1966

Estrogen therapy in the postmenopausal female

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ESTROGEN THERAPY IN THE POSTMENOPAUSAL FEMALE

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

February 1, 1966

Omaha, Nebraska

PREFACE

Recently, I chanced to be sitting in on the reading of x-ray films in the radiology department of a local community hospital. The roentgenologist placed before us the standard views of a routine chest x-ray. The provisional diagnosis on the requisition slip simply stated, "Osteoporosis--Age 74 years."

The two of us were aghast at what we saw: complete radiolucency of the thoracic rib cage, numerous pathological vertebral fractures, marked kyphosis, and a tortuous, kinked aorta. Many x-ray films shall pass before my eyes before I shall forget that celluloid evidence of the aging process.

The postmenopausal period is often accompanied by psychological changes as well as physiological. I have seen women approaching the climacteric phase demonstrated complete changes in personality. These women, who had been energetic and full of joy, caring for their mate and children, active in community life, enthusiastic about being with people, slowly begin to participate in fewer activities, become hardened, bitter, and anxious, to demonstrate complete

apathy toward the prospect of continuing life.

As the material for this paper was being compiled, my attention was drawn to the headlines of a number of articles in newsstand monthly magazines: "Miracle Drug Delays Aging--keeps your body young, prolongs your love life, stops menopause" "Pills to Keep Women Young" "Menopause: Is It Necessary?"

The secret is out! If they haven't been already, gynecologists, internists, orthopedists, and family physicians across the country are going to be bombarded by the female populace, avidly seeking the miracle of youth.

It is the purpose of this paper to review a number of the current publications by the proponents of active estrogen therapy. Also, a brief review will be made of the accumulated evidence that there is a cause-effect relationship between estrogen deficiency in the climacteric and development of atherosclerosis and osteoporosis.

Further, an attempt will be made to summarize these widespread and oft dissident thoughts into a program which the physician can utilize in treating his female patients as they transcend the climacteric.

I am indebted in particular to Dr. Warren H. Pearse, Chairman, Department of Obstetrics and Gynecology, and to Dr. John G. Foley, Associate Professor in Internal Medicine for their critical comments and helpful suggestions.

David H. Kuper

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ESTROGEN AND REPRODUCTION

Before entering the realm of the utilization of estrogens as therapeutic agents, we must first review the chemistry and physiology of the estrogens as they naturally occur and act in the reproductive female.

Estrogens are substances capable of producing certain biological effects, the most characteristic of which are the changes which occur in mammals at estrus. They induce growth of the female genital organs, the appearance of female secondary sex characteristics, growth of the mammary duct system, and numerous other phenomena which vary somewhat in different species.

The natural occurring estrogens are steroids. The term "steroid" is applied to the members of a group of compounds which have in common the cyclopentanoperhydrophenanthrene nucleus. This skeleton structure consists of a cyclopentane ring (D.) fused to a completely hydrogenated phenanthrene (A-B-C):

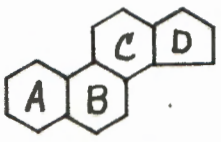


Fig. 1 (from Cantarow and Schepartz, Biochemistry, ed. 3, Saunders, 1962, p. 696.)

Substituents in the nucleus and on the commonly occurring side-chains are located by a standard numbering system:

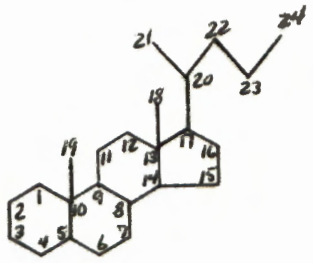
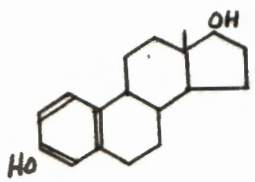
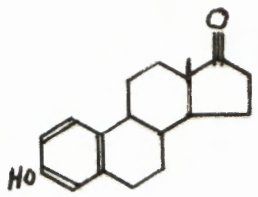


Fig. 2 (from Cantarow and Schepartz, p. 696.)

The naturally occurring estrogens in the human are Beta-estradiol, estrone, and estriol. One of the essential features of these estrogens in the human is the aromatic character of ring A (3 double bonds) with absence of a methyl group at C-10. Because of this characteristic, the OH group at C-3 possesses the properties of a phenolic hydroxyl group (weakly acid). (6)

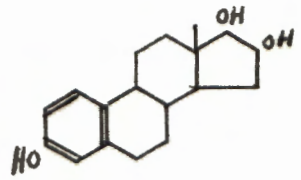


Estradiol



Estrone

Fig. 3 (from Cantarow and Schepartz, p. 700.)



Estriol

Fig. 4 (from Cantarow and Schepartz, p. 700.)

In the ovary, estrogens are produced by the maturing follicles and the corpus luteum. Estrogen is also formed in the adrenal cortex (male and female) and in the placenta.

