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HORMONE REPLACEMENT THERAPY, HEART DISEASE, AND OTHER CONSIDERATIONS

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ABSTRACT

Multiple observational studies suggest a marked reduction in risk of coronary heart disease (CHD) associated with postmenopausal estrogen use. A new meta-analysis presented here extends these results to estrogen plus progestin regimens. Although the findings from observational studies are strong and consistent, and there are several plausible mechanisms by which estrogen might reduce risk for CHD, most of the known biases would tend to exaggerate estrogen's benefit. Further, estrogen therapy clearly increases risk for endometrial hyperplasia and cancer, venous thromboembolic events and gallbladder disease, and long-term use probably also increases the risk of breast cancer. Therefore, until findings from randomized trials confirm and quantitate the benefit of estrogen therapy for prevention of CHD, we believe it should not be recommended to all postmenopausal women.

INTRODUCTION

Postmenopausal estrogen is the most commonly prescribed prescription drug in the United States. Between 1982 and 1992 the number of prescriptions

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increased from 13.6 to 31.7 million (118). The increasing use of 1 noncontraceptive estrogen reflects both the increasing number of postmenopausal women and the increasing number of postulated benefits of therapy. In this paper, we review the risks and benefits of postmenopausal estrogen therapy with a particular focus on the prevention of coronary heart disease, which is by far the largest potential benefit of hormone therapy.

CORONARY HEART DISEASE

Because coronary heart disease (CHD) is the most common and most deadly disease of women, any significant reduction in CHD risk due to hormone therapy would overwhelm any postulated adverse effect. If hormone therapy really reduces risk for CHD, estrogen replacement should be recommended for all postmenopausal women (26, 46). The recognition that estrogen might be cardioprotective has a long history, but the clinical trials necessary to evaluate and quantitate the association are just beginning.

Over 100 years ago, Osler noted that CHD was almost entirely a disease of middle-aged and older men (75). About 50 years later, several lines of evidence converged to suggest that this favored female status was due to estrogen, and that correction of postmenopausal estrogen deficiency might prevent heart disease. As reviewed elsewhere (10, 110), these observations are that: (*a*) coronary artery disease is rare before the age of menopause and more common in young women who have had both ovaries removed; (*b*) estrogen reduces diet-induced atherosclerosis in primates; and (*c*) estrogen raises HDL and lowers LDL cholesterol in men and women.

Nevertheless, the only large, randomized double-blind clinical trial of estrogen and heart disease was performed in men, not women, in the 1960s. Men with heart disease were randomized to five different lipid-lowering therapies or placebo in a trial called the Coronary Drug Project. Conjugated estrogen was used in two of the arms of this trial at doses of 2.5 mg or 5.0 mg daily—approximately four to eight times the dose commonly used in postmenopausal women today. Estrogen therapy was abandoned early in the trial because treated men were observed to have an increased rate of thromboembolic events, myocardial infarction, and cancer (as well as gynecomastia and impotence) (30, 31). The very high doses of estrogen used may have been responsible for the lack of a favorable effect.

At about the same time, studies in premenopausal women taking high-dose oral contraceptives suggested an increased risk of myocardial infarction. Thus, by the early 1970s, estrogen use was thought to increase CHD risk in women.

While there has been no single large trial in women, multiple small trials have been performed to investigate the effect of hormone therapy on variables such as bone density, lipoproteins, clotting factors, and endometrial hyperplasia. Hemminki & McPherson (57) recently identified 22 published randomized trials of estrogen therapy of more than three months (but usually less than 3 years) duration, giving a total of 1818 women assigned to hormones and 1041 assigned to placebo, vitamin supplements, or no treatment. With one exception, cardiovascular outcomes were incidental to the purpose of the trial (recorded only as reasons for drop-outs or adverse events), and the diagnostic criteria were not described. The calculated odds ratio for women taking hormones versus those not taking hormones, based on the pooled data, was 1.39 (95% confidence interval 0.48–3.95) for cardiovascular events (not including venous thromboembolic events). The authors calculated a low probability ($p = 0.03$) of finding a 1.39 odds ratio if estrogen truly halves the risk of cardiovascular disease.

In contrast, many observational studies have found a *lower* risk of CHD in women taking postmenopausal estrogen compared to nonusers. As reviewed below, the results are consistent and biologically plausible, but potential biases are large and most would be expected to spuriously enhance the observed cardioprotective effect.

META-ANALYSES OF OBSERVATIONAL STUDIES OF HORMONES AND HEART DISEASE

Estrogen

Three meta-analyses performed in the early 1990s summarized the findings of these observational studies and reported a 35–50% lower risk of CHD in estrogen users compared to nonusers (21, 46, 96). The meta-analysis shown in Figure 1 is based on a new search of the medical literature that includes all studies published through mid 1997 (1, 6, 13, 22, 33, 34, 39, 52, 53, 58, 59, 69, 71, 80, 82, 88, 89–91, 99, 100–102, 112, 114). Studies resulting in more than one publication were included in the summary estimate only once, using the most recently published risk estimate. General variance-based methods and a fixed effects model were used to calculate the summary estimate (49). Including recently published studies, the summary estimate of the relative risk for CHD among women who ever used estrogen compared to never users is 0.70 (CI, 0.65 to 0.75). Most of these 25 studies were conducted in Caucasian women from English-speaking countries, with the majority from the United States, where unopposed conjugated equine estrogen was by far the predominant regimen.

