ESTROGENS AND CANCER

Steven G. Silverberg/Francis J. Major, EDITORS

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Edited by

Steven G. Silverberg, M.D.
Francis J. Major, M.D.

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University of Colorado School of Medicine
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Contributors

George Betz, M.D., Ph.D., Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Denver, Colorado 80262

Paul A. Bloustein, M.D., Department of Laboratory Medicine, Wesley Medical Center, Wichita, Kansas 67202

Clarence E. Ehrlich, M.D., Department of Obstetrics and Gynecology, University of Indiana School of Medicine, Indianapolis, Indiana 46202

Lawrence H. Einhorn, M.D., Department of Medicine, Section of Oncology, Indiana University Medical Center, Indianapolis, Indiana 46202

Jack A. Faraci, M.D., Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Denver, Colorado 80262

Robert E. Fechner, M.D., Department of Pathology, The University of Virginia School of Medicine, Charlottesville, Virginia 22903

Veeba Gerkins, M.P.H., Department of Pathology, University of Southern California, School of Medicine, Los Angeles, California 90033

Annlia Hill, Ph.D., Department of Community Medicine, University of Southern California, School of Medicine, Los Angeles, California 90033

Thomas Mack, M.D., Department of Community Medicine, University of Southern California, School of Medicine, Los Angeles, California 90033

Francis J. Major, M.D., Department of Obstetrics and Gynecology, Denver General Hospital and University of Colorado School of Medicine, Denver, Colorado 80202

Edgar L. Makowski, M.D., Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Denver, Colorado 80262

Alexander Miller, M.D., Department of Pathology, Rush Medical School, Chicago, Illinois 60612

John McLean Morris, M.D., Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut 06516

Dennis Mullen, M.D., Department of Pathology, University of Colorado School of Medicine, Denver, Colorado 80262

Jaime Prat, M.D., Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts 02114

Stanley Robboy, M.D., Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts 02114

Ronald Ross, M.D., Department of Pathology, University of Southern California, School of Medicine, Los Angeles, California 90033

Steven G. Silverberg, M.D., Colorado Regional Cancer Center and Department of Pathology, University of Colorado School of Medicine, Denver, Colorado 80262

Sheldon C. Sommers, M.D., Department of Pathology, Lenox Hill Hospital, New York, New York 10021

Bruce V. Stadel, M.D., M.P.H., National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20014

Noel S. Weiss, M.D., Department of Epidemiology, University of Washington and Fred Hutchinson Cancer Research Center, Seattle, Washington 98195

William R. Welch, M.D., Department of Pathology, Massachusetts General Hospital, Boston, Massachusetts 02114

Peter C. M. Young, Ph.D., Department of Obstetrics and Gynecology, Indiana University Medical Center, Indianapolis, Indiana 46202

Preface

In the past few years, the subject of the multifaceted relationships between exogenous estrogen administration and the development of human tumors has become one of major practical as well as theoretical interest and importance. The recent demonstration of an almost epidemic increase in the incidence of endometrial carcinoma in this country has served to focus the attention of numerous investigators on the stimulation of the development of this tumor by endogenous and exogenous estrogenic hormones. Similarly, investigators have questioned the relationship of estrogens to other tumors and tumor-like conditions of the breast, cervix, vagina, and liver. The agents involved have included conjugated estrogens administered to postmenopausal women, estrogen-progesterone combinations administered as oral contraceptives, and diethylstilbestrol (DES) and related compounds administered during pregnancy.

Because large volumes of often conflicting data have been presented on these subjects in a very short time, and because serious questions still exist concerning not only the interpretation of these data but their translation into alternative courses of action, the Colorado Regional Cancer Center and the University of Colorado Medical Center co-sponsored an invitational symposium, "Estrogens and Cancer," in Denver on September 10, 1977. The presentations at this symposium form the substance of this book.

The goal of this book is to bring together epidemiologic, clinical, and pathologic data on the relationships between estrogens and naturally occurring human neoplasms, and to provide in a single source a compendium of current knowledge and future research directions in a variety of estrogenic compounds and human tumors. Specific objectives include the presentation of both sides of the estrogen-endometrial cancer controversy; ongoing investigations of the relation of postmenopausal estrogens, oral contraceptives, and in utero exposure to DES to human tumors and tumor-like conditions of various sites; and potential therapeutic uses of information relating to estrogen responsiveness of some tumors through the mechanism of the determination of receptor activity.