Beta-estradiol and estrone are synthesized from acetate, either directly, or indirectly via cholesterol, and from testosterone. These two estrogens exist in a state of equilibrium. Estrone can be converted by the uterus to estriol, the estrogen believed to be the principal one secreted by the placenta. (31)

Beta-estradiol ⟷ Estrone

Estriol

Fig. 4

Estrogens are present in the blood plasma partly in free form and partly conjugated, about 50-75% being closely bound to plasma proteins, mainly gamma-globulin. They are excreted in the urine, chiefly in conjugated form, as glucuronidates and sulfates of estriol, estrone, and estradiol. (6)

The naturally occurring hormone of the corpus luteum is progesterone with excretion product, pregnanediol. Progesterone is important not only because of its role in the maintenance of pregnancy but also because it is a prominent intermediate in the biosynthesis of adrenal, testicular, and gonadal steroids from cholesterol. (31)

Throughout childhood, estrogen is secreted at levels which are too low to cause development of the reproductive tissues. According to Harris, at the time of puberty there is a crucial change in sensitivity of the suprahypophysial tissues so that they require very much larger amounts of estrogen to signal inhibition of gonadotropins from the anterior pituitary lobe. Puberty, then, is initiated by an increased output of gonadotropins by the pituitary acting on instructions from the hypothalamus. (31)

In response to the gonadotropins, increasing amounts of estrogens are secreted by the ovary, producing growth of the epithelium and musculature of the fallopian tubes, stimulation of their contraction and motility. Further, they cause growth, increased tonus and rhythmic contractions of the uterine musculature, and development of the endometrial mucosa and blood vessels which play an important role in normal menstruation. They increase the vascularity of the cervix and stimulate secretion by the cervical glands, increasing the amount of cervical mucus with a lowered viscosity, thus favoring migration, motility, and longevity of spermatozoa. Estrogens cause a characteristic proliferation of the vaginal epithelium which forms the basis for one of the methods of bioassay of estrogenic activity (Allen-Doisy). They are responsible in large part for normal development of the external female genitalia, the duct system of the breasts and the nipples, and the secondary sex characteristics.

In the human being, progesterone produces characteristic changes in the estrogen-primed endometrium. It also causes an increase in glycogen, mucin, and fat in the lining epithelial cells.

Sudden decrease in progesterone and estrogen leads to a series of changes culminating in bleeding or menstruation. Progesterone modifies the action of estrogen on the vaginal epithelium during the menstrual cycle, causing desquamation and basophilia of the superficial layer of cells and leukocyte infiltration. In conjunction with estrogen, progesterone causes the development of the alveolar system of the breasts and sensitizes them for the action of lactogenic hormone. It counteracts the effect of estrogen on the fallopian tubes and uterine cervix. (6)

A complicated reciprocal relationship exists between the two main ovarian hormones, estrogen and progesterone, and the hypophysis which produces three gonadotropins: FSH, LH, and LTH or luteotropin.

At the very earliest stage of the menstrual cycle, several follicles can be seen to be undergoing beginning differentiation and growth, but when, in a very short time, the hypophysial gonadotropic stimulation begins with FSH, a single follicle is selected for maturation and ovulation and the others undergo regression or atresia. (31)

Under the stimulation of FSH, the thecal cells of the maturing follicle begin to produce estrogen. The estrogens in turn stimulate the appropriate endometrial changes.

At a critical state (either a critical estrogen concentration or a critical rate of estrogen increase) there is a sharp shift in the gonadotropin mixture from predominantly FSH to more LH. Now the predominantly LH gonadotropin secretion participates in causing ovulation and the ovum is extruded from the ruptured follicle.

After ovulation occurs in the middle of the cycle, the follicle transforms into the corpus luteum. Under the influence of the luteotrophic hormone of the anterior pituitary lobe, the developing corpus luteum produces progesterone along with, very possibly, decreasing amounts of estrogen. (9)

If fertilization does not occur, the large amounts of estrogen and progesterone constitute instructions to the pituitary by way of the hypothalamus to cut down the production and release of gonadotropins. Thus deprived of its gonadotropin

stimulus, the corpus atrophies and as it does so, there is abrupt withdrawal of progesterone and then of estrogen. In its turn, the endometrium, which has grown accustomed to lavish amounts of estrogen and progesterone, suddenly has an inadequate hormonal stimulus to sustain itself and it promptly deteriorates. Sloughing and bleeding occur and the cycle is begun again 3-4 days later. (31)

In general, it is now felt that estrogen stimulates FSH in small doses, inhibits FSH output in large doses, and stimulates LH release in moderate doses.

If fertilization and endometrial implantation of the fertilized ovum do occur, there is no drop in production of sex steroids by the corpus luteum and both estrogen and progesterone continue to exert their effects on the pregnant uterus.

The most obvious changes that occur in pregnancy are the great growth of the uterus to accommodate its growing contents, and the growth of the mammary glands as if in anticipation of their use following parturition. Estrogen, which functions as a specific growth hormone for uterus smooth muscle cells,

stimulates the growth of the uterine muscle mass. Progesterone, by its inhibiting effect on uterine smooth muscle, prevents the establishment of effective, coordinated uterine muscle contractions and insures that feeble, ineffectual, fibrillatory contractions persist until the appropriate signals for the expulsion of the fetus are given.

