric Endocrinology, Vol. 5, Raven Press, New York, 1978.

9. Lauritzen, C., and P.A. VanKeep. Frontiers of Hormone Research. S. Karger, Basel, Vol. 5, 1978.

10. Silverberg, S.G., and F.J. Major. Estrogens and Cancer. John Wiley and Sons, New York, 1978.

11. Quigley, M.M., and C.B. Hammond. Estrogen-replacement therapy - help or hazard? N. Engl. J. Med. 301:646-648, 1979.

12. Landau, R.L. What you should know about estrogens. JAMA 241:47-51, 1979.

13. Ryan, K.J. Estrogen after the menopause: risk vs. benefits. Consultant 1:218-221, April, 1980.

Following the introduction of estrogens into clinical medicine in the late 1930's their use in menopausal women become more and more widespread as the result of several interlocking phenomena. Within medicine, powerful advocates argued that needless suffering of millions of women could be prevented by adequate estrogen replacement therapy (14, 15).

FIG. 1. Woman showing some of the stigmata of "Nature's defeminization." The general stiffness of muscles and ligaments, the "dowager's hump" and the "negativistic" expression are part of a picture usually attributed to age alone. Some of these women exhibit signs and symptoms similar to those in the early stages of Parkinson's disease. They exist rather than live. (14)

14. Wilson, R.A., and T.A. Wilson. The fate of the nontreated postmenopausal woman: a plea for the maintenance of adequate estrogen from puberty to the grave. J. Am. Geriatr. Soc. 11:347-362, 1963.

15. Jern, H.Z. Hormone therapy of the menopause and aging. Charles C. Thomas, Springfield, IL, 1973. (Dedicated to millions of women suffering needlessly.)

This viewpoint was promoted aggressively by the pharmaceutical industry.

Fig. 2 *In answering advertisements please mention* JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM

The use of estrogen was made scientifically respectable by Fuller Albright who advanced the thesis that osteoporosis is the result of the menopausal state, that premature menopause is associated with worsening of osteoporosis, and that osteroporosis can be prevented by estrogen administration.

16. Albright, F., P.H. Smith, and A.M. Richardson. Postmenopausal osteoporosis. J. Amer. Med. Assoc. 116:2465-2474, 1941.

After the long term results of such treatment from Albright's clinic were published by Henneman and Wallach (17) it became generally accepted that osteoporosis was a preventable disease.

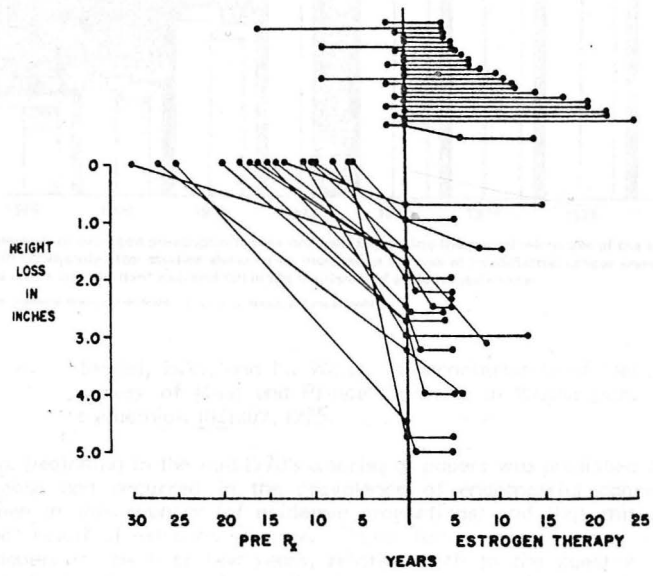


Figure 3. Loss of height in osteoporotic women treated with estrogen and untreated. [From Henneman and Wallach(17),Arch Intern Med **100**:715, copyright 1957 American Medical Association.]

17. Henneman, P.H., and S. Wallach. The use of androgens and estrogens and their metabolic effects. Arch. Int. Med. 100:715-723, 1957.

Simultaneously, the public at large was propagandized by advertisements, magazine articles, and books (such as Feminine Forever by Robert A. Wilson, M.D., published in 1966) to the belief that a perpetual Spring could be induced in the aging woman by the routine use of estrogens. By the mid 1960's it was acceptable, indeed standard practice in many areas, including the Endocrine Clinic of Parkland Memorial Hospital, to prescribe estrogens routinely for women undergoing natural or surgically induced menopause. By 1973 51% of menopausal women in Seattle, Washington, used estrogen for a median period of 10 years (18). By 1975 the use of estrogens in this country approached the status of a several hundred million dollar industry, involving some 30 million prescriptions per year.

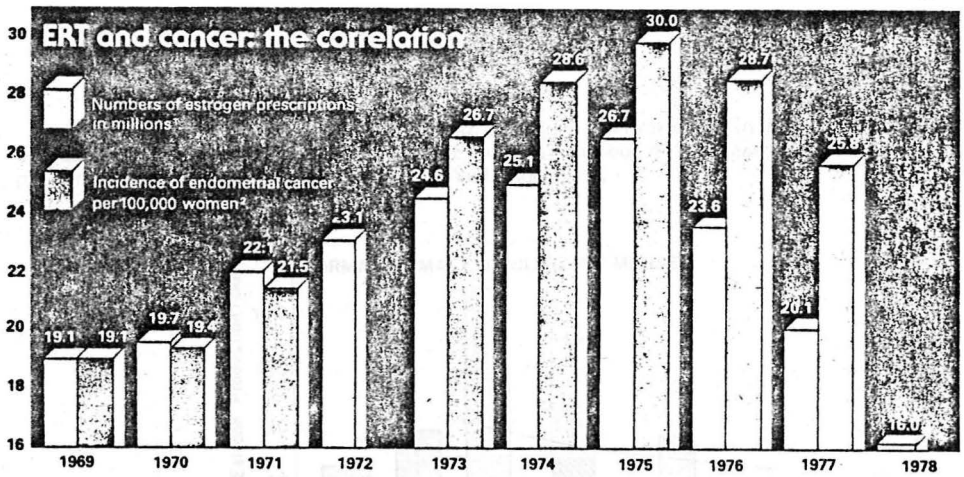


Fig. 4. **The numbers of estrogen prescriptions rose dramatically during the period when use of the synthetic hormones peaked, and then fell off sharply after studies showing an increase in the risk of endometrial cancer were publicized. Lagging somewhat behind was a concomitant rise and fall in the incidence of endometrial cancer.**

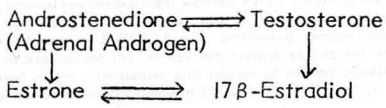
1. Source: National Prescription Audit. 2. Source: National Cancer Institute.

18. Stadel, B.V., and N. Weiss. Characteristics of menopausal women: a survey of King and Prince Counties in Washington, 1973-74. Am. J. Epidemiol. 102:209, 1975.

Then, beginning in the mid 1970's a series of papers was published to suggest that an increase had occurred in the prevalence of endometrial cancer in menopausal women in this country (of epidemic proportions) and that this increase was the direct result of estrogen therapy. These claims have provoked a literal avalanche of papers in the past few years, relating both to the question of the purported relation of estrogen administration to cancer and to the overall question of benefit to risk ratios of estrogen therapy. Coincidental to this new interest in the subject, the role of estrogen therapy in preventing osteoporosis is also undergoing reevaluation. What I propose to do today is to review the endocrine changes that take place at menopause, the current concepts of the pathophysiology of the menopausal syndrome, the comparative pharmacology of the estrogens now available for replacement therapy, and the effects and side effects of estrogens in the aging woman.

II. ENDOCRINOLOGY OF THE MENOPAUSE

One of the major developments in steroid hormone physiology during the past 20 years was the demonstration by Drs. MacDonald and Siiteri and their colleagues at this institution that circulating estrogens can be derived both from direct secretion by the ovary and from formation in peripheral tissues from C_{19} androgens (19, 20).



Prior to the menopause about 60% of estrogen formation is in the form of estradiol secreted into the plasma by the ovaries whereas 40% is estrone formed predominately by peripheral aromatization of androgens.

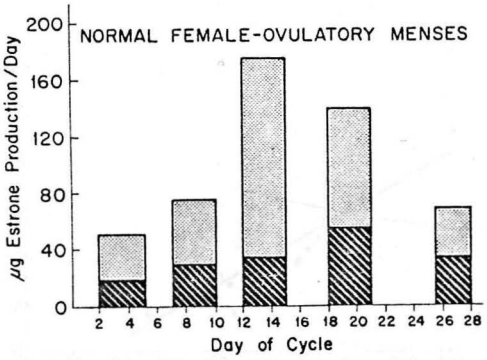


FIG. 5. Sources of estrogen production during a normal ovulatory menstrual cycle. Total height of bars represents sum of estrone and estradiol production; the *hatched portion*, that amount derived from plasma androstenedione. (Ref. 20)

As the result of the menopause, the ovarian component of direct estrogen production is virtually obliterated, but the peripheral aromatase system remains intact so that estrone production remains substantialy unchanged. As a result, there is a switch from estradiol to estrone as the predominant estrogen in the aging woman.

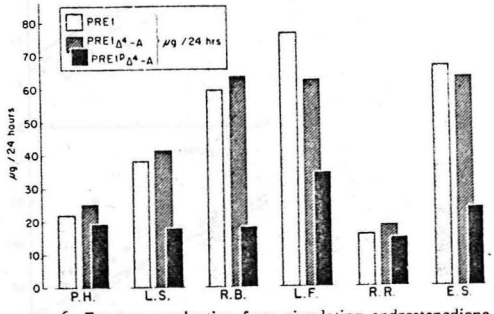


FIG. 6. Estrogen production from circulating androstenedione in normal postmenopausal women. PRE1, total estrone production rate; $PRE1_{\Delta^4\text{-}A}$, production rate of estrone from plasma androstenedione; and $PRE1^{P}{}_{\Delta^4\text{-}A}$, amount of estrone derived from androstenedione that enters the plasma as free estrone. As indicated in text, formation and release of estrone sulfate likely accounts for difference between $PRE1_{\Delta^4\text{-}A}$ and $PRE1^{P}{}_{\Delta^4\text{-}A}$. (Ref. 20)

The factors that regulate the rate of estrogen formation in peripheral tissues are largely undefined, but one major determinant is body weight, a relation that is true both for the rate of estrogen formation (20) and for the plasma levels of estrogens in postmenopausal women (4).