This volume begins with a general consideration of estrogen metabolism and the pathophysiology of menopause by Dr. Betz and of the treatment of menopausal signs and symptoms by Dr. Morris. The relationship between postmenopausal estrogen administration and endometrial cancer is discussed from different points of view by Drs. Weiss, Miller, and Sommers, while the current status of the relation of postmenopausal estrogen administration to breast cancer is presented by Dr. Ross. These presentations are followed by a discussion of the

risk/benefit ratios of postmenopausal estrogen administration. The status of oral contraceptives with relation to endometrial cancer, cervical and mammary cancers, and liver tumors is examined by Drs. Silverberg, Stadel, and Bloustein, respectively. Dr. Fechner presents an update of the pathology of oral contraceptive-related lesions. Another discussion follows on the relationship between contraception and cancer. Finally, Dr. Robboy discusses the current status of the relationship of in utero DES exposure and cervicovaginal cancer and other abnormalities, and Dr. Ehrlich gives an update on estrogen and progesterone receptors and cancer treatment.

As editors, we wish to thank the above-mentioned authors and their colleagues for their excellent contributions and their cooperation in helping us expedite the book's timely publication. We also thank our colleagues at the Colorado Regional Cancer Center and the University of Colorado Medical Center for their assistance with the many difficult organizational aspects of publishing a book such as this in the shortest possible time. We single out for particular praise and thanks Miss Virginia Brookhouser, who handled the administrative and organizational component of the symposium, and Mrs. Lavonne King, who typed the major portion of the manuscript. We also sincerely appreciate the cooperation of John Wiley & Sons, particularly of Miss Ruth Wreschner of their editorial staff. The cooperation and assistance of these and many other people has been invaluable to us in the text's preparation.

Steven G. Silverberg, M.D.
Francis J. Major, M.D.

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Estrogen Metabolism and Pathophysiology of Menopause

George Betz, M.D., Ph.D.

The consequences of the menopausal syndrome are manifold. Although many women undergo this biologic transition without overwhelming difficulty, estrogen deprivation in conjunction with the effects of aging may be devastating to some individuals. Because of the large population segment in this female age group, menopause deserves the attention afforded any public health problem. Fortunately for the impetus of research in this area, the profound endocrine and metabolic alterations attendant to ovarian failure have fascinated investigators. This discussion will attempt to summarize recent advances in our understanding of menopausal biology, including alterations of sex steroid biochemistry and the metabolic consequences of estrogen deprivation.

Age at the cessation of ovarian function has been reported to have increased over the past century, with the mean age changing from 45 to 50. Because of differences in reporting this kind of data between the present time and a century ago, these comparisons may not be reliable (1). The mean age of menopause (50 years) is currently the same in all industrialized nations studied, and the standard deviation of 3.8 years reported from The Netherlands is a representative value (2). The lower values for mean age of menopause, which have been observed currently in undeveloped countries, are probably a consequence of limited nutrition (3). The significance of other factors that might affect the age of menopause has not been established, with the possible exception of altitude (4). Thus, there appears to be no correlation among mean age of menopause and parity, age at menarche, body weight, or intercurrent disease states. The proportion of the population who have reached menopause is reported to be greater than 30% in England (5). Dewhurst has estimated that one fourth of these patients will seek medical help for problems related to menopause (6). To reiterate a previous statement concerning menopause, we are dealing with a major public health problem.

ETIOLOGY OF MENOPAUSE

Causative factors in the onset of the menopausal syndrome have not been clarified. Animal models of menopause require that primates be studied, since lower animals do not shed their endometrium. These observations have not been extensively recorded, and menopause is not well documented in primates other than humans partly because of their shorter life-span. A decline in fertility has been noted in laboratory animals, such as rats, and this decline is primarily manifested by decreases in litter size and in the frequency of gestation. In contrast to human ovaries at menopause, in which a drastic decline in the number of follicles occurs, the morphology of rat ovaries is not extensively altered (7). The decrease in fecundity of rodents appears to be due to uterine changes rather than to the ovarian failure that occurs in human menopause. Some of the events that lead to menopause have been recorded, and it is well documented in human females that cycle length decreases by 2–4 days in the final reproductive years (8, 9). In the final year, anovulation and gross menstrual irregularity are the rule. It was determined that the observed abbreviation of ovulatory cycles was due to a decreased length of the preovulatory phase of the cycle (9), whereas corpus luteum function continued for the usual duration of 14 days. Progesterone and luteinizing hormone (LH) were measured at the same levels as in younger women, but follicle-stimulating hormone (FSH) was increased markedly during the late proliferative phase of perimenopausal women. At the same time, estradiol levels were below normal. This apparent dissociation in the control of LH and FSH opens speculation concerning the factors that modulate the levels of these hormones. It is possible that follicles produce a substance analogous to testicular "inhibin," a hypothetical substance that appears to suppress FSH levels in men. Thus, inhibin may be a major factor in control of FSH, while LH is controlled by estrogen. The finding of a high FSH/LH ratio also corroborates an earlier finding that FSH is inversely related to the number of ovarian follicles, while LH is not as reliable an indicator of follicular status (10). When cycles finally become anovulatory, estradiol increases after the LH surge, but there is no resultant increase in progesterone.