Progesterone, in partnership with estrogen, helps to prepare the mammary glands for lactation by stimulating the formation of new glandular elements. (31)

ESTROGEN AND MENOPAUSE

Intensive investigation of the relationship between estrogens and malignancy of target organs (e.g. carcinoma of the breast) has revealed much well-documented information about estrogen production in the castrate woman. Utilization of this data has enabled investigators to make some significant facts availible concerning the physiology and endocrinology of the climacteric.

Ovulatory failure implies that a corpus luteum is not formed and progesterone is produced only at levels supported by adrenocortical function. At the same time, the well-recognized reciprocities between ovarian production of estrogen and anterior pituitary secretion of gonadotropins are maintained. Thus, so long as follicles produce estrogen, the urinary and blood levels of gonadotropin will approximate premenopausal titers. Eventually, a lack of responsive primordial follicles results in complete ovarian refractoriness to gonadotropin stimulation and circulating estrogen falls to very low levels. Relieved of the so-called "feedback" regulation of estrogens, the anterior pituitary secretion of gonadotropins becomes excessive, as shown by the large

amounts that are readily demonstrated in blood and urine. (28)

J.B. Brown has estimated the urinary excretion of estrogens in a group of postmenopausal women with a mean figure of 6.4 micrograms per 24 hours for total estrogen excretion. (4) Using essentially the same quantitative technique, R.D. Bulbrook et al. have estimated the urinary excretion of total estrogens to be 5.3 micrograms per 24 hours in premenopausal women who had undergone bilateral oophorectomy. (5) These latter values are of an appreciable level to indicate that estrogens are being synthesized in another endocrine site other than the hypofunctioning postmenopausal ovary.

Adrenolectomy in previously oophorectomized women resulted in pronounced decrease of total urinary estrogen excretion. There is little doubt among investigators that the ovaries and the adrenals are the principal sources of estrogens in the female.

Further, there is universal agreement that loss of ovarian function is followed by a marked increase in the excretion of gonadotropins. Loraine and Brown found relatively crude extracts of postmenopausal urine to be approximately 20 times as

potent as extracts from cycling females and to have approximately 16 times the luteinizing activity. (17)

With regard to progesterone, recent technique advances have established that the appreciable pregnanediol (one of the principal urinary metabolites of progesterone) seen in the urine of postmenopausal women, as well in that of men, has a source other than the ovary. Like estrogen, this progesterone is considered to be from the adrenal gland.

Briefly regarding the adrenocortical function, review of urinary excretion rates of 17-ketosteroids through the reproductive and postmenopausal years reveals varying levels at different ages. Like the total 17-ketosteroids, the 17-hydroxycorticosteroids rise sharply during pubertal years. There is, subsequently, a slow, progressive decline with age. There is no evidence that oophorectomy or physiological menopause affect the urinary steroid levels. Until proven otherwise, it is felt that cessation of ovarian function does not cause a compensatory increase in adrenocortical function.

There is no demonstrable proof of any thyroid hyperfunction in the postmenopausal state but

Oddie et al. demonstrated a slow decrease in I^{131} uptake after the menopause. (26) It has been postulated that actually thyroid function may be maintained at a uniform level by the ovary.

Summarizing, there is no concrete evidence that the menopause is followed by generalized anterior pituitary hyperactivity.

Many of the physiological changes occurring in the aging female are the result of a gradual decline in the functional capacity of the homeostatic mechanisms. Some are the direct result of loss of cellular tissues, while others are the result of diminished hormone stimulation. (15)

The physiological changes occurring with age are summarized by Carlson:

1. Gradual tissue desiccation.
2. Gradual retardation of cell division, capacity of cell growth and tissue repair, including reduced capacity to produce immune bodies.
3. Lowered rate of tissue oxidation and decreased B.M.R.
4. Cellular atrophy, degeneration, increased cell pigmentation, and fatty infiltration.
5. Gradual decrease in tissue elasticity, and degenerative changes in elastic connective tissue.
6. Decreased speed, strength, and endurance of skeletal muscle.
7. Progressive degeneration and atrophy of nervous tissue.
8. Gradual impairment of homeostasis. (7)

It is oft observed that the aging human body is not as capable of regulating blood glucose levels, pulse rate, blood pressure, and blood pH. Wound-healing and regenerative processes are slowed, there is loss of renal function with a decrease in effective renal plasma flow. Progressive respiratory acidosis occurs with the increase in residual air volume and decreased alveolar ventilation. Constipation is a common problem, most probably due to decreased motility of the intestine coupled with a decreased fluid intake. Hypochromic anemia is a common problem as achlorhydria develops.

Foreshortening and atrophy of the vagina carries the urethral meatus back along the roof of the vagina, a position which makes cystitis and urethritis more common. Stress and overflow incontinence are frequent because of shortening of the urethra and loss of tone of the bladder. (15)

The estrogen-dependent tissues of the genital system show characteristic changes in the postmenopause: atrophy of the vulva, loss of elasticity of the vaginal mucosa, thinning of the vagina, loss of muscle tone in the pelvic floor, flattening and loss of parenchyma in the breasts.