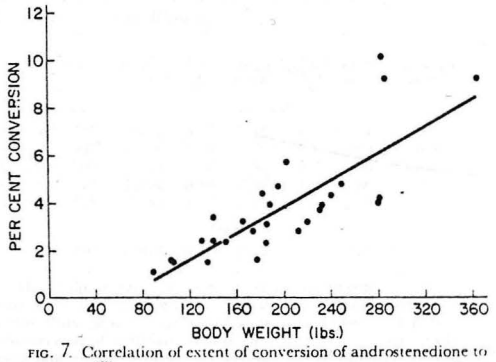


FIG. 7. Correlation of extent of conversion of androstenedione to estrone, $(\rho)^{\Delta 4}_{HE}$, with body weight in postmenopausal women. Correlation coefficient = 0.74. (Ref. 20)

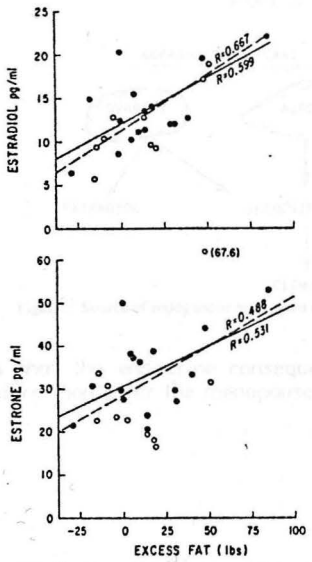


FIG. 8. Correlation of estradiol and estrone levels with excess fat in postmenopausal patients with endometrial cancer (●) and without endometrial cancer (○). Dashed regression line is for all patients, while solid line is for cancer patients only. (Ref. 21)

Exactly why peripheral aromatase activity is enhanced in obesity is unclear, presumably due to an increase in the number of adipocytes and pre-adipocytes (23).

In some postmenopausal women mean estrogen production may be as high or higher than prior to the menopause -- the predominant estrogen being changed and the secretory rate constant rather than intermittent (20).

TABLE I. *Estrogen Production in Postmenopausal Patients with Uterine Bleeding*

Patient	Age	Weight, lb	$MCR_{A,}$* liter/day	$C_{A,}$† μg/liter	$PR_{A,}$‡ mg/day	[ρ] $\frac{AE1}{BU.}$§ %	$PRE1,$‖ μg/day	$PRE1_{A,}$# μg/day
D.H.	73	195	1,992	0.57	1.14	4.4	57	47
B.B.	57	363	2,656	1.04	2.76	9.2	230	240
A.W.	69	200	1,924	0.98	1.89	5.7	96	101
A.O.	63	255	2,928	0.85	2.49	4.3	86	101
E.S.	63	185	2,548	1.04	2.65	2.0	49	50
				Mean				
	65	240	2,410	0.90	2.19	5.1	104	108

* Metabolic clearance rate of androstenedione. † Concentration of endogenous circulating androstenedione. ‡ Total daily production rate of androstenedione. § Extent of conversion of androstenedione to estrone. ‖ Total daily production rate of estrone. # Quantity of estrone derived from circulating androstenedione. (Ref. 20)

This shift in estrogen production can be summarized schematically as shown below: (Ref. 4)

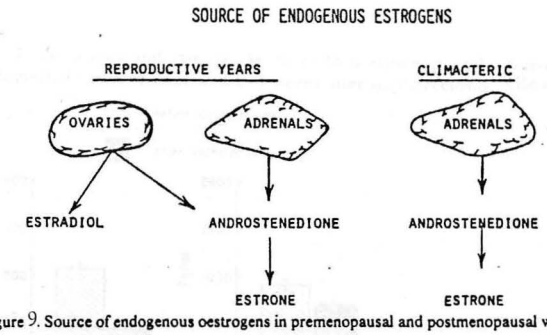


Figure 9. Source of endogenous oestrogens in premenopausal and postmenopausal women. (Ref. 22)

It follows that the endocrine consequences of removal of the ovaries are more striking before than after the menopause (21).

Fig. 10. The mean ± S.E. serum testosterone, androstenedione, estradiol, and estrone levels in five premenopausal women with endometrial cancer before and 6–8 weeks after oophorectomy. (Ref. 21)

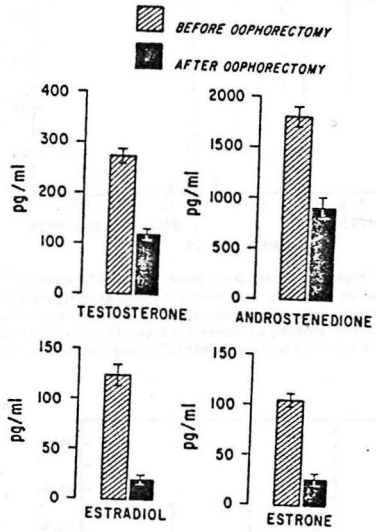
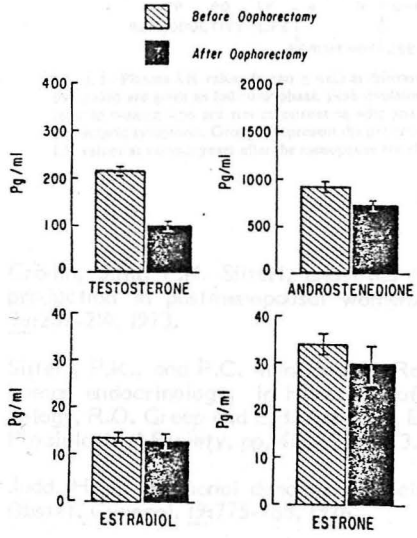


Fig. 11. Androgen and estrogen levels in 16 postmenopausal women with endometrial cancer before and 6–8 weeks after oophorectomy. (Ref. 21)



Plasma levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) also increase in the menopause (5).

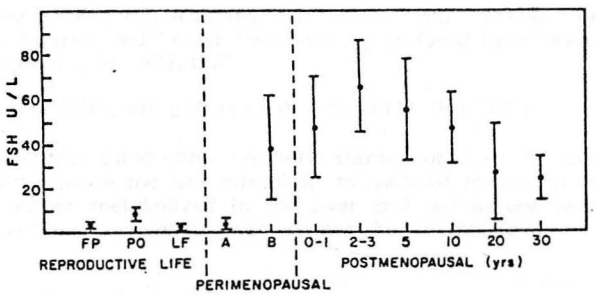


Fig. 12. Plasma FSH values (mean ± s.d.) at different ages. The normal values in the reproductive phase are given as follicular phase, peak ovulatory phase and luteal phase. Group A and B refer to women who are still menstruating who attended the menopausal clinic with apparent climateric symptoms. Group B represents the patients who complained of vasomotor symptoms. FSH values at various years after the menopause are also shown. (Ref. 5)

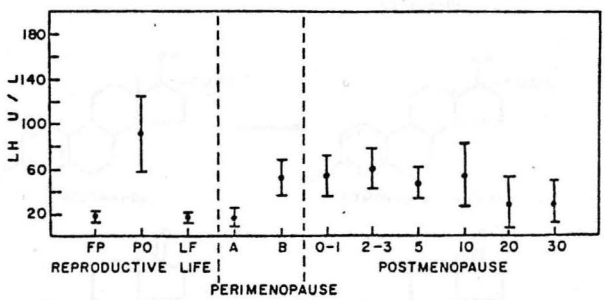


Fig. 13. Plasma LH values (mean ± s.d.) at different ages. The normal values in the reproductive phase are given as follicular phase, peak ovulatory phase and luteal phase. Group A and B refer to women who are still menstruating who attended the menopausal clinic with apparent climacteric symptoms. Group B represent the patients who complained of vasomotor symptoms. LH values at various years after the menopause are also shown. (Ref. 5)

19. Grodin, J.M., P.K. Siiteri, and P.C. MacDonald. Source of estrogen production in postmenopausal women. J. Clin. Endocrinol. Metab. 36:207-214, 1973.

20. Siiteri, P.K., and P.C. MacDonald. Role of extraglandular estrogen in human endocrinology. In Handbook of Physiology, Section 7: Endocrinology, R.O. Greep and E.B. Astwood, Eds. Washington, D.C., American Physiological Society, pp. 615-629, 1973.

21. Judd, H.L. Hormonal dynamics associated with the menopause. Clin. Obstet. Gynecol. 19:775-788, 1976.

22. Asch, R.H., and R.B. Greenblatt. Steroidogenesis in the postmenopausal ovary. Clin. Obstet. Gynecol. 4:85-106, 1977.

23. Siiteri, P.K., J.E. Wiiliams, and N.K. Takaki. Steroid abnormalities in endometrial and breast carcinoma: a unifying hypothesis. J. Steroid Biochem. 7:897-403, 1976.

III. ESTROGENS AVAILABLE FOR REPLACEMENT THERAPY

Estrogen therapy using either synthetic steroids or naturally derived hormone does not in fact replace the lost estradiol. In contrast to natural estradiol, oral estrogens are either metabolized in the liver and gut before reaching or are derivatives (17α-ethinyl steroids) that cannot be metabolized to the natural hormones (24).

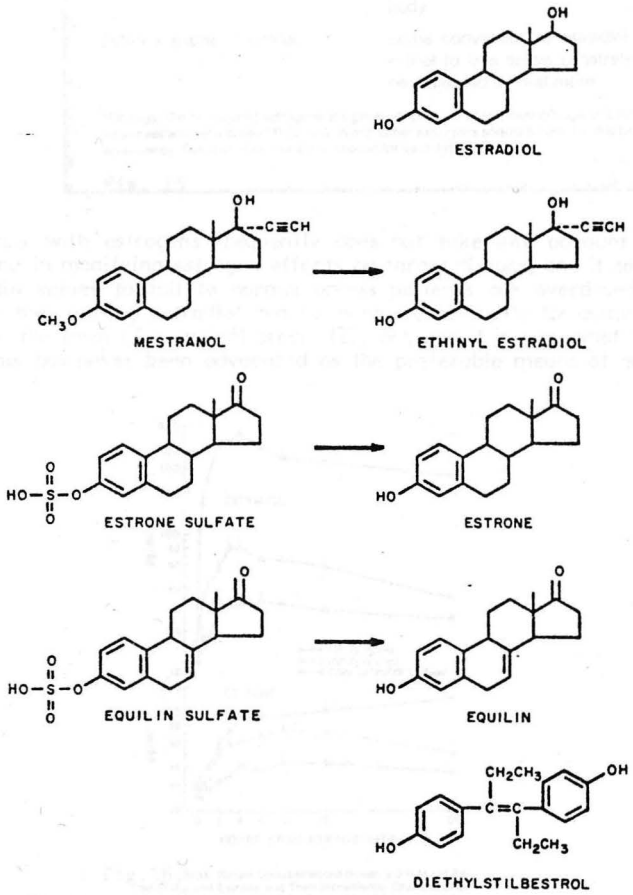


Fig. 14. Structure of estrogens. Estrogens without a 3-hydroxy group require biotransformation. (Ref. 24)

Estradiol given by mouth (either micronized or in a carrier is rapidly converted to estrone in the body.

Oral estrogens available for therapy*

Generic name	Comments
Estrone and "pregnant-mare estrogens"	Contain potassium estrone sulfate and other conjugated estrogens
Ethinyl estradiol	Synthetic derivative
Quinestrol	Derivative of ethinyl estradiol
Micronized estradiol	Rapidly converted to estrone in body
Estrone, estradiol, estriol	Some conversion of estradiol and estriol to less active substrates to be expected by oral route

*Dosage: The conjugated estrogens are generally prescribed at a daily dosage of 0.625 mg, ethinyl estradiol at a dose of 0.02 to 0.05 mg. Other estrogens should be used at this biologic equivalency. See manufacturer's information for each type used.