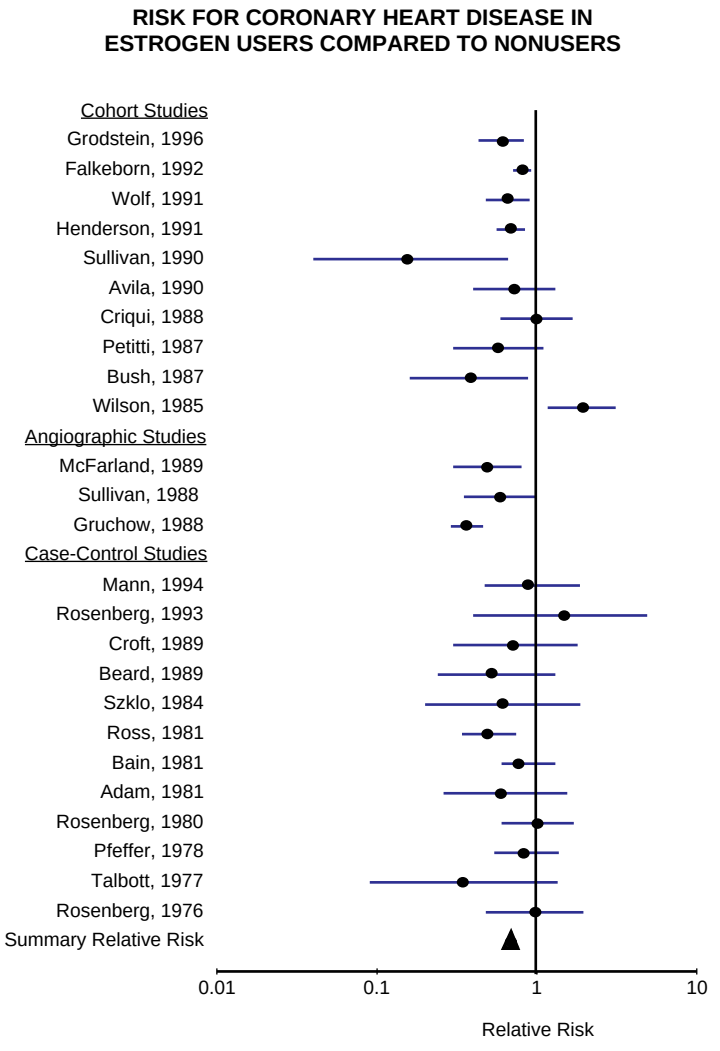

Figure 1 Meta-analysis of studies published up through mid-1997.

Estrogen Plus Progestin

Seven studies, also largely from the United States, have reported the effect of treatment with estrogen plus a progestin, usually medroxyprogesterone acetate (MPA), on CHD risk (39, 52, 69, 74, 85, 89, 103). The results of these studies and a summary estimate of relative risk using the same meta-analytic methods described above are shown in Figure 2. The summary relative risk for CHD

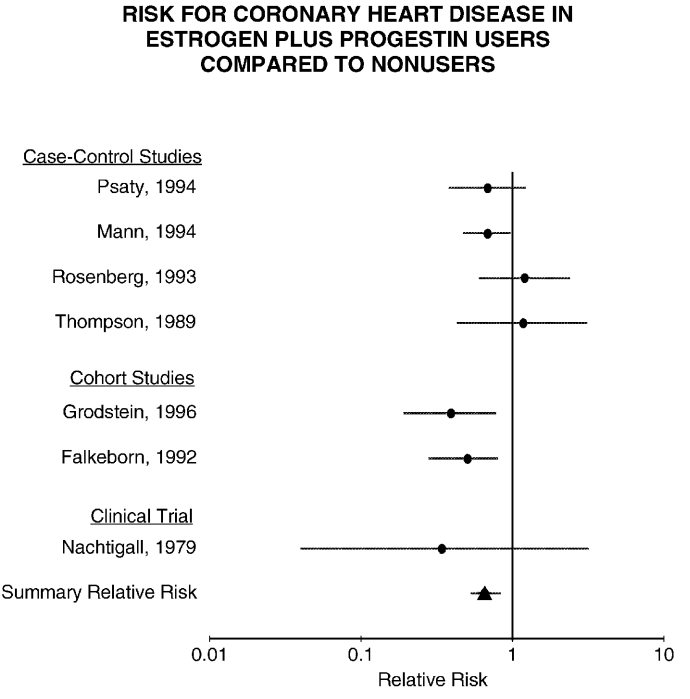

Figure 2 Meta-analysis of seven studies of estrogen plus progestin.

based on these studies is 0.66 (0.53–0.84), very similar to the estimate for unopposed estrogen treatment.

IS IT PLAUSIBLE THAT ESTROGEN REDUCES CHD RISK?

Estrogen has a plethora of possible receptor-mediated and nongenomic effects on many human tissues. Excellent reviews of possible mechanisms of cardioprotection have been published (54, 104). These mechanisms include favorable changes in lipids, lipoproteins, fibrinogen, PAI-1, antithrombin III, vascular reactivity, and antioxidant action. The fact that estrogen has been found to be associated with so many potentially favorable biologic and physiologic changes gives biological plausibility to the thesis that estrogen prevents heart disease.

The most widely appreciated cardiovascular effect of estrogen is on lipoproteins. Oral estrogen lowers LDL cholesterol and elevates HDL cholesterol; transdermal estrogen appears to have a much smaller effect on HDL cholesterol,

suggesting that estrogen's HDL-lowering is mediated by a "first pass" effect through the liver (106).