The vaginal epithelium is so related to quantitative amounts of estrogen that hormonal levels can be estimated with fair accuracy by using the maturation index (the relation of parabasal, precornified, and cornified cells). Maturation indices show premenstrual figures of 0-40-60 at ovulation, 5-70-15 immediately postmenopausal, and finally 25-65-10 when 30 or more years after the menopause. (19)

The first sign of menopause to the woman is usually the end of menstruation on a regular cyclic basis,, although anovulatory bleeding may continue for months. Statistically, this usually occurs at age 50, however 10% of females over age 53 demonstrate delayed menopause.

Atrophy of the myometrium progresses, the endometrium becomes thinner and loses much of its glandular and vascular tissue. McBride reported on 60 uteri from women at least two years postmenopausal who died from general medical conditions and found:

Atrophy	65%
Cystically dilated glands	20%
Endometrial polyps	15%
True hyperplasia	0%

The ovaries characteristically showed marked scarring and atrophy after many years postmenopausal. (20)

Conservatively speaking, Pearl and Plotz have stated, "A great many symptoms relating to almost every organ system in the body have been ascribed to the menopause." These have included the central nervous, gastro-intestinal, genito-urinary, and the musculo-skeletal. But, they continue, "To the best of our knowledge, only the characteristic vasomotor symptoms are specifically related, directly or indirectly, to a decline in estrogen production. These are the flushes, characterized by erythema involving the head, neck, and upper thorax; the hot flashes, characterized by hot tingling sensations or waves of heat which sweep over the body; and the sweats that accompany or immediately follow the flushes." (27)

As to the pathogenesis of these hot flushes, neither hypoestrogenism nor an increase in gonadotropin production by the pituitary is responsible, for both conditions are found in persons with primary ovarian failure. Yet such a patient frequently suffers hot flashes after cessation of prolonged estrogen therapy. Apparently, the hypothalamus, for years activated by estrogens, reacts upon their withdrawal by an upset in its temperature regulating function. (8)

Another theory as to the cause of the menopausal symptoms, especially the vasomotor, is the increasingly favored "theory of gonadotropin excess." Albright showed a high correlation of the severity of symptoms and the blood levels of the pituitary gonadotropins. (1) Clomiphene citrate, a drug which causes high excretion of gonadotropins, has been demonstrated to precipitate hot flushes.

Although many postmenopausal females have high blood and urinary levels of gonadotropins and yet never experience symptoms of consequence, it is quite likely that their system had adequate time for a period of adjustment. Often the most severe symptoms are seen in the premenopausal castrate woman. The probable explanation is that the vasomotor phenomena are precipitated by a relatively rapid withdrawal of estrogens after a long period of sensitization to the hormones. (28)

There is little doubt that many postmenopausal women have a number of highly disturbing symptoms which are psychogenic in origin. It is only reasonable that women in their later years are going to be concerned about the threats of loneliness and

age, of sexual decline, and loss of their feminine attractiveness. In many women, their whole life and existence has centered around their family and husband. Slowly, as their children mature, leave home, make lives for themselves, and as their husbands become more concerned about their place in the business world, the middle-aged woman develops anxieties, questions her further usefulness and purpose in life.

As McGoogan points out, often the first step in treatment of the climacteric is a "sympathetic understanding of the emotional and aging problems." (23) Certainly, tranquillizers are not the total answer. An energetic attempt must be made to direct the involutional woman toward new goals, activities, and interests.

In recent years, a number of papers have been presented to the medical profession advocating supplemental or replacement estrogen therapy for the climacteric woman. The proponent views are as widespread in approach as the field of endocrinology itself. More conservatively, some prescribe to supplementing the failing endogenous estrogen supply

followed by a reduction, then cessation, of treatment. (8) Others describe the climacteric as a real disease of hypofunction as diabetes mellitus, myxedema, or Addison's disease, and they enthusiastically believe that total replacement therapy is the treatment of choice. (2, 36)

Bakke has compiled a very complete table of the many reasons physicians in the past have been reluctant to give estrogen replacement therapy:

REASONS AGAINST INTERVENTION

1. Philosophic reluctance to interfere with nature.
2. Paucity of convincing clinical reports.
3. Fear of causing breast cancer.
4. Expense and inconvenience.
5. Inertia and lack of education (both lay and professional).
6. Undesirable side-effects of therapy such as:
   (a) Uterine bleeding--planned or unplanned.
   (b) Breast tenderness or growth.
   (c) Nausea and gastrointestinal upset.
   (d) Malaise.*
   (e) Excessive libido--pelvic congestion.*
   (f) Hyperpigmentation.
   (g) "Spiders."
   (h) Restlessness and irritability.*
   (i) Saline retention.*

*More likely with progestin.

Table 1. (from Bakke, John L., A Teaching Device to Assist Active Therapeutic Intervention in the Menopause, West. J. Surg. Obst. & Gyn., 71:241-5, 1963.)

Bakke continues with another table of rebuttal, listing reasons for intervention:

NEW REASONS FOR ACTIVE INTERVENTION

1. Population explosion of menopausal women.
2. Cancer not caused, but prevented.
3. Oral progestins availible.
4. New published reports.
5. Accumulating physiologic arguments.

Table 2. (from Bakke.)

All of these new reasons, I feel, are justification for a brief review of the more enthusiastic voices in the argument.