Fig. 15

Therapy with estrogens frequently does not take into account the role of progesterone in modifying estrogen effects on target tissues, and it seldom causes gonadotropin values to fall to normal unless patients are overdosed (13). It is interesting that plasma estradiol can be elevated promptly by administration of estradiol in the form of a vaginal cream (25, 26), and it is somewhat surprising to me that this has never been advocated as the preferable means of administering estrogen:

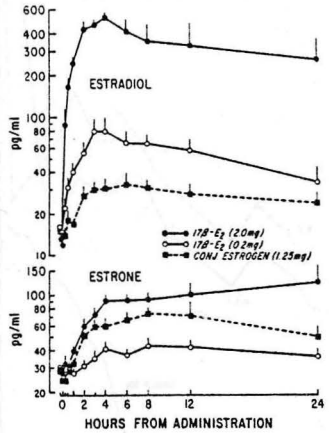


Fig. 16, Basal Serum Concentrations (Mean ± S.E.M.) of Estradiol (E_2) and Estrone and Their Incremental Changes after Intravaginal Application of E_2 Cream at 2.0-Mg and 0.2-Mg Doses as Compared with 1.25 Mg of Conjugated-Estrogen Cream in Six Hypogonadal Women with Severe Estrogen Deficiency (Note that the Estrogen Concentrations are Plotted on a Log Scale) (Ref. 26)

24. Eisenfeld, A.J. Estrogen receptors. Clin. Obstet. Gynecol. 19:767-774, 1976.

25. Schiff, I., D. Tulchinsky, and K.J. Ryan. Vaginal absorption of estrone and 17β-estradiol. Fertil. Steril. 28:1063-1066, 1977.

26. Rigg, L.A., H. Hermann, and S.S.C. Yen. Absorption of estrogens from vaginal creams. N. Engl. J. Med. 298:195-197, 1978.

IV. EFFECTS OF ESTROGEN ON SPECIFIC ASPECTS OF THE MENOPAUSE

A variety of claims have been made over the years as to purported benefits and/or toxic side effects of estrogen therapy on specific aspects of aging and the menopausal syndrome.

A. Vasomotor Instability

The pathogenesis of the menopausal flush remains unexplained. There is no clearcut correlation between hot flashes and the levels either of plasma gonadotropins or of estrogens (27) (the possibility has been suggested that the phenomenon may actually be due to a decrease in the potent estrogen metabolites, the catechol estrogens). Whatever the reason there is a uniform experience that the institution of estrogen therapy is followed by prompt fall in plasma FSH (mean decrease of 31%) and LH (mean decrease of 19%) and a disappearance (or decrease in frequency and intensity) of hot flashes (1, 5, 28).

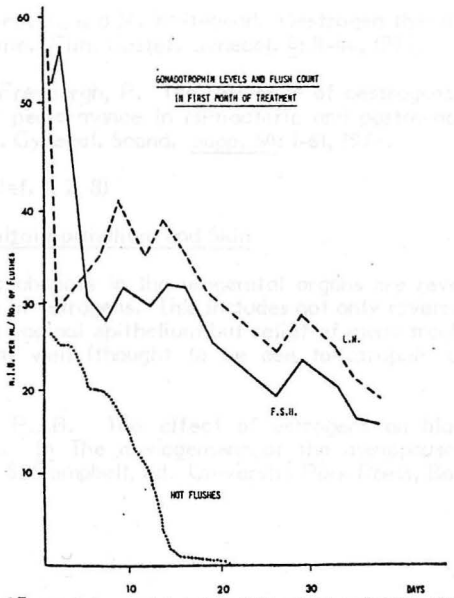


Fig 17 Daily flush score and plasma levels of FSH and LH in a patient taking 1.25 mg Premarin daily. (Ref. 28)

27. Aksel, S., D.W. Schomberg, L. Tyrey, and C.B. Hammond. Vasomotor symptoms, serum estrogens, and gonadotropin levels in surgical menopause. Am. J. Obstet. Gynecol. 126:165-169, 1976.

28. Schiff, I., Q. Regestein, D. Tulchinsky, and K.J. Ryan. Effects of estrogens on sleep and psychological state of hypogonadal women. JAMA 242:2405-2407, 1979.

(Also Ref. 1 and 5)

Interestingly, in those women who cannot tolerate estrogen therapy, depomedroxyprogesterone is about as effective as estrogen in lowering gonadotropins and preventing hot flashes.

29. Bullock, J.L, F.M. Massey, and R.D. Gambrell, Jr. Use of medroxyprogesterone acetate to prevent menopausal symptoms. Obstet. Gynecol. 46:165-168, 1975.

When administered double-blind, estrogen therapy also produces an improvement in the sense of well being and in a variety of psychological parameters including relief of depression, slowing of the natural deterioration in perception and memory, and improved sleep patterns (1, 28, 30-32). The magnitude of improvement is difficult to ascertain, but the unanimity of opinion about these changes is impressive.

30. Kantor, H.I., C. Michael, H. Shore, and H. Ludvigson. Administration of estrogens to older women, a psychometric evaluation. Am. J. Obstet. Gynecol. 101:658-661, 1968.

31. Campbell, S., and M. Whitehead. Oestrogen therapy and the menopausal syndrome. Clin. Obstet. Gynecol. 4:31-46, 1977.

32. Fedor-Freybergh, P. The influence of oestrogens as the wellbeing and mental performance in climacteric and postmenopausal women. Acta Obstet. Gynecol. Scand. Supp. 64: 1-61, 1977.

(Also Ref. 1, 2, 8)

B. Urogenital Epithelium and Skin

The atrophic changes in the urogenital organs are reversed or prevented by the administration of estrogens. This includes not only reversal of the degeneration and dryness of the vaginal epithelium but relief of many troublesome lower urinary tract symptoms as well (thought to be due to atrophic changes in the distal urethra).

33. Smith, P.J.B. The effect of estrogens on bladder function in the female. In The management of the menopause and postmenopausal years. S. Campbell, ed. University Park Press, Baltimore, 1976, pp. 291-298.

34. Harrison, R.F. Urethral profile studies on menopausal women and the effects of estrogen treatment. In The management of the menopause and postmenopausal years. S. Campbell, ed. University Park Press, Baltimore, 1976, pp. 299-306.

(Also Ref. 1 and 8)

Estrogens also have measurable effects on incorporation of thymidine and amino acids into skin explants and (in some studies at least) on epidermal thickness. Whether these changes are of clinical significance has never been documented.

35. Rauramo, L. Effect of castration and peroral estradiol valerate and estriol succinate therapy on the epidermis. In The management of the menopause and post-menopausal years. S. Campbell, ed. Universal Park Press, Baltimore, 1976, pp. 253-262.

C. Atherosclerosis, Myocardial Infarction, and Stroke

On the basis of autopsy studies it has been suggested that there is a greater incidence of the manifestations of atherosclerosis in women following castration.

36. Wuest, J.H., Jr., T.J. Dry, and J.E. Edwards. The degree of coronary atherosclerosis in bilaterally oophorectomized women. Circulation 7:801-809, 1953.

37. Rivin, A.U., and S.P. Dimitroff. The incidence and severity of atherosclerosis in estrogen-treated males, and in females with a hypoestrogenic or a hyperestrogenic state. Circulation 9:533-539, 1954.

This relation is more striking the earlier the age of menopause. In a followup of 146 women who had bilateral oophorectomy between the ages of 15 and 30 years as a part of a radical procedure for pelvic inflammatory disease, half died of the complications of atherosclerosis, and in the survivors the incidence of coronary vascular disease was markedly increased.

38. Johansson, B.W., L. Kaij, S. Kullander, H.-C. Lenner, L. Svanberg, and B. Astedt. On some late effects of bilateral oophorectomy in the age range 15-30 years. Acta Obstet. Gynecol. Scand. 54:449-461, 1975.

However, when controlled studies have been performed, it is not clear that either birth control pills or estrogen therapy in post-menopausal women or young oophorectomized women has any significant effect on symptomatic coronary artery disease (such as five year survival rates after myocardial infarction).

39. Ritterband, A.B., I.A. Jaffe, P.M. Densen, J.F. Magagna, and E. Reed. Gonadal function and the development of coronary heart disease. Circulation 27:237-251, 1963.

40. Walters, W.A.W., and Y.L. Lim. Cardiovascular dynamics in women receiving oral contraceptive therapy. Lancet 2:879-881, 1969.

41. Mann, J.I., Vessey, and M. Thorogord. Myocardial infarction in young women with special reference to oral contraceptive practice. Brit. Med. J. 2:241-245, 1975.

42. Beckenhoff, R., W. Vetter, H. Armbruster, J.A. Luetscher, and W. Siegenthaler. Plasma-aldosterone during oral-contraceptive therapy. Lancet I:1218-1219, 1973.

43. Burch, J.C., B.F. Byrd, Jr., and W.K. Vaughn. The effects of long-term estrogen on hysterectomized women. Amer. J. Obstet. Gynecol. 118:778-782, 1974.

44. Mann, J.I., and W.H.W. Inman. Oral contraceptives and death from myocardial infarction. Brit. Med. J. 2:245-248, 1975.

45. Rosenberg, L., B. Armstrong, and H. Jick. Myocardial infarction and estrogen therapy in post-menopausal women. N. Engl. J. Med. 294:1256-1259, 1976.

46. Rosenberg, L., B. Armstrong, and H. Jick. Myocardial infarction and estrogen therapy in premenopausal women. N. Engl. J. Med. 294:1290-1291, 1976.

There is also no clearcut effect -- either protective or harmful -- of estrogen on the risk of stroke.

47. McDowell, F., S. Louis, and E. McDevitt. A clinical trial of premarin in cerebrovascular disease. J. Chron. Dis. 20:679-684, 1967.

48. Pfeffer, R.I., and S. Van Den Noort. Estrogen use and stroke risk in postmenopausal women. Amer. J. Epidemiol. 103:445-456, 1976.

Pharmacological doses of estrogen (5 mg of conjugated estrogen per day) cause an increased number of myocardial infarctions, pulmonary embolisms, and episodes of thrombophlebitis (just as do similar doses in men treated with diethylstilbestrol for carcinoma of the prostate).

49. The Coronary Drug Project Research Group. The coronary drug project. JAMA 214:1303-1313, 1970.

It is of interest that estrogen therapy does lower triglyceride levels and increases the level of plasma α-lipoprotein, and it is conceivable that if given in the proper dose and manner its use could be associated with retardation in the development of atherosclerosis.

50. Oliver, M.F., and G.S. Boyd. Influence of reduction of serum lipids on prognosis of coronary heart-disease. A five-year study using oestrogen. Lancet 2:499-505, 1961.