In the Postmenopausal Estrogen/Progestin Interventions (PEPI) study (115), the first large, long-term randomized placebo-controlled trial of estrogen's effect on common heart disease risk factors, 875 relatively healthy postmenopausal women were randomly assigned to one of five treatment regimens for three years. Treatments were placebo; daily conjugated equine estrogen (CEE); CEE + cyclic MPA; CEE + daily MPA; and CEE + cyclic micronized progesterone (MP). All active treatments significantly reduced LDL cholesterol and increased HDL cholesterol compared to placebo, but CEE alone or with MP raised HDL significantly more than either CEE + MPA regimen. Because nearly one third of PEPI women assigned to unopposed CEE were required to stop taking their medication when they developed endometrial hyperplasia, a separate analysis was performed restricted to women who were able to continue 80% of their assigned medication for three years. In these adherent women, unopposed CEE was associated with a significantly greater increase in HDL than in women adherent to CEE + MP, although CEE + MP remained superior to either CEE + MPA regimen (11).

In women enrolled in PEPI, all active treatment regimens not only raised HDL cholesterol but also raised triglycerides (115). Elevated triglycerides are thought to be a heart disease risk factor, particularly in women, but naturally occurring hypertriglyceridemia is usually accompanied by low HDL cholesterol levels. The clinical significance of the concurrent elevation in both triglycerides and HDL associated with oral estrogen therapy is unknown. Alcohol and bile acid sequestrants also raise both HDL and triglyceride levels and are thought to be cardioprotective.

All active treatment regimens in PEPI also prevented the rise in fibrinogen observed in women assigned to placebo (115), a change expected to reduce the risk of heart disease in women (65). PEPI found no beneficial effect of hormone therapy on several other risk factors previously reported in cross-sectional studies to be improved in women using estrogen therapy. Thus, neither estrogen alone nor estrogen with the progestin formulations used in PEPI had a significant effect on weight, waist-hip ratio, blood pressure, fasting glucose or insulin.

The fact that the LDL and HDL changes are not large enough to explain all of estrogen's apparent CHD benefit suggests that estrogen has other cardioprotective effects. Bush et al (22) and Gruchow et al (53) used statistical modeling to show that only 25% to 50% of the apparent cardioprotection due to estrogen was mediated by favorable changes in HDL-cholesterol. Other reported estrogen effects that would be expected to reduce CHD risk include antioxidant inhibition of oxidation of LDL cholesterol (87), a calcium antagonist effect (28), and prevention of endothelial cell apoptosis (95). Favorable effects on vascular stiffness and endothelin dependent and independent vasodilation (42, 86) have

attracted the most attention and appear to be sex specific. In one study (29), infusion of 17 β-estradiol attenuated acetylcholine-induced coronary artery constriction in women but not men.

Progestins are generally added to the estrogen regimen for treatment of women with a uterus in order to decrease the risk of endometrial cancer (44). As noted above, the addition of either cyclic or continuous MPA to daily estrogen therapy in the PEPI trial resulted in 75–80% less increase in HDL compared to women taking estrogen alone (115). Progestins also appear to block other vascular effects of estrogen in laboratory models and in nonhuman primates. In cynomolgus monkeys, MPA halves the effect of estrogen on coronary artery dilation (111) and essentially ablates estrogen's protective effects on coronary artery atherosclerosis (3). These untoward effects appear to be restricted to MPA, and are not seen with micronized progesterone (2).

BIAS AND THE ESTROGEN-CHD ASSOCIATION

The evidence from observational studies is very consistent, but there are several potential sources of bias that might account for these findings.

Selection Bias

Essentially all of the studies of estrogen and CHD are observational studies, not clinical trials, and therefore are subject to bias—most of which would falsely elevate the apparent benefit of estrogen (see Table 1). In cross-sectional studies, women taking estrogen have more favorable lifestyles, better levels of several heart disease risk factors, and less diabetes than untreated women. Thus, some of estrogen's putative benefits might be spurious, reflecting "a healthy woman effect," in that women prescribed estrogen tend to be: (*a*) more educated and of higher social class, (*b*) leaner with more positive health behaviors, (*c*) healthier, and (*d*) more compliant (7). Education and social class are strongly, independently, and inversely associated with the risk of coronary heart disease in both men and women (63). Matthews and colleagues (70) followed 355 women through the menopause and found that women who elected to take estrogen after the menopause had more favorable levels of multiple coronary

Table 1 Biases for hormone replacement therapy and coronary heart disease

Factors that could falsely increase the observed benefit of hormone replacement therapy:
Not prescribed if cardiovascular disease, hypertension, or diabetes present
Not prescribed if lower socio-economic status, less education
Prescribed for menopause symptoms (thin women)
Prescribed to women with better metabolic risk factors
Prescribed to women with healthier life-style
Used by compliant women (>50% do not continue)

risk factors *before* the menopause than women who chose not to take estrogen. Specifically, they had more favorable HDL cholesterol, fasting insulin, and blood pressure levels, and reported more physical activity, alcohol intake, and education than untreated women. Until recently, sick women were less likely to be prescribed estrogen because hypertension, diabetes, and heart disease were listed as contraindications on the estrogen package-insert.