Although decreased numbers of follicles are found in the perimenopausal ovary, significant numbers of follicles persist after cessation of menses (11). Therefore, the cessation of estrogen production in the physiologic menopause does not occur by exactly the same mechanism as in Turner's syndrome, in which no follicles are present. Nevertheless, the report by Fang et al. (12) may be of importance in understanding ovarian failure. These investigators found a spontaneous increase in sex chromosome monosomy with advancing age (third decade compared to seventh decade) in gonadal tissue. Somatic tissues did not demonstrate this change. Unfortunately, the proportion of XO cells at age 70 is only 3%. To invoke this loss of chromosomal material as a cause of ovarian failure will require other information.

Another interesting speculation is that menopausal follicles lose their receptors to LH or FSH or become desensitized to gonadotropins. The techniques required to solve this problem are currently under development but have not been applied to menopausal biology.

STEROIDS IN MENOPAUSE

Steroid hormone production undergoes marked changes during menopause. The most striking alteration is, of course, the decline in estrogen synthesis. This change has recently been studied by measurement of estrogen production rates. This technique estimates the quantity of a hormone that leaves the circulation over a given time period (which should nearly equal the quantity that enters the blood). It is necessary to determine the blood clearance rate, which is accomplished by injecting the radiolabeled hormone of interest intravenously and then determining its disappearance rate by sampling at subsequent intervals. The clearance rate, expressed as milliliters of blood per 24 hr, is multiplied by the blood concentration of the hormone (micrograms/milliliter) to yield a production rate in micrograms per 24 hr. Although this calculation gives an estimate of daily synthesis, this method gives no information about the source of the steroid, as is determined by secretion rates where the tissue of origin is known. These techniques may be utilized, however, to estimate the percentage conversion of one steroid to another in the peripheral circulation, and a quantitative calculation may be made of the amount of hormone derived from circulating precursors. Hormone synthesis in nonendocrine tissue is described as "extraglandular."[1] In determining production rates, it was found that the blood concentration of two of the estrogens decreased from premenopausal levels of about 100 pg/ml to 13 and 30 pg/ml (13) for estradiol and estrone, respectively. Clearance rates for each estrogen were decreased by 20% (estradiol, 790 liters/24 hr/m^2 to 580 liters/24 hr/m^2) (14). Production rates of estradiol in the normal menstrual cycle were found to fluctuate from 80 to 500 μg/day, and estrone production varied from 90 to 300 μg/day, with the highest production occurring prior to ovulation. From the above measurements, it was found that after menopause, estradiol production declines to 12 μg/day and estrone to 45 μg/day (13, 14). As may be noted, estrone is now more significant, quantitatively, than estradiol, which was the predominant estrogen in reproductive years. The reduced clearance rates observed for both estrogens are probably due to a mass action effect of decreased substrate for metabolic processes. There appears to be no quantitative difference in estrogen decline or ultimate levels attained whether ovarian failure occurs as a result of surgery, radiation, or menopause. The decrease of estradiol always exceeds that of estrone (13).

Androgen production after ovarian failure also is changed. The mean concentration of androstenedione declines by one half, while testosterone decreases very little after physiologic menopause (15). Production rates of testosterone in one report were almost unchanged from pre- to postmenopause (16), while the production rate of androstenedione was reduced from 3 to 1.5 mg/day (17). The concentrations of several other steroids are also decreased over 50%, including dehydroepiandrosterone and its ester sulfate (18). This finding is surprising because these steroids are predominately adrenal in origin in premenopausal women. The ^{21}C compounds 17-hydroxypregnenolone and 17-hydroxyprogesterone were also lower after menopause (18, 19).