51. Furman, R.H., P. Alaupovic, and R.P. Howard. Effects of androgens and estrogens on serum lipids and the composition and concentration of serum lipoproteins in normolipemic and hyperlipidemic states. Progr. Biochem. Pharmacol. 2:215-249, 1967.

52. Barrett-Connor, E., V. Brown, J. Turner, M. Austin, M.H. Criqui. Heart disease risk factors and hormone use in postmenopausal women. JAMA 241:2167-2169, 1979.

There is in fact one important paper comparing 301 treated and 309 control patients who were followed in the Duke gynecology clinic in which it is claimed that the incidence of cardiovascular disease was less. This finding runs counter to the prevailing view and requires confirmation. The problem with the study is that it is a retrospective study, and it is not clear exactly how the patients were selected. Its best feature for this particular issue may be that the patients are weighted toward women who were oophorectomized before age 40.

Table II. Cardiovascular disease states by major category and subcategory found in the two groups,* as diagnosed prior to entry ("pre-existing disease") and upon conclusion of the study interval ("new occurrence")

Disease category	*Pre-existing disease*			*New occurrence*		
	NoE	*E*	*p*	*NoE*	*E*	*p*
Cardiovascular disease:						
Stroke syndromes	0	1	N.S.	14	3	<0.05
Coronary artery disease	7	4	N.S.	44	14	<0.01
Thrombophl ceoitis embolus	4	6	N.S.	13	5	N.S.
Congestive heart failure	4	2	N.S.	32	7	<0.001
Arrhythmia	3	1	N.S.	3	3	N.S.
ASCVD	8	5	N.S.	37	7	<0.001
Cardiomegaly	4	1	N.S.	4	0	N.S.
Others	12	24	<0.05	38	21	<0.05
Total diagnoses	42	44	N.S.†	185	60	<0.001†
Total patients	29 (9.4%)	29 (9.6%)	N.S.†	88 (28.5%)	28 (9.3%)	<0.001‡

N.S. = not significant ($p > 0.05$).

*301 patients treated with estrogen; 309 patients without estrogen.

†Significance unchanged after correction for age, race, and duration of follow-up (Mantel-Haenszel).

‡$p < 0.01$ after correction for age, race and duration of follow-up (Mantel-Haenszel). (Ref. 53)

53. Hammond, C.B., F.R. Jelovsek, K.L. Lee, W.T. Creasman, and R.T. Parker. Effects of long-term estrogen replacement therapy. I. Metabolic effects. Am. J. Obstet. Gynecol. 133:525-536, 1979.

In summary, there is no convincing evidence that estrogens in reasonable doses either decrease or increase the risk of manifestations of atherosclerosis.

D. Hypertension

Most of our knowledge about the incidence of hypertension following estrogen administration is extrapolated from studies of patients on estrogen-containing birth control pills. New cases of hypertension develop at a rate of 7 per 1000 per year among users versus one per 1000 per year among non-users. There appears to be an age effect, and the mechanism appears to be an abnormal renin response to an estrogen-induced increase in the synthesis of renin substrate by the liver. In some, the hypertension may be serious, but in general it disappears when the medication is discontinued. There is suggestive evidence that the development of hypertension is less striking in post-menopausal women -- possibly because of the greater incidence of pre-existing hypertension (53), but at the very least blood pressure must be monitored closely in all patients on estrogens. Estrogens should be discontinued if the blood pressure increases.

54. Walters, W.A.W., and Y.L. Lim. Cardiovascular dynamics in women receiving oral contraceptive therapy. Lancet 2:879-881, 1969.

55. Saruta, T., G.A. Saade, and N.M. Kaplan. A possible mechanism for hypertension induced by oral contraceptives. Diminished feedback suppression of renin release. Arch. Intern. Med. 126:621-626, 1970.

56. Crane, M.G., J.J. Harris, and W. Winsor III. Hypertension, oral contraceptive agents, and conjugated estrogens. Ann. Intern. Med. 74:13-21, 1971.

57. Spellacy, W.N., and S.A. Birk. The effect of intrauterine devices, oral contraceptives, estrogens, and progestogens on blood pressure. Amer. J. Obstet. Gynecol. 112:912-919, 1972.

58. Kaplan, N.W. Hypertension with pregnancy and the pill. In Clinical Hypertension, Ch. 11, 2nd Edition, Williams and Wilkins Co., Baltimore, 1978, pp. 325-351.

59. Kaplan, N.W. The complication of the birth control pill. Chapter in Harrison's Update in Internal Medicine, In Press.

E. Thromboembolic Disease

After correcting for other risk determinants, an equal frequency of use of conjugated estrogens was found in patients with and without thromboembolic disease. The annual incidence of thromboembolic events (1.1 per 10,000 women on estrogens) was similar in both groups of post-menopausal women to that in premenopausal women not taking oral contraceptives. It was concluded that there must be some unexplained difference between postmenopausal estrogen users and premenopausal women who take birth control pills.

60. Boston Collaborative Drug Surveillance Program. Surgically confirmed gallbladder disease, venous thromboembolism, and breast tumors in relation to postmenopausal estrogen therapy. N. Engl. J. Med. 290:15-19, 1974.

(Also Ref. 5 and 8)

F. Gallbladder Disease

In the Boston Collaborative Drug Surveillance Program (60) the relative risk for surgically confirmed gallbladder disease in otherwise healthy women taking conjugated estrogens was 2.5 (22 versus 9 per 10,000 patients). This increased incidence of symptomatic gallstones may be the consequence of the fact that estrogen therapy causes gallbladder bile to become more saturated with cholesterol, thus predisposing to development of cholesterol stones.

61. Bennion, L.J., R.L. Ginsberg, M.B. Garnick, and P.H. Bennett. Effects of oral contraceptives on the gallbladder bile of normal women. N. Engl. J. Med. 294:189-192, 1976.

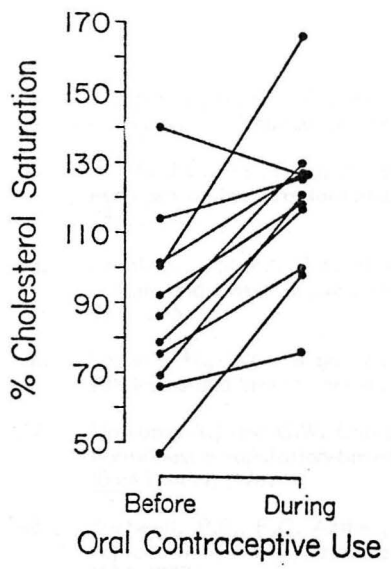


Fig. 18. Saturation of Gallbladder Bile with Cholesterol in 11 Women before and Then during Daily Ingestion of Oral Contraceptives.

Per cent saturation was calculated according to the maximal cholesterol solubility limits of Hegardt and Dam[17] and Holzbach et al.[18] Subjects had been taking oral contraceptives for an average of 7.5 weeks when the samples during treatment were taken. Bile was significantly less saturated before treatment during normal menstrual cycles than during use of contraceptive steroids ($P < 0.01$). (Ref. 61)

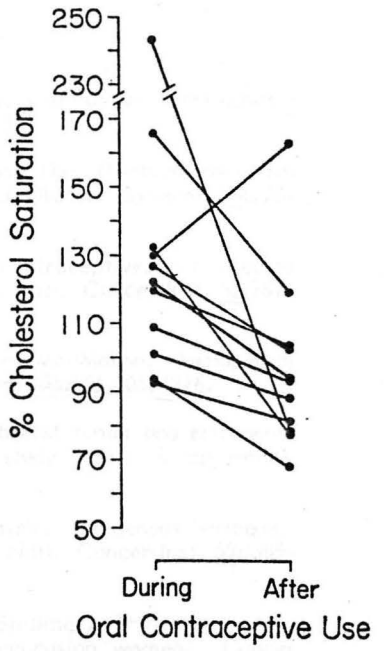


Fig. 19. Saturation of Gallbladder Bile with Cholesterol in 11 Women during Treatment with Oral Contraceptives and Then after Cessation of Treatment and Resumption of Normal Menstrual Periods.

Samples during use of oral contraceptives were obtained after the subjects had been taking the medication in a routine manner for an average of 37 months. Samples after resumption of normal menstrual function were taken an average of 14 weeks after cessation of medication. Bile was significantly more saturated during contraceptive steroid treatment than afterward ($P < 0.01$). (Ref. 61)

G. Benign and Malignant Breast Tumors

In some studies it has been concluded that long term estrogen therapy (> 15 years) may be associated with a slight increase in relative risk for cancer (1.3 to 2.0). However in careful studies in which other known predisposing features were factored out and patients were matched for age, parity, weight, previous hysterectomy, and prior breast disease, no relation has been shown between breast cancer and estrogen therapy. Nor does the prior estrogen therapy appear to influence the mortality of breast cancer (60, 68-70). Thus, it appears that estrogen therapy does not increase the incidence or severity of breast carcinoma. Most authors feel nevertheless that estrogens should not be started if pre-existing breast disease is present and should be discontinued if benign or malignant breast disease develops.

62. Burch, J.C., and B.F. Byrd, Jr. Effects of long-term administration of estrogen on the occurrence of mammary cancer in women. Am. Surg. 174:414-418, 1971.

63. MacMahon, B., P. Cole, and J. Brown. Etiology of human breast cancer: a review. J. Natl. Cancer Inst. 50:21-42, 1973.

64. Burch, J.C., B.F. Byrd, Jr., and W.K. Vaughn. The effects of long-term estrogen on hysterectomized women. Am. J. Obstet. Gynecol. 118:778-782, 1974.

65. Fasal, E., and R.S. Paffenbarger, Jr. Oral contraceptives as related to cancer and benign lesions of the breast. J. Natl. Cancer Inst. 55:767-773, 1975.

66. Hoover, R., L.A. Gray, Sr., P. Cole, and B. MacMahon. Menopausal estrogens and breast cancer. N. Engl. J. Med. 295:401-405, 1976.

67. Nomura, A., and G.W. Comstock. Benign breast tumor and estrogenic hormones: a population-based retrospective study. Amer. J. Epidemiol. 103:439-444, 1976.

68. Sartwell, P.E., F.G. Arthes, and J.A. Tonascia. Exogenous hormones, reproductive history and breast cancer. J. Natl. Cancer Inst. 59:1589-1592, 1977.

69. Wynder, E.L., F.A. MacCornack, and S.D. Stellman. The epidemiology of breast cancer in 785 United States caucasian women. Cancer 41:2341-2354, 1978.

70. Ross, R.K., A. Paganini-Hill, V.R. Gerkins, T.M. Mack, R. Pfeffer, M. Arthur, B.E. Henderson. A case control study of menopausal estrogen therapy and breast cancer. JAMA 243:1635-1639, 1980.