Compliance Bias

Compliance with hormone therapy requires particularly motivated women who are willing to make regular physician visits, take a daily medication (or two medications if a progestin is added), and tolerate associated uterine bleeding and other side effects. A majority of women prescribed postmenopausal hormones are noncompliant (56). In the NHANES I Follow-up Study, 45% of a representative cohort of US women had used estrogen for at least one month in the early 1970s, but only 20% continued use for five or more years (19). Less than half of women in a Minnesota prescription plan continued estrogen therapy after filling the first prescription (16). Women who take estrogen are an unusually compliant subset of all women, and good compliance has been shown in randomized double blind clinical trials to reduce the risk of CHD events 40% to 60%, even when the medication is placebo. Thus, men in both the Coronary Drug Project (32) and the Beta-Blocker Heart Attack Trial (60) who were highly compliant with their assigned placebo had 50% fewer cardiovascular events than men who did not take the placebo regularly. Similarly, women in the Beta-Blocker Heart Attack trial who were compliant with placebo had a 60% decreased risk of mortality compared to women who were noncompliant (41). Adjustment for multiple known predictors of coronary disease did not explain the decreased risk for coronary disease associated with good adherence to medication. The amount of CHD risk reduction in compliant subjects assigned to placebo is similar to the 50% reduction attributed to estrogen in observational studies.

Diagnostic Detection and Follow-Up Bias

Cross-sectional studies have reported that, among women referred for angiography, estrogen users have less severe coronary atherosclerosis than nonusers (53, 71, 99). However, women taking estrogen are more likely to have ST segment elevation during a graded exercise tolerance test than women not taking estrogen, possibly due to a digitalis-like effect of estrogen (12, 73). Because ST elevation during exercise is one of the most common reasons for referral for coronary angiography, women with normal coronary arteries may be more likely to be referred for angiography if they are taking estrogen. This selection of healthy hormone-using women for angiography could explain some of the observed "antiatherogenic" effect of estrogen. Follow-up of women classified by estrogen use status and severity of atherosclerosis on angiography would be

informative, but the only published study (100) is difficult to interpret because the majority of women with severe coronary atherosclerosis were lost to follow-up.

ESTROGEN USE AND OTHER RISKS AND BENEFITS

Total Mortality

Several observational studies have reported decreased risk of death from nearly all diseases in estrogen users compared to nonusers (23, 37, 40, 58). The largest and most recent of these studies includes about 18 years of observation of postmenopausal nurses (51). In that study, past use of estrogen had no effect on risk for dying, but current use decreased overall risk about 25%. Some consider this universal benefit to be too good to be true—additional evidence for a healthy woman effect (84, 105). The absence of any benefit after two years of discontinuing therapy (51) could also be interpreted as evidence for compliance bias.

Osteoporosis

The best-established benefit of long-term estrogen therapy is a reduced risk of osteoporotic fractures. Multiple observational studies and one clinical trial (68) suggest a 25–50% reduced risk of hip fractures with long-term estrogen use and probably a larger benefit for prevention of spine fractures (25, 108). The validity of these observational study results is supported by clinical trials showing that hormone therapy increases bone density (94, 117), an important predictor of fractures. Addition of progestins, at least the relatively nonandrogenic formulations usually used in the United States, does not significantly alter this benefit (117).

Breast Cancer

The most important and controversial potential adverse effect of hormone therapy is an increased risk of breast cancer, the most common cancer in women and the most feared disease. Multiple epidemiologic studies of estrogen therapy and breast cancer risk have been performed. Four meta-analyses based on the data from these studies found no increased risk for breast cancer in women who ever took estrogen (generally $\leq$5 years of use) compared to nonusers (5, 36, 43, 98). In contrast, a majority of studies suggest an increased risk of breast cancer among women who take estrogen for five to ten years or longer. Figure 3 shows the results of a new meta-analysis based on all eight case-control studies and three cohort studies that provided data on long-term users (15, 20, 27, 38, 61, 66, 67, 72, 78, 93, 97, 113). The summary relative risk estimate based on the findings of these studies is 1.32 (95% CI 1.16–1.51) for women who reported long-term use compared to never users. An increased risk of breast cancer may not persist after estrogen therapy is discontinued

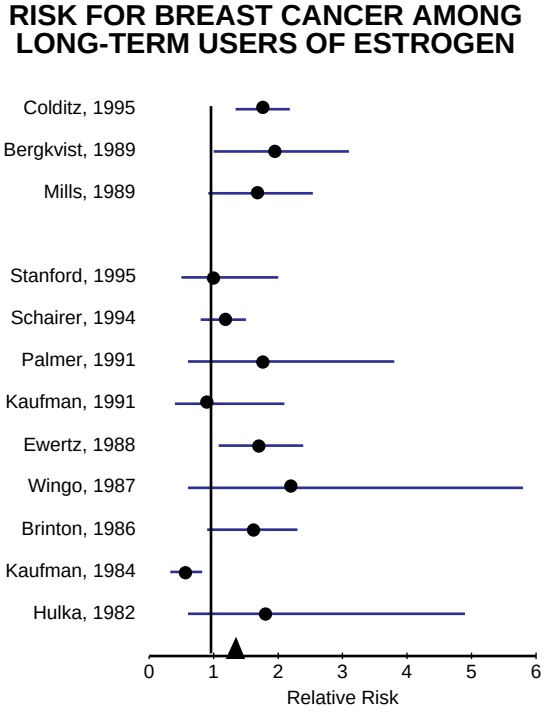

Figure 3 Meta-analysis based on 16 case-control studies.