In summary, menopause is associated with a profound decrement in estradiol, but the decrease in estrone is much less marked. Androstenedione concentration

and production decrease to 50%, but testosterone decreases only slightly. Dehydroepiandrosterone and its sulfate, 17-hydroxyprogesterone, and 17-hydroxypregnenolone also decrease after menopause.

Steroid Hormone Source

The source of steroid hormones in the postmenopausal female has attracted much research interest. It was previously thought that although the postmenopausal ovary had little function, some reserve for estrogen production persisted to a variable degree in individual patients. This tissue was thought to be the site of estrone production, which was equal to that of the early follicular phase of premenopausal females (20).

The adrenal gland has also been suspect as a de novo source of estrogens, but direct catheterization revealed that the quantities of phenolic steroids in the adrenal vein effluent are very low (21). In contrast, suppression of adrenal activity by administration of dexamethasone to postmenopausal women produced a 75% decrease in estrone concentration but no significant change in estradiol (22). Similarly, ACTH administration to oophorectomized, postmenopausal females causes a doubling of estrogen excretion (23).

To further diminish the role of the postmenopausal ovary in estradiol synthesis, no change in the production rate of this steroid was noted following ovariectomy in postmenopausal women (24). It was also demonstrated that the postmenopausal ovary in vitro retained no capacity for estrogen synthesis when incubated with radioactive precursors (25). In addition, measurement of differences in estrone and estradiol in peripheral blood and ovarian venous effluent indicated that the role of the postmenopausal ovary in the production of these estrogens was negligible (26).

The postmenopausal ovary has, however, been shown to retain some steroidogenic activity. In vitro conversion of pregnenolone to ^{19}C compounds has been demonstrated in postmenopausal ovarian tissue (25). There is also a marked difference in the concentration of the steroids testosterone and androstenedione in ovarian and peripheral venous blood of postmenopausal women, and a significant correlation exists between testosterone (but not androstenedione) concentrations from these sources (26). These authors suggest that testosterone secretion may be higher after menopause as a result of elevated gonadotropin levels, and other investigators have also arrived at this conclusion (27). This increase in testosterone may explain the hirsutism and other signs of defeminization that sometimes appear after menopause. To corroborate the role of gonadotropin in postmenopausal testosterone synthesis, it has been shown that estrogen administration decreases the blood concentration of this androgen (15). Quantitative estimates, arrived at from studies conducted before and after ovariectomy, indicated that the postmenopausal ovary contributes greater than 50% of the total testosterone production, but only 20% of the androstenedione came from this tissue (15, 19). In an extensive study, Vermeulen (28), using differential suppression and stimulation (dexamethasone, ACTH, human chorionic gonadotropin) demonstrated that in the postmenopausal female, progesterone and 17-hydroxyprogesterone are adrenal in origin and that de-

hydroepiandrosterone and its ester sulfate are secreted mostly by the adrenal. Testosterone, dihydrotestosterone, and androstenedione are both ovarian and adrenal in origin. All of the above steroids demonstrated a diurnal variation, which is consistent with the concept of adrenal participation in synthesis.

As previously noted, the decrement in dehydroepiandrosterone ester sulfate is much in excess of that expected, because most (90%) of this steroid is adrenal in origin. Abraham and Maroulis (29) reported that estrogen apparently has an affect on adrenal steroidogenesis, since dehydroepiandrosterone and its ester sulfate are both restored to near normal concentrations by estrogen treatment. The mechanism of this effect of estrogen is not clear.

Thus, the roles of the postmenopausal ovary and adrenal gland in androgen production seem to be established. It is also unlikely that the postmenopausal ovary plays any role in estrogen secretion. The role of the adrenal gland in postmenopausal estrogen secretion was not immediately apparent, as direct sampling of adrenal effluent yields no estrogenic substances. It was clear, however, that manipulation of adrenal activity by suppression or stimulation leads to marked changes in the concentration of estrone. These findings led to the conclusion that the adrenal gland synthesizes a precursor of estrone and that because of the structural similarities between the steroids, the most likely precursor was androstenedione.

Estrone Production

Estrone production in the postmenopausal woman and the factors that affect this process have been the objects of much study. The possibility that androgens are the precursors of estrone has been recognized since the finding that administration of testosterone to men increased estrogen excretion (30). The possibility that androgen is a substrate for an aromatase activity, not located in steroid-synthesizing tissue, was realized 20 years later (31). This experiment involved administration of testosterone to oophorectomized, adrenalectomized females and demonstrated a resultant increase in estrogen excretion.