One of the first and, coincidentally, one of the most complete studies done was that by S. Wallach and P.H. Henneman. In a review of estrogen therapy in 292 postmenopausal women, spanning more than 25 years, the authors concluded "that prolonged, cyclic, oral estrogen therapy combined with periodic pelvic and vaginal cytological examinations is a safe and effective therapy for postmenopausal women with disabling menopausal symptoms..."

Ninety-four of their patients were treated specifically for alleviation of the symptoms of the "menopause syndrome" as previously described. Many of these postmenopausal women had unsuccessfully been

treated with barbiturates and other sedatives. In 93 of these patients, there was complete remission of the hot flashes and their related symptoms. (32)

In reviewing the fate of the untreated menopausal woman, Wilson presents a pertinent question, "The hypogonal woman of 20 or 30 years of age is not denied hormone augmentation. Fundamentally, the postmenopausal hypogonal woman of 60 or 70 years is little different--just older. Why should she be denied therapy? Who is to decide the age of denial? Substitution therapy excites no comment in thyroid, pancreatic, and adrenal deficiencies. There is no age barrier." (36)

Robert S. Greenblatt is not the least bit equivocal about his feelings on this matter of replacement therapy. "The menopausal woman must be considered physiologic castrate and replacement therapy should be administered to everyone with evidence of an estrogen lack." (10)

Continuing in the same vein, Dr. Bakke writes, "Because the menopause happens to every woman it has generally been thought to be normal and not a disease. As long as there was no remedy, this

was a comforting idea. However, the universality of a bodily change does not necessarily mean that it is desirable for good health. Because we all lose the ability to read smaller print as we grow older we do not say, 'Middle-age near-sightedness (presbyopia) is universal; it happens to everyone, therefore, I shall not treat it by wearing glasses.' Death is universal, yet we struggle against it." (2)

Much remains to be decided concerning which type of estrogen is the best for therapy: natural estrogens, synthetics, or steroid derivatives. In general, natural estrogens (e.g. conjugated equine estrogens) are better tolerated; synthetic estrogens (e.g. diethylstilbesterol) are less expensive; and steroid derivatives (e.g. ethinyl estradiol, estradiol-3-methyl ether) are more active biologically.

Multiple patterns of administration may be used in replacement therapy. Examples are:

I. Estrogen from day 1-25.
Progestin from day 16-25.

II. Estrogen from day 1-25.
Combined estrogen and progestin from day 16-25.

The combined estrogen and progestin (e.g. Ortho-Novum®, Enovid-E®, Norlestin®) is generally well tolerated and usually the menses which follows is predictable, reduced, and often painless.

III. Estrogen daily
Combined estrogen and progestin from day 16-25.

Table 3. (adapted from McEwen, D.C., Ovarian Failure and the Menopause, Canad. Med. Ass. J., 92.2:962-9, 1965.)

As Wilson points out, some women may require more estrogen than others, particularly those in high-stress situations. (36) Regimen III (above) may be the best for such a woman.

It is a fact that the progestin will precipitate uterine bleeding in the postmenopausal woman. However, this cyclic shedding will prevent endometrial hyperplasia.

Wilson recommends that the postmenopausal female receive one 1.25 mg. tablet of conjugated estrogens (Premarin®) daily for 42 consecutive days and one 10 mg. tablet of medroxyprogesterone acetate (Provera®) daily on and from day 31 and including day 42. On the 45th day, menstruation can be expected. He further directs that the conjugated estrogens be resumed on the fifth day of the bleeding. Then, if repeated vaginal smears do not show adequate

response, he recommends an increase to 1½ or more tablets daily.

With regard to breakthrough bleeding, he suggests doubling the dose of conjugated estrogens from day 18 to day 42. If this fails to control bleeding in 3 days, the secretory phase may be initiated ahead of time by giving the daily 10 mg. of medroxyprogesterone acetate for 12 days. Spotting or bleeding during cyclic estrogen therapy can be avoided by keeping the estrogen intake even, or by increasing it slowly during the proliferative phase. Sudden drops in the body level of estrogen result in a lack of endometrial support with areas of focal necrosis and resultant bleeding. (35)

It should be noted that failure to control spotting demands curettage of the endometrium.

What about androgen therapy? There is little evidence in the availible literature to indicate that androgens have any particular place in postmenopausal hormone therapy. They may be of value for an anabolic effect in old age. However, minimal amounts of androgenic metabolites are availible as a result of adrenocortical secretion.

It is extremely important to add this bit of caution. Estrogen replacement therapy cannot be routinely given to all postmenopausal women. It is most important that estrogens be given on an individual basis. We still treat the patient, not the disease. It cannot be over-emphasized that each patient, prior to therapy, should have her medical history fully reviewed. This is then complemented with a complete physical examination which includes a pelvic examination and Papanicolaou smear. The maturation index or smear cell count is also advised as a basis for therapy response. As the patient receives her therapy, she should be encouraged to do weekly self-examinations of her breasts. It is the physician's responsibility to see that the patient has a regular breast and pelvic examination with a yearly Pap smear.

At present, it appears to be the concurrence of most advocates of estrogen replacement therapy that any woman who has had a known cancer of the breast or genital system within the past five years is not a candidate for cyclic estrogen.