(51), suggesting that estrogen acts as a promoter rather than a cause of breast cancer.

As reviewed elsewhere (8, 62), estrogen and progestin affect breast tissue differently, and the combination might make breast tissue more susceptible to malignant transformation. In one publication from the Nurse's Health Study (27), the estimated risk of breast cancer associated with estrogen alone was 1.36 compared to 1.50 for estrogen plus progestin therapy. A more recent analysis from the same cohort found that women who took unopposed estrogen had a 5% per year increased risk of breast cancer compared to 9% per year in women taking estrogen plus progestin (GA Colditz, presented at Society for Epidemiologic Research, June 1997).

There is, as yet, no proven intermediate variable that has been studied in clinical trials to either support or refute the observational findings regarding hormone therapy and breast cancer. The most promising marker is the increase in breast density that occurs in 15–50% of women who take replacement estrogen (48). Greater breast density has been found to be independently associated

with an increased risk of breast cancer in at least eight studies (18, 24, 92, 107). This increased risk persists for up to nine years post-mammography, suggesting that masking of breast cancer in denser tissue is not the sole cause of the observed association.

The observational data on postmenopausal estrogen and breast cancer risk are susceptible to bias. The risk for breast cancer among estrogen users may be falsely low if a negative mammogram is usually required before prescription, or falsely high if women who take estrogen are more closely evaluated and more likely to have cancer diagnosed. Earlier studies suggested that women with estrogen-associated breast cancer had a better prognosis than women with breast cancer who were not being treated with estrogen, suggesting diagnostic detection bias; more recent studies, however, suggest an increase in fatal breast cancer as well (51). Selection bias could spuriously decrease observed risk if estrogen has been withheld from women at increased risk for breast cancer (e.g. positive family history of breast cancer) or selectively prescribed to women at reduced risk (e.g. early oophorectomy). Most of the biases would be expected to minimize the true risk (Table 2) (9).

Endometrial Cancer

Estrogen therapy taken without progestin substantially increases the risk for endometrial cancer: Over 30 epidemiologic studies have documented the strong association of unopposed estrogen use with increased endometrial cancer risk (44). The risk increases with increasing dose of estrogen, and particularly with increasing duration of use, such that women with more than ten years of unopposed use have about a tenfold increased risk of endometrial cancer (44). An increased risk of endometrial cancer persists for years after estrogen is discontinued (8).

All of the data linking unopposed estrogen therapy to endometrial cancer are observational and susceptible to bias, but in this case there is an excellent intermediate marker for risk. Several large randomized trials have shown that estrogen therapy markedly increases the risk of atypical endometrial hyperplasia, a

Table 2 Biases for hormone replacement therapy and breast cancer

Factors that could falsely reduce observed risk:
Not used if positive family history of breast cancer
Used after negative mammogram
Used after oophorectomy
Used if upper socio-economic status
Prescribed for menopause symptoms (thin women)
Factors that could increase observed risk:
Frequent examinations and mammograms

premalignant lesion. In the PEPI Trial (116), 30% of women taking unopposed estrogen for three years developed adenomatous or atypical endometrial hyperplasia. Progestins antagonize the effects of estrogen on the endometrium and prevent the development of endometrial hyperplasia. Standard cyclic and daily progestin regimens have each been shown to be effective in reducing risk of hyperplasia (4, 116). Prevention of endometrial hyperplasia and cancer appears to be dependent on adequate dose and duration of progestin use (83, 109). Recent observational studies showing a small increased risk of endometrial cancer after long-term hormone replacement therapy may reflect poor compliance with added progestins (14, 47).

Other Risks and Benefits

Two other risks are well documented: Estrogen therapy causes about a twofold increased risk of gallbladder disease (17, 79, 81) and a two- to threefold increased risk of venous thromboembolic events (35, 45, 50, 55, 64). Other possible but less frequent and less well-documented risks include retinal vein thrombosis and asthma.

Another possible benefit that has received much recent attention is the prevention of Alzheimer's disease. Although several observational studies suggest that estrogen may prevent or delay dementia, the results are not consistent, and most studies lack appropriate control for major confounders such as age, education, and depression (77). Because senile dementia of the Alzheimer's type frequently coexists with multi-infarct dementia, it is noteworthy that observational studies provide no consistent evidence of an estrogen-associated reduced risk of stroke in postmenopausal women (46, 76)—despite the remarkably consistent reduced risk of CHD noted above.

WHY WE NEED CLINICAL TRIALS

Strong evidence suggests that estrogen therapy increases risk for endometrial cancer, but adding a progestin to the estrogen regimen substantially reduces or eliminates this risk. Strong evidence also suggests that hormone therapy reduces risk for fractures, and women at high risk for osteoporotic fractures are likely to benefit. However, the real controversy over hormone replacement therapy is whether *all* women are likely to benefit. The answer to this question is totally dependent on the effect of hormone therapy on CHD risk. If CHD risk is reduced by 30% or more, as suggested in the observational studies, then all women will benefit. If, however, overall risk for CHD is not reduced and risk for breast cancer is increased, the average woman will not benefit and may be harmed. Unfortunately, the evidence regarding breast cancer, the major potential risk of therapy, and CHD, the major potential benefit, is inconclusive.