The role of androstenedione as a substrate for extraglandular aromatization, in contrast to the role of testosterone, becomes apparent when the quantities of each steroid are considered. In the postmenopausal female, the production rate of testosterone is 350 μg/day (16). Since only 0.12% conversion to estradiol occurs (32), this androgen could account for only a few micrograms of estrogen production. Androstenedione production, at 1500 μg/day, with a conversion of 1.3%, is a more significant source of estrogen. This quantity of estrone still is only 20 μg/day and is less than that found in the early proliferative phase of the menstrual cycle. This value is also less than the reported postmenopausal production rate of 40–50 μg/day (13, 14). It was then reported by Siiteri and MacDonald (20) that in contrast to premenopausal women, in whom the extent of conversion of androstenedione to estrone is 1.3%, the conversion in postmenopausal women is more than doubled. If the total estrone production is determined by the standard isotope dilution method and the result compared to the amount of estrone synthesized from androstenedione conversion, the results

are nearly identical. Thus, the entire source of estrone in the postmenopausal female is from extraglandular conversion of androstenedione (20).

These observations led to further interesting postulates by the above authors (20). In a study of postmenopausal patients with a history of abnormal bleeding, increased estrone production was found. This abnormal estrone synthesis might have been due to increased quantity of precursor or to an increase in the conversion fraction. Instead of the usual 2–3% conversion, these patients demonstrated conversion of up to 9%. The most obvious factor in common about these patients was that their mean body weight was 100 lb above normal. A subsequent study that involved more patients showed a strong correlation between body weight and percentage conversion of androstenedione to estrone. A logical explanation of this increase in conversion is that adipose tissue has an active aromatizing system. At least two in vitro experiments have demonstrated such conversion in fat tissue (33, 34), although activities are low.

Further support for the role of obesity in abnormal estrone synthesis comes from the studies by Judd et al. (35). In these experiments, blood estrone and estradiol concentrations were found to correlate significantly with body weight and excess weight in these obese patients. As anticipated, ovariectomy did not alter estrogen concentration nor was there a correlation among height, age, or years after the menopause. A weight-matched group of patients was studied with and without endometrial carcinoma. No difference in estrogen concentration was found between these two groups.

An extensive study undertaken to further clarify the significance of the conversion percentage (androstenedione to estrone) was reported by Rizkallah et al. (36). They determined conversion fractions by simultaneous injection of [^{14}C]-androstenedione (A) and [^{3}H]estrone (E_1), as described by Siiteri and MacDonald (20). Urine was collected for 5 days. Estrone was isolated and recrystallized until constant isotopic ratios were attained. The conversion fraction equals

$$\frac{R^{I}E_1 - {}^{3}H}{R^{I}A - {}^{14}C} \div \frac{{}^{3}H}{{}^{14}C} E_1,$$

where R^{I} is the amount of radioactivity infused. Tritiated estrone serves as an internal standard, and this calculation represents the amount of androstenedione aromatized at the tissue site rather than reflecting androstenedione excreted as a urinary metabolite of estrone. Rizkallah et al. point out that the mathematical model on which these calculations of conversions are based (37) is only valid under certain conditions. It is requisite that both isotopic forms of estrone undergo the same metabolic fate as the endogenous hormone. This condition might not be met because of metabolism of the tracers prior to mixing. Because of the numerous tissues that are known to effect aromatization, variations in conversion ratio would add complex factors to the above equation. Any product of androstenedione aromatization other than estrone would also result in miscalculation. Further considerations include metabolic isotope effects and variable release rates of estrone from extravascular compartments. The conclusion was reached that conversion fractions calculated by the above equation can be little better than rough approximations of the true value. Nevetheless, these authors found a strong correlation between excess weight (above ideal weight) or

the height/weight ratio and conversion fraction. They also found an increase in conversion fractions after menopause. The conversion fraction also correlated strongly with the estrone production rate determined by isotopic dilution in patients who had abnormal endometrium (carcinoma, hyperplasia) but not in postmenopausal women with normal endometrium. The reason for this difference is not clear. Thus, although the exact meaning of the conversion fraction is unknown, the method of calculation yields a value with some significance.