ESTROGEN AND ATHEROSCLEROSIS

Impressive statistics have recently become availible illustrating that in the middle age, coronary artery disease is primarily a disease of men. The Framingham Study by the National Heart Institute of over 5,000 men and women revealed eight year heart attack rates of 21 and 0 per 1,000 men and women respectively for the 30-39 year age group. For ages 40-49, the rates were men 48 and women 7; age 50-59, 94 for men and 20 for women. (14)

This, of course, raised the question: why do men of middle age have so much higher rates of heart attacks as compared to women? And, secondly, why do women after the menopause show an increasing rate that has been reported by some to match nearly that of men in the 60-69 age group?

The complete pathophysiology of atherosclerosis is yet to be worked out. Numerous etiological factors have been presented. The more significant of these include cholesterol-lipid-lipoprotein metabolism, diet, smoking, and blood pressure. It is not the object of this paper to explore the many avenues

of thought concerning the evolution of inevitable plaque formations in our blood vessels. Rather, it is to consider the possible relationship that estrogens play in the deterring of this vicious health problem.

An extensive series of animal studies by Stamler et al. may be the answer. Using two groups of cockerels, these investigators first gave one group "prophylactic" doses of estradiol. Both groups were put on high cholesterol diets and all animals were sacrificed after several weeks. Microscopic examination revealed that although both groups developed marked atherosclerosis of the aorta, the estrogen group of birds, as contrasted to the "normal", showed few atherosclerotic changes in the coronary arteries.

Further, it was found that therapeutic doses of estrogen were able to reverse the already present cholesterol-induced plaques in the coronary arteries. This was observed even when the chicks were continuously on high-cholesterol diets. Similar findings were demonstrated using the natural equine conjugated estrogens and the synthetic estrogens.

Continuing, the experimenters found that in egg-laying hens, atherosclerotic changes could not be induced in the coronaries. However, this was a direct contrast to the changes in mature roosters on high-cholesterol diets.

Now objective researchers might interpose that possibly the egg-laying itself might be a way in which hens rid themselves of coronary changes. So, the oviducts of the hens were ligated. Much to the satisfaction of the experimenters, the results were the same. In addition, it was found that ovariectomized hens, now lacking endogenous estrogens, readily developed grossly elevated cholesterol/phospholipid ratios and extensive coronary atherosclerotic plaques.

Similar findings were also discovered using rats. Now inference could be expanded to mammals that estrogens have a significant protective role in the impairment of atherosclerosis. (3)

How does this apply to the human? In recent years, a number of series based on autopsy findings and clinical observations have shown that estrogens apparently do play a significant part in the impairment of the ravages of atherosclerotic heart disease.

In one investigation, the degree of coronary atherosclerosis was quantitatively graded for 49 women who came to autopsy 2 or more years after bilateral oophorectomy and compared with control groups of men and women. The average degree of coronary atherosclerosis was found to be greater decade for decade in the castrated women than in the controls. Further, the average grade of sclerosis in the castrated women closely approached that of the age-matched male controls. (37)

In another impressive investigation, Higano et al. did a detailed cardiovascular history and physical examination on two groups of women. One group included women who had undergone bilateral oophorectomy before the age of 45 years. The other group included women who had only a hysterectomy, with or without removal of a single ovary, before the age of 45 years. The investigation was supplemented by electrocardiograms, x-rays of the the abdominal aorta and chest, complete blood counts, fasting blood sugars, urea nitrogen, serum lipids, and urinalyses.

Also, a small group (45) of women who had undergone bilateral oophorectomy prior to age 45 years

and who had been taking daily oral estrogen therapy was included. The tabulated total events occurring in these women after surgery was as follows:

Group	No. of Patients	Angina Pectoris	Myocardial Infarction	Peripheral Vascular Disease	Cerebral Thrombosis	Total Events	Percentage
		no. of cases	no. of cases	no. of cases	no. of cases	no. of cases	
Castrate (no estrogen)	102	16	5	4	1	26	25.4
Control (no estrogen)	112	4	1	0	0	5	4.4
Castrate (on estrogen)	45	2	0	0	1	3	6.6

Table 4. (from Higano, N. et al., Increased Incidence of Cardiovascular Disease in Castrated Women, N. Engl. J. Med., 268:1123-5, 1963.)

The authors concluded that "whenever possible, bilateral oophorectomy should be avoided in premenopausal women. If such a procedure is necessary, prolonged estrogen replacement therapy should be started with sufficiently high doses, physiologically comparable to those produced by the functioning ovaries, to avoid premature atherosclerosis....This is additional evidence that estrogens have a protective role against the development of atherosclerotic cardiovascular disease in women." (13)

Even studies on males have been reported. One study of autopsy findings revealed significantly less coronary atherosclerosis in a group of men with carcinoma of the prostate who had received large doses of estrogens as compared to a group with the same disease but who had gone untreated. (29)

Investigation tends to indicate that the use of estrogens is recommended for postmenopausal women, not only for the symptoms of menopause, but as a part of a program of prophylaxis against the atherosclerotic changes of the coronary arteries. Certainly, this is not the total answer. Other factors must be considered in the health of the aging female such as diet, weight, hypertension, smoking, and early detection of diabetes mellitus.