Randomized trials are required to determine if the findings from observational studies are biased by confounding or compliance. Two large randomized trials are now underway in the United States. The Heart and Estrogen-progestin Replacement Study (HERS) is a secondary prevention trial among 2763 postmenopausal women with known heart disease (and an intact uterus) who were randomly assigned to daily CEE plus MPA therapy or placebo for five years. The primary outcome is new CHD events. This study is scheduled for closure in early 1998, with findings expected later the same year. The Women's Health Initiative (WHI) is a primary prevention trial among 27,500 postmenopausal women. In this trial, women with a uterus are being randomized to daily CEE plus MPA or placebo, and those without a uterus are being randomized to CEE or placebo. Unless the findings require early closure, WHI women will be followed for about 10 years for CHD events, osteoporotic fractures, and cancer. The WHI trial is still enrolling, and results are not expected until about 2005. Other large trials are beginning in the United Kingdom and several European countries, using different hormone regimens.

CONCLUSIONS AND RECOMMENDATIONS

The findings from observational studies that postmenopausal estrogen, with or without a progestin, reduces the risk of coronary heart disease are strong and consistent, and there are several plausible mechanisms by which estrogen might reduce the risk for CHD. However, estrogen therapy clearly increases risk for endometrial hyperplasia and cancer, venous thromboembolic events, and gallbladder disease. Long-term therapy probably also increases the risk of breast cancer. Despite these risks, estrogen therapy would benefit all postmenopausal women if it truly reduces risk for CHD 30% or more. However, if the observed CHD benefit is the result of selection or compliance bias, these risks would balance or outweigh a reduced risk of osteoporotic fractures associated with estrogen therapy. Thus, until findings from randomized trials confirm the benefit of estrogen therapy for prevention of CHD, we believe it should not be routinely recommended for this purpose.

Literature Cited

1. Adam S, Williams V, Vessey M. 1981. Cardiovascular disease and hormone replacement treatment: a pilot case-control study. *Br. Med. J.* 282:1277–78
2. Adams MR, Kaplan JR, Manuck SB, Koritnik DR, Parks JS, et al. 1990. Inhibition of coronary artery atherosclerosis by 17-beta estradiol in ovariectomized

monkeys. Lack of an effect of added progesterone. *Arteriosclerosis* 10:1051–57
3. Adams MR, Register TC, Golden DL, Wagner JD, Williams JK. 1997. Medroxyprogesterone acetate antagonizes inhibitor effects of conjugated equine estrogens on coronary artery atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* 17:217–21
4. Archer D, Pickar J, Bottiglioni F. 1994. Bleeding patterns in postmenopausal women taking continuous combined or sequential regimens of conjugated estrogens with medroxyprogesterone acetate. *Obstet. Gynecol.* 83:686–92
5. Armstrong B. 1988. Oestrogen therapy after the menopause—boon or bane? *Med. J. Aust.* 148:213–14
6. Bain C, Willett W, Hennekens C, Rosner B, Belanger C, et al. 1981. Use of postmenopausal hormones and risk of myocardial infarction. *Circulation* 64:42–46
7. Barrett-Connor E. 1991. Postmenopausal estrogen and prevention bias. *Ann. Intern. Med.* 115:455–56
8. Barrett-Connor E. 1992. Hormone replacement and cancer. *Br. Med. Bull.* 4:345–55
9. Barrett-Connor E. 1994. Postmenopausal estrogen and the risk of breast cancer. *Ann. Epidemiol.* 4:177–80
10. Barrett-Connor E, Bush TL. 1991. Estrogen and coronary heart disease in women. *JAMA* 265:1861–67
11. Barrett-Connor E, Slone S, Greendale G, Kritz-Silverstein D, Espeland M, et al. 1997. The postmenopausal estrogen/progestin interventions (PEPI) study: primary outcomes in adherent women. *Maturitas* 27:261–74
12. Barrett-Connor E, Wilcosky T, Wallace RB, Heiss G. 1986. Resting and exercise electrocardiographic abnormalities associated with sex hormone use in women: The Lipid Research Clinics Program Prevalence Study. *Am. J. Epidemiol.* 123:81–88
13. Beard CM, Kottke TE, Annegers JF, Ballard DJ. 1989. The Rochester Coronary Heart Disease Project: effect of cigarette smoking, hypertension, diabetes, and steroidal estrogen use on coronary heart disease among 40- to 59-year-old women, 1960 through 1982. *Mayo Clin. Proc.* 64:1471–80
14. Beresford SA, Weiss NS, Voigt LF, McKnight B. 1997. Risk of endometrial cancer in relation to use of oestrogen combined with cyclic progestagen therapy in postmenopausal women. *Lancet* 349:458–61
15. Bergkvist L, Adami H, Persson I, Hoover R, Schairer C. 1989. The risk of breast cancer after estrogen and estrogen-progestin replacement. *N. Engl. J. Med.* 321: 293–97
16. Berman RS, Epstein RS, Lydick E. 1997. Risk factors associated with women's compliance with estrogen replacement therapy. *J. Women's Health* 6:219–26
17. Boston Collaborative Drug Surveillance Program. 1974. Surgically confirmed gallbladder disease, venous thromboembolism, and breast tumors in relation to postmenopausal estrogen therapy. A report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. *N. Engl. J. Med.* 290:15–19
18. Boyd NF, Byng JW, Jong RA, Fishell EK, Little LE, et al. 1995. Quantitative classification of mammographic densities and breast cancer risk—results from the Canadian National Breast Screening Study. *J. Natl. Cancer Inst.* 87:670–75
19. Brett KM, Madans JH. 1997. Use of postmenopausal hormone replacement therapy: estimates from a nationally representative cohort study. *Am. J. Epidemiol.* 145:536–45
20. Brinton L, Hoover R, Fraumeni J. 1986. Menopausal oestrogens and breast cancer risk: an expanded case-control study. *Br. J. Cancer* 54:825–32
21. Bush TL. 1990. The epidemiology of cardiovascular disease in postmenopausal women. *Ann. NY Acad. Sci.* 592:263–71
22. Bush TL, Barrett-Connor E, Cowan LD, Criqui MH, Wallace RB, et al. 1987. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program follow-up study. *Circulation* 75:1102–9
23. Bush TL, Cowan LD, Barrett-Connor E, Criqui MH, Karon JM, et al. 1983. Estrogen use and all-cause mortality. Preliminary results from the Lipid Research Clinics Program Follow-Up Study. *JAMA* 249:903–6
24. Byrne C, Schairer C, Wolfe J, Parekh N, Salone M, et al. 1995. Mammographic features and breast cancer risk. Effects with time, age, and menopause status. *J. Natl. Cancer Inst.* 87:1622–29
25. Cauley J, Seeley D, Ensrud K, Ettinger B, Black D, et al. 1995. Estrogen replacement therapy and fractures in older women. *Ann. Intern. Med.* 122:9–16
26. Col NF, Eckman MH, Karas RH, Pauker SG, Goldberg RJ, et al. 1997. Patient-specific decisions about hormone replace-