H. Endometrial Carcinoma

Beginning in 1975, an enormous body of information has been assembled to suggest that an increase in the frequency of endometrial cancer was occurring in the U.S. and that this epidemic is due to estrogen treatment after the menopause. It has been known for some years that the constitutional features associated with endometrial carcinoma in postmenopausal women (aging and obesity) are those that result in enhanced production of estrogen at extraglandular sites. In a variety of case-control studies done at different centers and in different parts of the country, it is clear that the relative risk of endometrial cancer in postmenopausal women taking estrogens, irrespective of dose on duration, ranges between 6 and 8, that the relative risk goes up with the duration of treatment (to about 11.5-15 fold after 10 years or more of therapy), and in most studies that the risk rises with larger doses of estrogens (up to 12.7 fold for 1.25 mg tablets of conjugated estrogens).

Table III Annual Incidence Rates* of Cancer of the Uterine Corpus in Selected Areas of the United States, According to Year, 1969-73.

Area	Incidence Rates				
	1969	1970	1971	1972	1973
Connecticut†	18.0	19.2	21.8	23.0	25.9
Hawaii	26.6	21.1	23.8	23.2	35.6
Los Angeles County†	‖	‖	‖	34.6	33.5
New Mexico	10.2	13.0	16.8	20.7	17.9
Oregon†·§·¶	27.9	24.2	30.4	36.2	‖
San Francisco Bay area	24.9	27.9	30.9	35.2	40.3
Seattle–Tacoma	‖	‖	‖	‖	45.6**
Utah†	‖	19.3	21.6	29.9	23.9

*Per 100,000 women, standardized to age distribution of the 1970 US population; excludes adenocarcinoma in situ unless otherwise indicated.

†Rates include those for in situ cancers.

‡Whites only (excluding Mexican-Americans).

§Inter-censal estimates of population size not available for this area; 1970 population used as basis for rates in all yr.

¶Incidence of uterine adenocarcinoma (both corpus & cervix).

‖Data unavailable for that yr.

**Annual rate estimated from data from 1st 6 mo of 1974. (Ref. 73)

Table IV Observed versus expected* malignancies for the uterine corpus (adenocarcinoma of the endometrium), the breast, and all sites listed by the two study groups and by race. These data are compared to the expected incidences as documented by the Third National Cancer Survey for the Southeastern Region and are also age-matched

	No E		E	
Site of malignancy	*White*	*Nonwhite*	*White*	*Nonwhite*
Uterine corpus:†				
Expected	1.85	0.60	1.18	0.02
Observed	2	1	11	0
Risk ratio‡	1.1	–	9.3	–
95% Confidence interval	0.1-3.9		4.7-16.7	
Breast:				
Expected	5.69	1.90	3.77	0.09
Observed	3	1	4	0
Risk ratio	0.5	0.5	1.06	–
95% Confidence interval	0.1-1.5	0.0-2.9	0.3-2.7	
All Sites:†				
Expected	20.99	8.75	12.5	0.31
Observed	17	9	24	1
Risk ratio	0.8	1.03	1.92	–
95% Confidence interval	0.5-1.3	0.5-2.0	1.2-2.9	

*Calculated from age/race incidence data presented in the Third National Cancer Survey.

†Carcinoma in situ not included.

‡Risk ratio = observed/expected. (Ref. 81)

71. Smith, D.C., R. Prentice, D.J. Thompson, and W.L. Herrmann. Association of exogenous estrogen and endometrial carcinoma. N. Engl. J. Med. 293:1164-1167, 1975.

72. Ziel, H.K., and W.D. Finkle. Increased risk of endometrial carcinoma among users of conjugated estrogens. N. Engl. J. Med. 293:1167-1170, 1975.

73. Weiss, N.S., D.R. Szekeley, and D.F. Austin. Increasing incidence of endometrial cancer in the United States. N. Engl. J. Med. 294:1259-1262, 1976.

74. Ziel, H.K., and W.D. Finkle. Association of estrone with the development of endometrial carcinoma. Amer. J. Obstet. Gynecol. 124:735-740, 1976.

75. Mack, T.M., M.C. Pike, B.E. Henderson, R.I. Pfeffer, V.R. Gerkins, M. Arthur, and S.E. Brown. Estrogens and endometrial cancer in a retirement community. N. Engl. J. Med. 294:1262-1267, 1976.

76. Edwards, R.G., Ed. Doubts about oestrogen therapy in postmenopausal women. Res. Reproduction 8:1-2, 1976.

77. Sartwell, P.E. Estrogen replacement therapy and endometrial carcinoma epidemiologic evidence. Clin. Obstet. Gynecol. 19:817-823, 1976.

78. Gray, L.A., W.M. Christopherson, and R.N. Hoover. Estrogens and endometrial carcinoma. Obstet. Gynecol. 49:385-389, 1977.

79. Lauritzen, C. Oestrogens and endometrial cancer: a point of view. Clin. Obstet. Gynecol. 4:145-167, 1977.

80. Antunes, C.M.F., P.D. Stolley, N.B. Rosenshein, J.L. Davies, J.A. Tonascia, C. Brown, L. Burnett, A. Rutledge, M. Pokempner, and R. Garcia. Endometrial cancer and estrogen use. N. Engl. J. Med. 300:9-13, 1979.

81. Hammond, C.B., F.R. Jelovsek, K.L. Lee, W.T. Creasman, and R.T. Parker. Effects of long-term estrogen replacement therapy II. Neoplasia. Am. J. Obstet. Gynecol. 133:537-547, 1979.

82. McDonald, T.W. J.F. Annegers, W.M. O'Fallon, M.B. Dockerty, G.D. Malkasian, and L.T. Kurland. Exogenous estrogen and endometrial carcinoma: case control and incidence study. Am. J. Obstet. Gynecol. 127:572-580, 1977.

83. Weiss, N.S., D.R. Szekely, D.R. English, A.I. Schweid. Endometrial cancer in relation to patterns of menopausal estrogen use. JAMA 242:261-264, 1979.

84. Jick, H., R.N. Watkins, J.R. Hunter, B.J. Dinan, S. Madsen, K.J. Rothman, A.M. Walker. Replacement estrogens and endometrial cancer. N. Engl. J. Med. 300:218-222, 1979.

Both the increased frequency and association of endometrial carcinoma with estrogen administration have also been observed in Canada (85) but not in Finland (86). Rauramo attributes the lack of increased prevalence in Finland to the fact that much smaller doses of estrogens are prescribed there as compared to the U.S. and Canada.

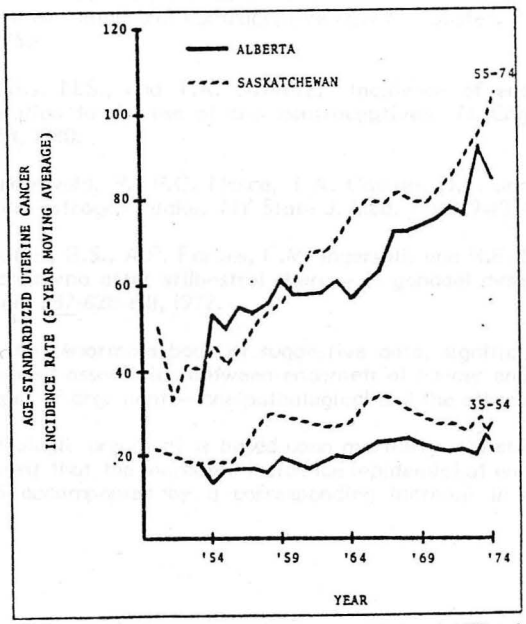


Fig. 20 —Incidence of uterine cancer for Alberta (1953 through 1974) and Saskatchewan (1950 through 1974). (Ref. 85)

85. Wigle, D.T., M. Grace, and E.S.O. Smith. Estrogen use and cancer of the uterine corpus in Alberta. Can. Med. Assoc. 118:1276-1278, 1978.

86. Rauramo, L. Estrogen replacement therapy and endometrial carcinoma. Front. Hormone Res. 5:117-125, 1978.

There is no doubt that estrogen administration to susceptible animals such as the rabbit can produce endometrial cancer (87). The preponderance of data indicate that the carcinogenic activity is related to estrogenic potency directly and not to some unique property of the drugs akin to the mechanisms believed to be responsible for most instances of chemical carcinogenesis (88).

87. Meissner, W.A., S.C. Sommers, and G. Sherman. Endometrial hyperplasia, endometrail carcinoma, and endometriosis produced experimentally by estrogen. Cancer 10:500-509, 1957.

88. Shellenberger, T.E., and D.M. Sheehan. Estrogens, estrogen receptors, and biological responses in experimental animals. Front. Hormone Res. 5:203-219, 1978.

Furthermore, in selected patient groups the relative risk of endometrial cancer following estrogen therapy appears to be even greater. Virtually all young women who develop endometrial carcinoma are on oral contraceptives (89), and the risk appears to be much greater for specific preparations (90). Exposure to diethylsterol in utero has resulted in 22 instances of carcinoma of the vagina and cervix in New York State alone (91), and it appears that there is a striking increased risk of endometrial carcinoma in women with gonadal dysgenesis treated for 5 or more years with estrogens (92).

89. Silverberg, S.G., and E.L. Makowski. Endometrial carcinoma in young women taking oral contraceptive agents. Obstet. Gynecol. 46:503-506, 1975.

90. Weiss, N.S., and T.A. Sayvetz. Incidence of endometrial cancer in relation to the use of oral contraceptives. N. Engl. J. Med. 302:551-554, 1980.

91. Greenwald, P., P.C. Nasca, T.A. Caputo, D.T. Janerich. Cancer risk from estrogen intake. NY State J. Med. 77:1069-1074, 1977.

92. Cutler, B.S., A.P. Forbes, F.M. Ingersoll, and R.E. Scully. Endometrial carcinoma after stilbestrol therapy in gonadal dysgenesis. N. Engl. J. Med. 287:628-631, 1972.

Despite this enormous body of suggestive data, significant doubt has arisen about the apparent association between endometrial cancer and estrogen ingestion, due to two types of argument -- one pathological and the other epidemiologic.

The pathologic argument is based upon mortality statistics. All statisticians are in agreement that the increased incidence (epidemic) of endometrial carcinoma has not been accompanied by a corresponding increase in mortality from the

disease (93). This has suggested to many students, since endometrial proliferation can be difficult to distinguish from low grade endometrial malignancy by histological criteria, that the increased prevalence is due to overdiagnosis and not a true increase in incidence. Another possibility is that diagnosis is earlier in estrogen users (because of bleeding) and that the cause-effect association seems to be greater for the least aggressive malignant lesions (93). With this problem in mind, two of the original cause-effect series have been rereviewed by independent pathologists who are in agreement that any histological overinterpretation is slight and that the original estimates are fundamentally sound (94, 95). Furthermore, the counter argument has been advanced that the mortality rates for endometrial cancer in this country should be falling significantly due to the increase in the number of hysterectomies performed between 1965 and 1973 (60% increase), which has altered the population at risk for uterine malignancy whereas published incidence rates do not correct for this phenomenon. Using such corrections the mortality from endometrial carcinoma appears to be rising (96). Nevertheless, it appears clear that the current increased diagnostic frequency will not be followed by a corresponding increase in absolute mortality rates.

93. Weiss, N.S. Noncontraceptive estrogens and abnormalities of endometrial proliferation. Ann. Int. Med. 88:410-412, 1978.