ESTROGEN AND OSTEOPOROSIS

Studies show that approximately 25 percent of postmenopausal women are plagued by the crippling bone disorder called osteoporosis. Lutwak and Whedon estimate 4 million persons in the United States have significant osteoporosis. (18)

In postmenopausal osteoporosis, there is simply a decrease in bone mass. This apparently occurs in the face of normal osteoblast and osteoclast activity, normal bone marrow, normal vasculature, normal serum calcium levels, normal to slightly elevated serum phosphorus levels, and normal serum alkaline phosphotase levels.

What then is the cause of this bone imbalance that is illustrated on roentgenograms by thinning of the sella turcica floor, expansion of the intervertebral discs, wedging of the vertebrae, and generalized thinning of the cortices in the pelvis and long bones.

The Albright school of thought which began during World War II is that osteoporosis is due to decreased osteogenesis caused by decreased estrogens from the ovary. This, coupled with the inactivity

which accompanies old age, reduces the stimulation for bone formation.

Albright and his students felt that the decrease in bone mass was a gradual occurrence of disproportion between a decreased rate of formation and a normal rate of resorption. In the presence of a normal functioning hepatic system, the serum alkaline phosphotase is an index of the rate of bone formation. Osteoblasts are rich in alkaline phosphotase, consequently, with increased osteoblastic activity, there is an increase in serum levels. Therefore, Albright and others concluded that serum alkaline phosphotase levels are not elevated because osteoblastic activity is normal or decreased in osteoporosis. And, because there is a normal rate of bone resorption, serum calcium and phosphorus are normal.

However, recent studies utilizing calcium balance and refined morphologic techniques have shown that new bone formation is commonly normal in postmenopausal and senile osteoporosis, that immobilization is associated with an increase in skeletal turnover rather than skeletal decrease, and that calcium supplements alone will induce prolonged positive balance in osteoporosis. (11)

This brings us to the other school of thought. Nordin, Lutwak, and Whedon feel that calcium deficiency may produce or contribute to postmenopausal osteoporosis. Nordin has reported nutritional surveys which show that the calcium intake was lower in women developing osteoporosis. (24) In fact, Nordin, Lutwak, and Whedon have reported relief of pain and positive calcium balance in postmenopausal osteoporotic women treated with high calcium intakes.

However, studies by Lafferty, Spencer, and Pearson have shown a lack of concomitant phosphorus retention in persons treated with high calcium intake. (16) Henneman states, "Lack of concomitant phosphorus retention is a serious criticism of the high calcium intake theory for one cannot conceive of increased bone formation which does not contain phosphorus." (12)

The controversy may well continue for many years. However, a recent editorial by Robert P. Heaney may well reconcile the two schools of thought. He defines osteoporosis as "a multifactorial disease, in its homeostatic varieties produced whenever bone is forced to provide calcium which the organism fails to obtain from its environment." (11)

He points out that bone formation and resorption are not independent but are homeostatically linked. "Dietary calcium deficiency and the intestinal malabsorption syndromes may produce osteoporosis simply by presenting the organism with less mineral than needed for minimal daily losses." Calcium homeostasis is dependent, not on the total body calcium, but the level of ionized calcium in the body fluids. A need for ionized calcium activates the parathyroid gland to secrete increased levels of hormone which, in turn, mobilizes calcium from the bony skeleton to the fluids. And further, "relative or absolute deficiency of gonadal hormones, the cornerstone of the Albright theory, would lead to negative calcium balance because of increased bone resorption, not so much because these hormones decrease resorption per se, but because they appear to moderate the resorptive response of osteoclasts to homeostatic stimuli, and in their absence bone becomes hyperresponsive to parathyroid hormone." (11)

Utilizing all the conclusions of the investigators of osteoporosis, it would seem that the best possible treatment, both prophylactic and therapeutic, would have three components. First, the

encouragement of full activity, especially walking, appears to be of value. Second, the importance of a diet sufficient in calcium to meet the daily requirements and in vitamin D, necessary for the absorption of calcium from the intestine, cannot be over-emphasized. And finally, studies such as those by Wallach and Henneman (32) would indicate that replacement estrogen therapy has a prominent part in the treatment of osteoporosis.

ESTROGEN AND CARCINOMA

As Bakke described, one of the reasons physicians have been reluctant to give estrogen replacement therapy is the fear of initiating cancer in the postmenopausal woman. (See Table 1.) One man who feels that there is an estrogen-cancer relationship is Edmund Novak. He feels that hormone therapy is too often given without any rationale and that many times is administered with complete lack of discrimination. "It is probable that one of the major causes of postmenopausal bleeding is hormone therapy. Estrogen is generally conceded to be the normal stimulus to the pathologic entity termed endometrial hyperplasia. Furthermore, it has been well documented and repeatedly observed that excessive estrogen therapy in the postmenopausal woman may produce endometrial atypia to such an extreme degree that it sometimes cannot be distinguished from a genuine endometrial adenocarcinoma." (25)

However, Dr. Novak admits, himself, "Although this cause-effect relation should by no means be regarded as conclusively proved, one can build up

a very suggestive series of approaches suggesting that estrogen may be a causative factor in the genesis of endometrial cancer in many women, although there are probably such other causes as genetic predisposition." (25)

I think that Dr. Novak's statement is worth noting in that indiscriminate use of hormones is to be abhorred. This point has been emphasized previously in this paper. And, I also feel that the problem of endometrial hyperplasia has also been well-treated in the discussion of cyclic therapy. The periodic shedding of the endometrium as described should eliminate the threat of carcinoma evolution. Also, it is well known that endometrial carcinoma is more commonly a problem of the postmenopausal female, not of the cycling young woman.