ment therapy in postmenopausal women. *JAMA* 277:1140–47
27. Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, et al. 1995. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N. Engl. J. Med.* 332:1589–93
28. Collins P, Rosano GM, Jiang C, Lindsay D, Sarrel PM, et al. 1993. Cardiovascular protection by oestrogen—a calcium antagonist effect? *Lancet* 341:1264–65
29. Collins P, Rosano GM, Sarrel PM, Ulrich L, Adamopoulos S, et al. 1995. 17 beta-estradiol attenuates acetylcholine-induced coronary arterial constriction in women but not men with coronary heart disease. *Circulation* 92:24–30
30. Coronary Drug Project Research Group. 1970. The Coronary Drug Project—initial findings leading to modifications of its research protocol. *JAMA* 214:1303–13
31. Coronary Drug Project Research Group. 1973. Findings leading to discontinuation of the 2.5 mg/day estrogen group. *JAMA* 226:652–57
32. Coronary Drug Project Research Group. 1980. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. *N. Engl. J. Med.* 303:1038–41
33. Criqui MH, Suarez L, Barrett-Connor E, McPhillips J, Wingard DL, et al. 1988. Postmenopausal estrogen use and mortality. Results from a prospective study in a defined, homogeneous community. *Am. J. Epidemiol.* 128:606–14
34. Croft P, Hannaford P. 1989. Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners Oral Contraception Study. *Br. Med. J.* 298:165–68
35. Daly E, Vessey M, Hawkins M, Carson J, Gough P, et al. 1996. Risk of venous thromboembolism in users of hormone replacement therapy. *Lancet* 348:977–80
36. Dupont W, Page D. 1991. Menopausal estrogen replacement therapy and breast cancer. *Arch. Intern. Med.* 151:67–72
37. Ettinger B, Friedman GD, Bush T, Quesenberry CP Jr. 1996. Reduced mortality associated with long-term postmenopausal estrogen therapy. *Obstet. Gynecol.* 87:6–12
38. Ewertz M. 1988. Influence of noncontraceptive exogenous and endogenous sex hormones on breast cancer risk in Denmark. *Int. J. Cancer* 42:832–38
39. Falkeborn M, Persson I, Adami HO, Bergstrom R, Eaker E, et al. 1992. The risk of acute myocardial infarction after oestrogen and oestrogen-progestogen replacement. *Br. J. Obstet. Gynaecol.* 99:821–28
40. Folsom AR, Mink PJ, Sellers TA, Hong C-P, Zheng W, et al. 1995. Hormonal replacement therapy and morbidity and mortality in a prospective study of postmenopausal women. *Am. J. Public Health* 85:1128–32
41. Gallagher EJ, Viscoli CM, Horwitz RI. 1993. The relationship of treatment adherence to the risk of death after myocardial infarction in women. *JAMA* 270:742–44
42. Gilligan DM, Badar DM, Panza JA, Quyyumi AA, Cannon RO III. 1994. Acute vascular effects of estrogen in postmenopausal women. *Circulation* 90:786–91
43. Grady D, Ernster V. 1991. Does postmenopausal hormone therapy cause breast cancer? *Am. J. Epidemiol.* 134: 1396–400
44. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. 1995. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet. Gynecol.* 85:304–13
45. Grady D, Hulley SB, Furberg C. 1997. Venous thromboembolic events associated with hormone replacement therapy. *JAMA* 278:477
46. Grady D, Rubin SM, Petitti DB, Fox CS, Black D, et al. 1992. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann. Intern. Med.* 117:1016–37
47. Grady E, Ernster VL. 1997. Hormone replacement therapy and endometrial cancer: Are current hormone replacement regimens safe? *J. Natl. Cancer Inst.* 89:1088–89
48. Greendale GA, Melton B, Sie A, Gatewood O, Olson LK, et al. 1997. The effects of estrogen and estrogen/progestin treatments on mammographic density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. Submitted
49. Greenland S. 1987. Quantitative methods in the review of epidemiologic literature. *Epidemiol. Rev.* 9:1–30
50. Grodstein F, Stampfer M, Goldhaber S, Manson J, Colditz G, et al. 1996. Prospective study of exogenous hormones and risk of pulmonary embolism in women. *Lancet* 348:983–87
51. Grodstein F, Stampfer MJ, Colditz GA, Willett WC, Manson JE, et al. 1997. Postmenopausal hormone therapy and mortality. *N. Engl. J. Med.* 336:1769–75
52. Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Willett WC, et al. 1996. Post-