94. Szekely, D.R., N.S. Weiss, and A.I. Schweid. Incidence of endometrial carcinoma in King County, Washington: A standardized histological review. J. Nat. Cancer Inst. 60:985-987, 1978.

95. Gordon, J., J.W. Reagan, W.D. Finkle, and H.K. Ziel. Estrogen and endometrial carcinoma: an independent pathologic review supporting original risk estimate. N. Engl. J. Med. 297:570-571, 1977.

96. Lyon, J.L., and J.W. Gardner. The rising frequency of hysterectomy: Its effect on uterine cancer rates. Am. J. Epidemiol. 105:439-443, 1977.

The epidemiologic attack upon the causative role of estrogens has come largely from Feinstein and Horwitz and is based upon objections to the use of case controls in retrospective studies. In this instance, they argue that the fact that many estrogen users bleed and consequently are subjected to dilatation and curettage means that endometrial cancer is diagnosed earlier and more frequently than in non users. They argue that if controls are derived from a single group of patients who all received the same diagnostic procedure (the so called trohoc technique) such bias is removed or prevented. Thus, among demographically matched cases and controls who all received D and C because of bleeding, the increased risk was 1.3 to 2 rather than 7.9-8.3 when determined by the usual case control technique. They have concluded that no association has been documented between exogenous estrogens and cancer of the endometrium. [From my standpoint, this is a meaningless argument because postmenopausal bleeding from all causes is known to be associated with a high incidence of endometrail carcinoma. No one has ever maintained that estrogen administration was a more important predisposing factor for endometrial carcinoma than enhanced endogenous estrogen production due to obesity, for example.]

97. Feinstein, A.R., and R.I. Horwitz. A critique of the statistical evidence associating estrogens with endometrial cancer. Cancer Res. 38:4001-4005, 1978.

98. Horwitz, R.I., and A.R. Feinstein. Alternative analytic methods for case-control studies of estrogens and endometrial carcinoma. N. Engl. J. Med. 299:1089-1094, 1978.

99. Horwitz, R.I., and A.R. Feinstein. Methodologic standards and contradictory results in case-control research. Am. J. Med. 66:556-564, 1979.

Most epidemiologists concede to Feinstein that certain ascertainment biases may have falsely enhanced the association between cancer and exogenous estrogens (100-102). The review by Cramer and Knapp (101) from the Harvard School of Public Health is the most balanced statement of the problem available. Their conclusions are as follows:

1. There has been an increase in the incidence of endometrial carcinoma associated with increased estrogen sales. The increase appears to be confined to localized disease. No change in mortality of endometrial cancer has been seen.

2. Etiologic studies have established an association between estrogens and endometrial cancer. Several biases may have falsely increased the magnitude of this association but are unlikely to have produced an entirely spurious one.

3. The risk ratio for estrogen and endometrial cancer increased with greater dosage, longer usage, and, probably, use in a continuous manner.

4. The association is strongest for local disease and weakest for more invasive disease, implying that the etiology of the more dangerous lesions is largely unaccounted for by estrogen use.

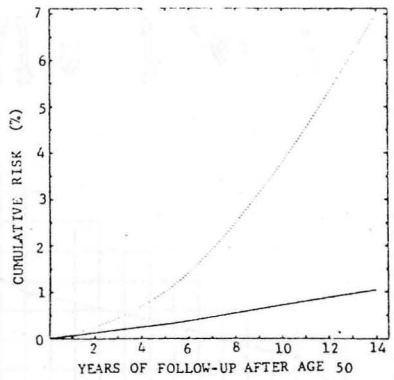


Figure 21 Comparison of cumulative risk for endometrial cancer of a 50-year-old woman followed for 15 years without estrogen therapy (solid line) and with estrogen therapy (interrupted line) (Ref. 101)

100. Sartwell, P.E. Estrogen replacement therapy and endometrial carcinoma: epidemiologic evidence. Clin. Obstet. Gynecol. 19:817-823, 1976.

101. Cramer, D.W., and R.C. Knapp. Review of epidemiologic studies of endometrial cancer and exogenous estrogen. Obstet. Gynecol. 54:521-526, 1979.

102. Jick, H. Estrogens and increased endometrial cancer. Fact or artifact? CA - A Cancer Journal 29:250-251, 1979.

It is essential that another aspect of this issue be kept in perspective. If the cumulative risk to the non-estrogen user is 1% after 15 years and 7% to the estrogen user after the same period of time and if this increased risk were associated with greater mortality, it could still be possible that the net effect could be a prolongation of life if the benefits outweighed the disadvantages. The real issue is whether the therapy has a salutary effect on osteoporosis and its associated morbidity and mortality.

I. Osteoporosis

Osteoporosis is one of the dread afflictions of aging. The problem is not bone loss per se but fracture. Approximately a fourth of aging women and a tenth of aging men sustain at least one cervical or trochanteric fracture between the ages of 60 and 90. In women cervical failure is twice as common as hip fracture whereas in men these are equally common.

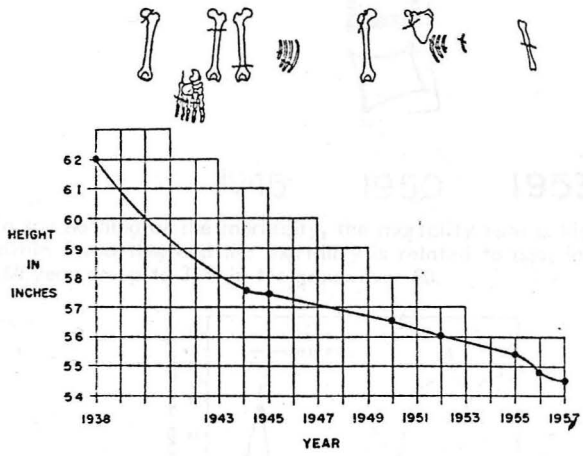


Fig. 22 — The clinical course of a patient with idiopathic osteoporosis. Above are indicated the sites of fractures at the dates indicated below. Also shown are the recorded heights of this patient over the 19 years of progressive osteoporosis. The urinary calcium excretion (not shown) was high during the early course of osteoporosis but subsequently was not dramatically increased.

(Ref. 17)

Fig. 23 —Superimposed tracings of the vertebral outlines as seen in radiographs of 1945, 1950, and 1953 in a patient (same as Fig. 1) with idiopathic osteoporosis. The lumbar vertebrae have been aligned. The radiographic technique and posture may not have been identical in the three radiographs. Note the increasing kyphosis and loss of height equivalent to at least two vertebral bodies, whereas the changes in individual vertebrae were relatively inapparent. (Ref. 17)

1945 1950 1953

To say nothing of the morbidity, the mortality rate is high. Overall, 17% are dead within 3 months, and the mortality is related to age, increasing from 7% in the 60-64 year group to 33% in the group over 80.

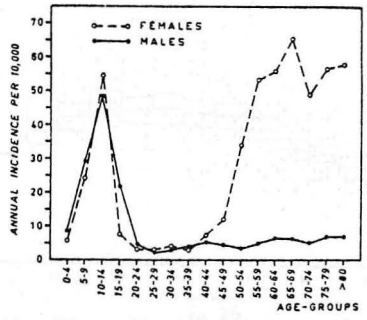


Fig 24 Incidence of fracture of the wrist shows the increase in older women. [Reprinted from Alffram et al. (4), J Bone Joint Surg 44A:105, 1962.] (Ref. 103)

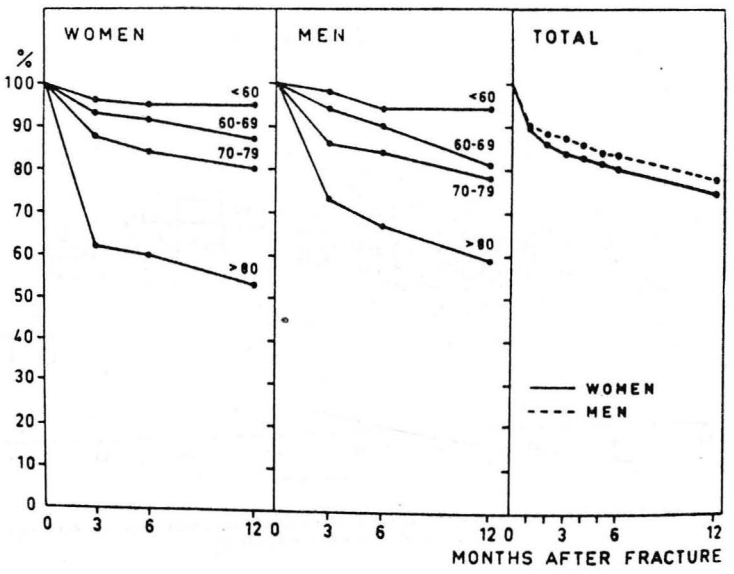


Figure25 Survival rates 3, 6, and 12 months after hip fracture according to age and sex. [From Alffram (103).]

These fractures are the result of the interplay of three factors --trauma, disease, and skeletal fragility associated with aging. Disease states associated with increased incidence include diabetes, previous radiotherapy, paralysis, arthritis, hyperthyroidism, and gastric surgery. It is not surprising that these predisposing factors and trauma are involved. The question is whether hormonal deprivation is the cause of increased bone fragility with advancing age. In the original Albright formulation, the thesis was advanced that osteoporosis (defined by him as atrophy of bone matrix) is the result of estrogen deprivation in the postmenopausal state, that premature or artificial menopause is associated with worsening of osteoporosis, and that osteoporosis can be prevented by estrogen administration — a view that is widely held.

In fact, however, the menopause is probably not central to the problem for three reasons. One, the decline in bone density in women commences before the menopause (104, 105).