In fact, Wilson points out that estrogen and progesterone may be protective against breast and genital cancer to an unknown degree. He reports a review of 304 women exposed to high doses of exogenous estrogen (based on vaginal smear), primarily conjugated equine estrogens. Each patient

was examined, including a vaginal smear, every 6 to 8 months. All patients were instructed in self-examination of the breasts and all were prompted to report any unusual bleeding. With an expected rate of 18 cases of breast and genital cancer, none were detected. Wilson concludes, "It would seem advisable to keep women endocrine rich and, consequently, cancer poor throughout their lives." (34)

Bakke has tabulated 5 studies, including Wilson's, that tend to show that breast and genital cancer is significantly reduced by long-term estrogen replacement therapy:

TREATMENT PREVENTS CANCER

Observer	Patient-Yrs.	Patient-No.	Duration (Yr.)	Cancer Expected	Cancer Found
Gordan	1,200	120	14	12-15	0
Wilson	2,604	304	17	20	0
Wallach	1,480	292	25	(22)*	5**
Schleyer-Saunders	....	500	15	(30)*	0
Geist	....	206	55	(12)*	0
Totals		1,422		96	5**

*Parentheses indicate author's estimate.
**All uterine cancer. Only one of the 5 occurred after 1945, when oral intermittent estrogens were substituted for continuously active injectable estrogen.

Table 5. (from Bakke, J.L., A Teaching Device to Assist Active Therapeutic Intervention in the Menopause, West. J. Surg. Obst. & Gyn., 71:241-5, 1963.)

It has been roughly estimated that approximately 7 million women in the United States are on a form of estrogen therapy, yet there does not appear to be a rise in incidence of breast and genital cancer. Of course, it must be remembered that in recent years, women have become more careful about self-evaluation and that incidence rates may show concomitant change. Also, women on estrogen therapy who are followed carefully may show lower rates, especially those undergoing such procedures as curettage and conization.

The more extensive studies published would tend to discount the belief that there is a cause-effect relationship between estrogens and cancer. In fact, active estrogen therapy may be responsible for a lower incidence of breast and genital cancer.

SUMMARY

It has been the purpose of this paper to briefly review some of the more recent medical literature on the subject of estrogen replacement therapy. Initially, the chemistry of the estrogens is presented and their interaction in the physiological menstrual cycle. The physiologic and chemical changes that occur at menopause are presented with a review of the more significant work in estrogen therapy for the postmenopausal female. A few therapeutic programs are given which the physician may utilize in applying estrogen therapy.

The role of estrogens in the pathophysiology of coronary atherosclerosis and osteoporosis is reviewed. This has included some of the experimental work with animals that has been done and the results are then applied to the atherosclerosis occurring so commonly in humans. Although much investigation remains to be done in the study of atherosclerosis and estrogens, the results of a survey by Higano et al. seem to be significant and are, therefore, presented. Osteoporosis, another common disease of the elderly, especially the female elderly, is discussed. Although the role of estrogens

in the treatment of this disease has been extensively reported, recent evidence tends to favor other factors as equally important in its attenuation.

One of the primary arguments physicians have presented against estrogen replacement therapy is that such treatment is carcinogenic. This thought is quite fully dissected and recent evidence that the opposite effect may be true is presented.

CONCLUSIONS

1. Estrogens and progesterone are secreted by the adrenal gland as well as by the ovary.
2. The vaginal epithelium is a readily accessible and quite reliable source for quantitative determination of estrogen levels and estrogen therapeutic response.
3. The menopause is followed by marked increase in gonadotropin levels.
4. The menopausal symptoms (hot flushes) are precipatated by a relatively rapid withdrawal of estrogens rather than by "gonadotropin excess."

5. Many symptoms in the menopause may be psycogenic and should be treated as such when recognized.

6. New reasons for active intervention in the "menopausal syndrome" appear to be quite plausible.

7. The postmenopause appears to be actually a disease of hypofunction and warrants treatment with oral estrogens and/or progestins.

8. Failure to control uterine bleeding during estrogen therapy demands curettage.

9. Androgens have no place in postmenopausal hormone therapy.

10. Estrogen therapy must be preceded by a thorough medical examination which includes a pelvic examination and Papanicolaou smear.

11. Regular, routine breast, pelvic, and vaginal smear examinations are imperative during estrogen therapy.

12. Estrogens have a protective role in the prevention or, at least, in the impairment of coronary atherosclerosis.

13. Estrogens, as well as other factors such as

calcium intake, adequate vitamin D, and exercise may be important in the prevention of osteoporosis.

14. There appears to be no cause-effect relationship between estrogens and cancer of the breast and genital system.

15. Yet to be fully evaluated, estrogens may actually cause a lower incidence of breast and genital cancer.

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