In contrast to the above paper, which is in partial agreement with the work of Siiteri and MacDonald, the work of Marshall et al. (38) suggests that the conversion fraction is of limited consequence. These investigators find no correlation between conversion rate and body weight. Instead, they present evidence to show that the plasma concentration of androstenedione is the critical factor in determining estrone concentration. A comparison of estrone concentrations in four groups of patients (perimenopausal, postmenopausal, postovariectomy, posthysterectomy) was undertaken. The mean value of estrone in the perimenopausal group was about twice that of the other groups. The same finding occurred when androstenedione was measured. Correlation of the two steroid concentrations is found in each of the above groups, suggesting that the cause of elevated estrone was a high level of androstenedione. In an abstract, Siiteri and coworkers (39) state that they observed elevated androstenedione production rates in patients with endometrial cancer.

Although many uncertainties exist, the source and significance of postmenopausal estrone production are being elucidated. Several studies cited herein show a relation between estrone synthesis and either endometrial cancer, hyperplasia, or such factors as obesity, which are related to cancer. It is also true that several studies demonstrate no correlation between steroid metabolism and cancer and that many patients with endometrial cancer are of normal weight. Siiteri et al. (40) have postulated that long-term exposure to estrone in the virtual absence of other estrogens may be a critical factor in the genesis of estrogen-related tumors.

METABOLIC CONSEQUENCES OF THE MENOPAUSE

The metabolic and tropic alterations that occur after menopause have not been fully delineated. It is known that estrogen plays a role in the most striking immediate symptom of menopause, the hot flash. Known target tissue, such as vaginal mucosa, undergoes involution in the absence of estrogen. These problems are easily managed, if necessary, by estrogen administration. Much evidence has also accumulated that postmenopausal osteoporosis develops as a result of estrogen deprivation. The role of the menopause in coronary artery disease in women is much less clear, and understanding of the effects of estrogen on such tissues as skin also requires more investigation. The lack of estrogen as a cause of perimenopausal psychiatric problems is particularly difficult to unravel. Certainly, hot flashes and atropic vaginitis are a further threat to femininity that is already threatened by cessation of menses. Estrogen therapy is not adequate treatment for a menopausal involutional psychosis, but such treatment may be helpful as adjunctive therapy. Because of a paucity of factual information about

other facets of menopause, this discussion will be limited to the available information concerning osteoporosis and coronary artery disease.

Osteoporosis

The presence of osteoporosis has been a major rationale for the administration of estrogen to postmenopausal women. Up to 25% of women over age 60 may suffer fractures from this disorder. The original classic publication relating these two syndromes was published in 1941 by Albright et al. and promoted the theory that the absence of estrogen's anabolic activity resulted in a decrease in osteoid. Absence of osteoid, the protein matrix for mineralization, led to a decrease in bone strength (42). Since that time, it has been recognized that several factors, such as diet and activity, play a role in the development of osteoporosis. There does appear to be a definite association of bone loss with menopause (43), and this change is more nearly related to the duration of estrogen deprivation than to age (44). The original concept of estrogen's relationship to bone tissue is much more complex, however, than the effect of a positive nitrogen balance induced by the hormone. Over the past decade, it has been realized that estrogen, instead of promoting bone mineralization, acts to prevent bone resorption (45) and thus is an antagonist of parathyroid hormone, among other factors that cause bone turnover. It is therefore not surprising that estrogen has never been reported to be effective in promoting remineralization of osteoporotic bone.

In contrast, several studies cited in a recent review by Heaney (46) demonstrate that postmenopausal bone loss can be prevented by estrogen in daily doses as low as 23 μg of mestranol. The clinical significance of these findings is clouded by the fact that no study has spanned the latent period from menopause to the onset of osteoporotic fractures, which may be 15 years in duration. The only study that purports to demonstrate fracture protection is based on a difference in height loss between treated and untreated groups (47).

In summary, there is good evidence that estrogen therapy will prevent the bone loss associated with menopause. There is only fragmentary data to indicate that the effects of estrogen will be clinically significant in preventing fractures. Since postmenopausal osteoporosis affects only one of five women, it would be helpful if a prediction could be made as to which patients should be treated. Unfortunately, no such predictions can be made concerning women at risk for fracture.

Cardiovascular Disease

Prevention of cardiovascular disease has also been the object of postmenopausal estrogen replacement. The employment of this therapy was based on the apparent fact that women seem to be protected from coronary artery disease until menopause (48). It was also noted that estrogen reversed serum lipid profiles associated with coronary artery disease (49). Another early study that supports this application of estrogens demonstrated inhibition, and even disappearance, of coronary atheromata in estrogen-treated chicks (50). These observations led to the treatment with estrogen of groups of men who had had a single myocar-