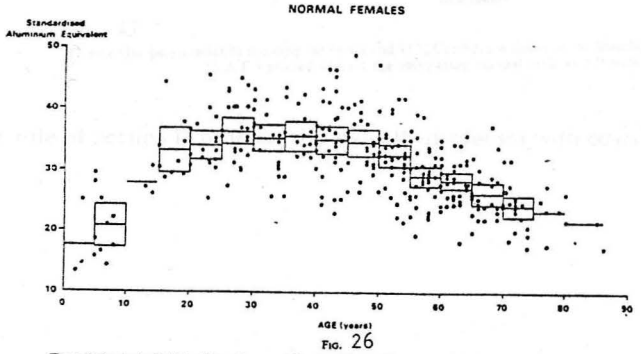


FIG. 26
The variation in the S.A.E. with age in normal female subjects. The mean and two standard error range within 5 year age groups is illustrated. (Ref. 104)

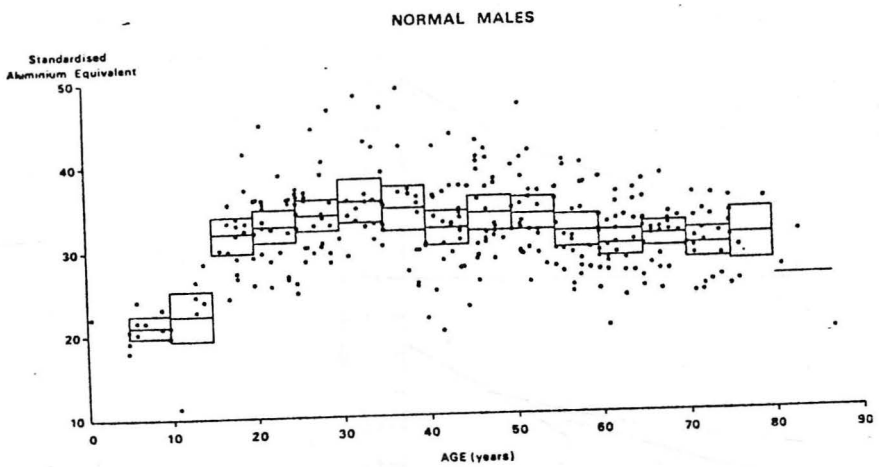


Fig. 27

The variation in the S.A.E. with age in normal male subjects. The mean and two standard error range within 5 year age groups is illustrated. (Ref. 104)

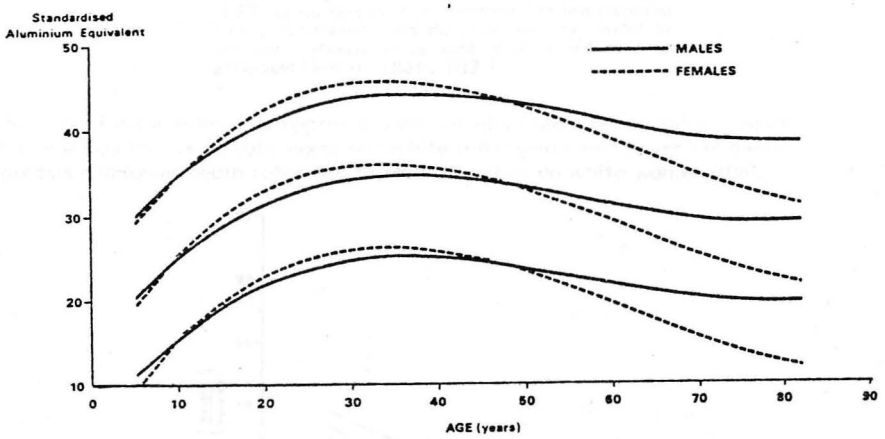


Fig. 27

Third order polynomial fit showing the mean and 95% Confidence limits of the Standardised Aluminium Equivalent (S.A.E.) plotted against age comparing normal male and female subjects. (Ref. 104)

Two, the rate of decline in bone density actually decreases with advancing age (106, 107).

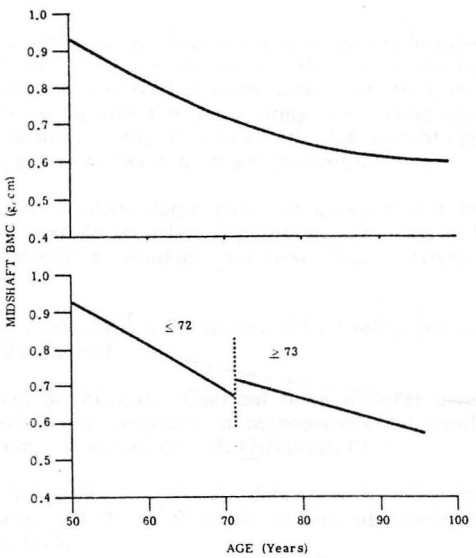


FIGURE 28 Cross-sectional measurements on 530 women. (Top) The regression curve of bone mineral measurements of 530 women aged 50–96 yr. (Bottom) The two regression lines were obtained when the population was divided by age into a younger group, aged 50–72 yr and an older group aged 73–96 yr. (Ref. 107)

Three, the loss of bone density is approximately equal in both sexes and in blacks and whites whereas blacks of both sexes and white men have much lower incidence of osteoporosis and lower death rates due to fractures than do white women (108).

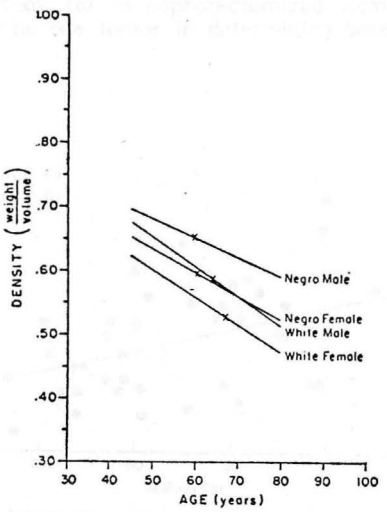


Fig. 29. Regression lines based on combined slopes of ten series of bones in each sex-race group. The mean density of the ten series is indicated by x at the mean age of each group. (Ref. 103)

According to this view, the factor that predisposes white women to osteoporosis is the fact that their bone density is lower to begin with. Since the incidence of vertebral fractures is inversely proportional to bone mineral content, the lower the bone mineral content before menopause the more likely the normal bone loss will result in osteoporosis and fracture. Thus, the loss of mineral content appears to be the result primarily of aging per se rather than the menopause.

103. Alffram, P.-A. An epidemiologic study of cervical and trochanteric fractures of the femur in an urban population. Analysis of 1,664 cases with special reference to etiologic factors. Acta Orthopaed. Scand. Suppl. 65:109, 1964.

104. Smith, D.A., J.B. Anderson, J. Shimmins, C.F. Speirs, and E. Barnett. Clin. Radiol. 20:23-31, 1969.

105. Meema, H.E., and S. Meema. Cortical bone mineral density versus cortical thickness in the diagnosis of osteoporosis: a roentgenologic-densitometric study. J. Amer. Geriat. 17:120-141, 1969.

106. Smith, D.A., M.R.A. Khairi, and C.C. Johnston, Jr. The loss of bone mineral with aging and its relationship to risk of fracture. J. Clin. Invest. 56:311-318, 1975.

107. Smith, D.M., M.R.A. Khairi, J. Norton, and C.C. Johnston, Jr. Age and activity effects on rate of bone mineral loss. J. Clin. Invest. 58:716-721, 1976.

108. Trotter, M., G.E. Broman, and R.R. Peterson. Densities of bones of white and Negro skeletons. J. Bone Joint Surg. 42A:50-58, 1960.

Furthermore, no clearcut endocrine differences have been documented between women with and without osteoporosis (109). [There is a relation between plasma E_2 and the percentage of body fat in oophorectomized women, suggesting that estrogen production may be one factor in determining bone loss following the menopause (110).]

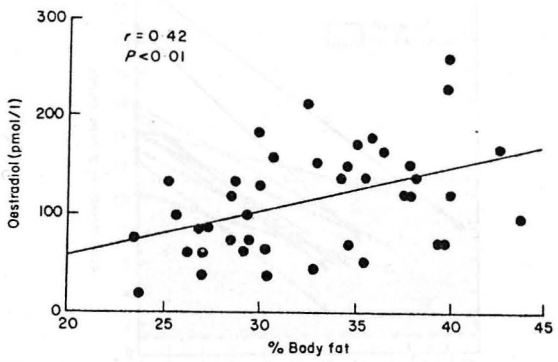


Fig. 30 The relationship between plasma oestradiol levels (pmol/l) and the percentage of body fat in oophorectomized women. Line fitted by method of least squares. (Ref. 110)

Despite the evidence that osteoporosis is not primarily a disease of estrogen deprivation, every investigator who has addressed the issue is in agreement that early oophorectomy (before age 45) is associated with increased prevalence (and symptoms) of osteoporosis (38, 111).

109. Riggs, B.L. R.J. Ryan, H.W. Wahner, N.-S. Jiang, and V.R. Mattox. Serum concentrations of estrogen, testosterone and gonadotropins in osteoporotic and noneosteoporotic postmenopausal women. J. Clin. Endocrinol. Metabl. 36:1097-1099, 1973.

110. Lindsay, R., J.R.T. Coutts, and D.M. Hart. The effect of endogenous oestrogen on plasma and urinary calcium and phosphate in oophorectomized women. Clin. Endocrinol. 6:87-93, 1977.

111. Aitken, J.M., D.M. Hart, J.B. Anderson, R. Lindsay, D.A. Smith, and C.F. Speirs. Osteoporosis after oophorectomy for non-malignant disease in premenopausal women. Brit. Med. J. 2:325-328, 1973.

(Also Ref 38)

The question of the role of menopause per se in the increased bone fragility of aging women is irrelevant, of course, if estrogen therapy does in fact prevent osteoporosis. Albright in reference 16 and subsequently in his book The Parathyroid Glands and Metabolic Bone Disease, 1948, reported that estrogen therapy improves calcium balance in patients with osteoporosis and actually prevents development of the disorder. The weakness of the data upon which this concept was based became apparent when the data from Albright's unit was published in detail by Henneman and Wallach (17), namely young women with artificially induced menopause were being compared with older women many years after natural menopause.

When balance studies are done in which comparable groups are compared it is apparent that the major effect of estrogen in postmenopausal osteoporosis is a short-term decrease in the rate of bone resorption and that this favorable effect is negated after long-term treatment by a secondary decrease in bone formation and increase in parathyroid hormone values. Thus, as assessed by balance techniques, the positive effect of estrogen is of limited duration (112).

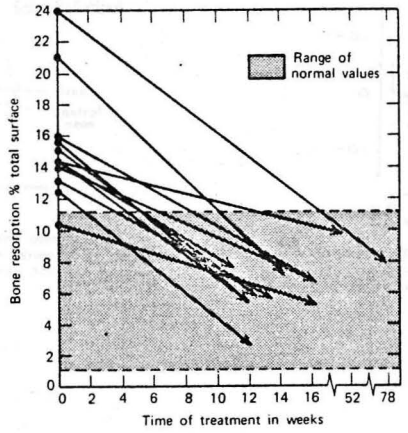


Figure 31 Effect of estrogen on bone resorption in 11 menopausal women. [From Riggs et al. Used with copyright permission from The American Society of Clinical Investigation.] (Ref. 112)

112. Riggs, B.L., J. Jowsey, R.S. Goldsmith, P.J. Kelly, D.L. Hoffman, and C.D. Arnaud. Short- and long-term effects of estrogen and synthetic anabolic hormone in postmenopausal osteoporosis. J. Clin. Invest. 51:1659-1663, 1972.

The impressive fact remains that several groups have reported clinical studies in which it is claimed that estrogen treatment prevents both osteoporosis and fracture. For example, Gordan followed 220 women for 1868 patient years and reported that the incidence of vertebral fracture fell from 40/1000 patient years to 3/1000 patient years in women taking 125 mg premarin per day (114, 115). Burch et al reported that the number of fractures of the radius fell from 2.7 to 0.8 per 1000 patient years (117). Virtually all these studies suffer from common faults -- poor or missing controls, weighing of the groups toward young women with surgical menopause, and a lack of improvement in trochanteric or vertebral fractures (the real source of morbidity and mortality).

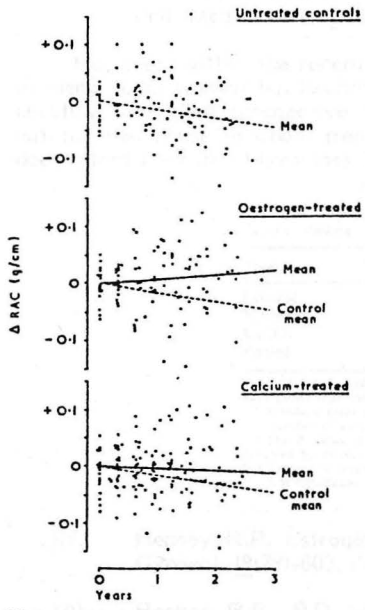


Fig. 32 Sequential changes in mineral content of radius (ΔRAC) in postmenopausal women observed by densitometry at four- to six-month intervals over two years or more. (Ref. 118)

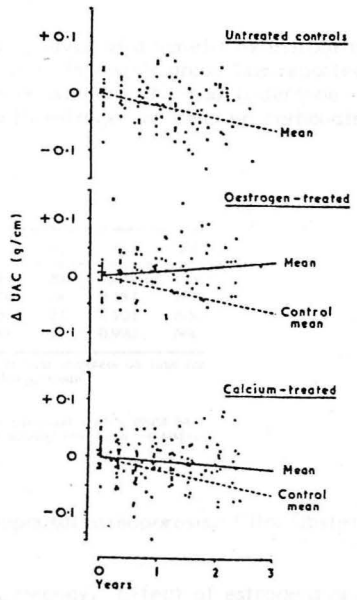


Fig. 33 Sequential changes in mineral content of ulna (ΔUAC) in postmenopausal women observed by densitometry at four- to six-month intervals over two years or more. (Ref. 118)

113. Davis, M.E., L.H. Lanzl, and A.B. Cox. Detection, prevention and retardation of menopausal osteoporosis. Obstet. Gynecol. 36:187-198, 1970.

114. Gordan, G.S., J. Picchi, and B.S. Roof. Antifracture efficacy of long-term estrogens for osteoporosis. Trans. Assoc. Am. Physicians 86:326-332, 1973.

115. Gordan, G.S. Postmenopausal osteoporosis: cause, prevention, and treatment. Clin. Obstet. Gynecol. 4:169-178, 1977.

116. Aitken, J.M., D.M. Hart, and R. Lindsay. Oestrogen replacement therapy for prevention of osteoporosis after oophorectomy. Brit. Med. J. 3:515-518, 1973.

117. Burch, J.C., B.F. Byrd, and W.K. Vaughn. The effects of long term estrogen on hysterectomized women. Amer. J. Obstet. Gynecol. 118:778, 1974.

118. Horsman, A., J.C. Gallagher, M. Simpson, and B.E.C. Nordin. Prospective trial of oestrogen and calcium in postmenopausal women. Brit. Med. Journal 2:789-792, 1977.

However, within the recent past, the data in favor of a benefit by estrogens in menopausal women has become more convincing. Heaney's group has reported careful, controlled prospective studies in elderly women who had undergone a natural menopause in whom treatment either with estrogen or calcium carbonate does retard the rate of bone loss (119, 120).

Table V Radiogrammetric Summary

Treatment	Mean*	SEM†	n‡	t§	P§
Control	−0.01247	0.00374	20	3.334	0.01
Hormone	−0.00154	0.00319	18	0.483	NS¶
$CaCO_3$	−0.00229	0.00254	22	0.902	NS
Pooled	−0.00196	0.00198	40	0.990	NS

* The mean slope of the regression of cortical thickness on time for each group expressed as mm of cortical thickness/month.
† Standard error of the mean.
‡ Number of subjects.
§ The P value is the probability that the particular t score could have occurred by chance if the mean slope were actually zero given the respective degrees of freedom.
¶ Not significant. (Ref. 120)

119. Heaney, R.P. Estrogens and postmenopausal osteoporosis. Clin. Obstet. Gynecol. 19:791-803, 1976.

120. Recker, R.R., P.D. Saville, and R.P. Heaney. Effect of estrogens and calcium carbonate on bone loss in postmenopausal women. Ann. Int. Med. 87:649-655, 1977.

In prospective studies Lindsay and coworkers have similarly reported that estrogen treatment prevents loss in bone mineral, even when started years after the onset of a natural menopause (121, 122), and Meema and Meema have reported similar results (123, 124).

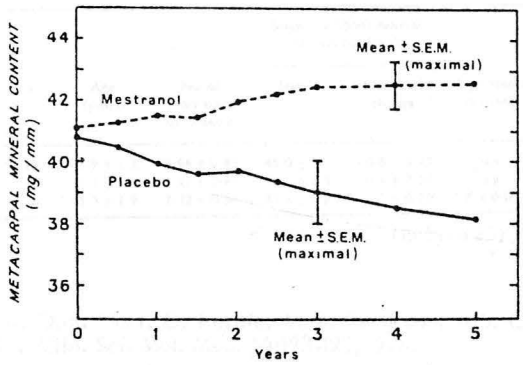


Fig. 34 Mean metacarpal mineral content during 5-year follow-up after bilateral oophorectomy. [From Lindsay et al (12), Lancet 1:1038, 1976. Used by permission.] (Ref. 121)

121. Lindsay, R., D.M. Hart, J.M. Aitken, E.B. MacDonald, J.B. Anderson, and A.C. Clarke. Long-term prevention of postmenopausal osteoporosis by oestrogen. Evidence for an increased bone mass after delayed onset of oestrogen treatment. Lancet I:1038-1040, 1976.

122. Lindsay, R., and D.M. Hart. Oestrogens and post-menopausal bone loss. Scott. Med. J. 23:13-18, 1978.

123. Meema, H.E., and S. Meema. Prevention of postmenopausal osteoporosis by hormone treatment of the menopause. Can. Med. Assoc. J. 99:248-251, 1968.

124. Meema, S., M.L. Bunker, and H.E. Meema. Preventive effect of estrogen on postmenopausal bone loss. Arch. Int. Med. 135:1436-1440, 1975.

Also impressive although not truly prospective) are the data from Duke that indicate that the number of new fractures is cut in half by estrogen treatment (again it is not clear that this is vertebral or trochanteric fracture) (53).

Table VI Other disease states by major category and subcategory found in the two groups, as diagnosed prior to entry ("pre-existing disease") and upon conclusion of the study interval ("new occurrence")

	Pre-existing disease					*New occurrence*				
	NoE		*E*			*NoE*		*E*		
Disease category	*No.*	*%*	*No.*	*%*	*p*	*No.*	*%*	*No.*	*%*	*p*
Hypertension	86	27.8	49	16.3	<0.001	98	31.7	49	16.3	<0.001*
Diabetes mellitus	14	4.5	14	4.6	N.S.	35	11.3	10	3.3	<0.001†
Fractures	56	18.1	37	12.3	<0.05	49	15.9	26	8.6	<0.01
Osteoporosis	33	10.7	44	14.6	N.S.	79	25.6	17	5.6	<0.001‡
Degenerative disc	2	0.6	8	2.7	N.S.	8	2.6	10	3.3	N.S.‡

N.S. = Not significant ($p > 0.05$).

*$p < 0.05$ after correction for age, race, and duration of follow-up (Mantel-Haenszel).

†$p > 0.05$ (N.S.) after correction for weight (Mantel-Haenszel).

‡Significance unchanged after correction for age, race, and duration of follow-up (Mantel-Haenszel). (Ref. 53)

Lindsay's data suggest, furthermore, that progestagens may be as effective as estrogen in this receptor (125).

Table VII *Initial bone mineral content and change during treatment*
Values are given as mean ± SE; *n* = number of patients. n.s., Not significant

Treatment group	*n*	Age (years)	No. of years since menopause	Metacarpal bone mineral content (mg/mm)		
				Initial	Mean yearly change	Significance of change
Mestranol	10	46·9 ± 2·3	2·94 ± 0·82	45·0 ± 1·6	+0·6 ± 0·43	n.s.
Gestronol	10	45·1 ± 2·4	2·55 ± 0·81	44·1 ± 1·4	+0·1 ± 0·57	n.s.
Placebo	10	45·3 ± 1·9	2·72 ± 0·86	45·2 ± 1·9	−1·7 ± 0·50	$P < 0.01$

(Ref. 125)

125. Lindsay, R., D.M. Hart, D. Purdie, M.M. Ferguson, A.S. Clark, and A. Kraszewski. Clin. Sci. Mol. Med. 54:193-195, 1978.

Although none of these studies are definitive, they are impressive nevertheless and provide a general optimism that estrogen therapy does in fact have a role to play in prevention of osteoporosis.

126. Marx, J.L. Osteoporosis: New help for thinning bones. Science 207:628-630, 1980.

V. CONCLUSIONS

In conclusion, the menopause can no longer be viewed as a simple estrogen deprivation state but instead is a situation in which estrogen production is decreased (usually) and in which the form of the hormone secreted is shifted from estradiol to estrone. Low dose estrogen therapy to the menopausal women clearly improves hot flashes and atrophy of the urogenital epethelium. There appears to be no documented benefit or adverse effect of such therapy on the incidence or severity of thromboembolic disease, breast cancer, hypertension, or cardiovascular disease. It appears that there is a greater risk for symptomatic gallbladder disease and for low grade, non-invasive endometrial malignancy; neither of these complications appears to have a significant effect on mortality. Although evidence in favor of beneficial effect in retarding the development of osteoporosis is pretty good, it has yet to be established that such therapy in fact ameliorates the astonishing high mortality and morbidity from fractures of the vertebrae and hip in aging white women.

It seems reasonable to formulate some tentative therapeutic recommendations:

1. Whenever estrogens are used long term they should be used in minimal doses (0.3-0.6 mg conjugated equine urinary estrogen or 0.01-0.02 mg ethinyl

estradiol per day). Most authors recommend that in women with uterus intact they should be given for 3 weeks followed by a daily progestin during the last week of estrogen administration.

2. Such therapy is routinely indicated in women undergoing premature menopause (surgically induced or spontaneous). Everyone is in agreement that such therapy is appropriate (probably mandatory) at least until the age of normal menopause.

3. Estrogen therapy is also indicated routinely in women of all ages who have severe, symptomatic hot flashes or atrophy of the urogenital epethelium. Hot flashes rarely persist for longer than 4 years, so that if the therapy is given for this purpose the duration of therapy can be limited.

4. Whether or not estrogens should be given routinely to menopausal women is unsettled. The complications do not appear to be very important; the benefits, though not overwhelming and uncertain, may be real. It appears to me that the bulk of evidence is in favor of their routine use.

5. Under every circumstance each patient has to be monitored constantly and frequently.

127. Kase, N. Yes or no on estrogen replacement therapy? - A formulation for clinicians. Clin. Obstet. Gynecol. 19:825-833, 1976.

(Also see Ref 1-13)