menopausal estrogen and progestin use and the risk of cardiovascular disease. *N. Engl. J. Med.* 335:453–61
53. Gruchow HW, Anderson AJ, Barboriak JJ, Sobocinski KA. 1988. Postmenopausal use of estrogen and occlusion of coronary arteries. *Am. Heart J.* 115:954–63
54. Guetta V, Cannon RO III. 1996. Cardiovascular effects of estrogen and lipid-lowering therapies in postmenopausal women. *Circulation* 93:1928–37
55. Gutthann S. 1997. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *Br. Med. J.* 314:796–800
56. Hemminki E, Brambilla DJ, McKinlay SM, Posner JG. 1991. Use of estrogens among middle-aged Massachusetts women. *Ann. Pharmacother.* (DICP) 25:418–23
57. Hemminki E, McPherson K. 1997. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *Br. Med. J.* 315:149–53
58. Henderson BE, Paganini-Hill A, Ross RK. 1991. Decreased mortality in users of estrogen replacement therapy. *Arch. Intern. Med.* 151:75–78
59. Hernandez-Avila M, Walker AM, Jick H. 1990. Use of replacement estrogens and the risk of myocardial infarction. *Epidemiology* 1:128–33
60. Horwitz RI, Viscoli CM, Berkman L, Donaldson RM, Horwitz SM, et al. 1990. Treatment adherence and risk of death after a myocardial infarction. *Lancet* 336:542–45
61. Hulka B, Chambless L, Deubner D, Wilkinson W. 1982. Breast cancer and estrogen replacement therapy. *Am. J. Obstet. Gynecol.* 143:638–44
62. Hulka BS. 1990. Hormone-replacement therapy and the risk of breast cancer. *CA Cancer J. Clin.* 40:289–96
63. Iribarren C, Luepker RV, McGovern PG, Arnett DK, et al. 1997. Twelve-year trends in cardiovascular disease risk factors in the Minnesota heart survey: Are socioeconomic differences widening? *Arch. Intern. Med.* 157:873–81
64. Jick H, Derby L, Myers M, Vasilakis C, Newton K. 1996. Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. *Lancet* 348:981–83
65. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. 1987. Fibrinogen and risk of cardiovascular disease. The Framingham Study. *JAMA* 258:1183–86
66. Kaufman D, Miller D, Rosenberg L, Helmrich S, Stolley P, et al. 1984. Noncontraceptive estrogen use and the risk of breast cancer. *JAMA* 252:63–67
67. Kaufman D, Palmer J, DeMouzon J, Rosenberg L, Stolley P, et al. 1991. Estrogen replacement therapy and the risk of breast cancer: results from the Case-Control Surveillance Study. *Am. J. Epidemiol.* 134:1375–85
68. Lufkin EG, Wahner HW, O'Fallon WM, Hodgson SF, Kotowicz MA, et al. 1992. Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann. Intern. Med.* 117:1–9
69. Mann RD, Lis Y, Chukwujindu J, Chanter DO. 1994. A study of the association between hormone replacement therapy, smoking and the occurrence of myocardial infarction in women. *J. Clin. Epidemiol.* 47:307–12
70. Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. 1996. Prior to use of estrogen replacement therapy, are users healthier than nonusers? *Am. J. Epidemiol.* 143:971–78
71. McFarland K, Boniface M, Hornung C, Earnhardt W, Humphries J. 1989. Risk factors and noncontraceptive estrogen use in women with and without coronary disease. *Am. Heart J.* 117:1209–14
72. Mills P, Beeson W, Phillips R, Fraser G. 1989. Prospective study of exogenous hormone use and breast cancer in Seventh-Day Adventists. *Cancer* 64:591–97
73. Morise AP, Dalal JN, Duval RD. 1993. Frequency of oral estrogen replacement therapy in women with normal and abnormal exercise electrocardiograms and normal coronary arteries by angiogram. *Am. J. Cardiol.* 72:1197–99
74. Nachtigall LE, Nachtigall RH, Nachtigall RD, Beckman EM. 1979. Estrogen replacement therapy II: a prospective study in the relationship to carcinoma and cardiovascular and metabolic problems. *Obstet. Gynecol.* 54:74–79
75. Osler W. 1896. Lectures on angina pectoris and allied states. *NY Med. J.* 64:20–44
76. Paganini-Hill A. 1995. Estrogen replacement therapy and stroke. *Progr. Cardiovasc. Dis.* 38:223–42
77. Paganini-Hill A. 1996. Oestrogen replacement therapy and Alzheimer's disease. *Br. J. Obstet. Gynaecol.* 103 (Suppl. 13):80–86
78. Palmer J, Rosenberg L, Clarke E, Miller D, Shapiro S. 1991. Breast cancer risk after estrogen replacement therapy: results from the Toronto Breast Cancer Study.

Am. J. Epidemiol. 134:1386–95
79. Petitti DB, Friedman GD, Klatsky AI. 1981. Association of a history of gallbladder disease with a reduced concentration of high-density-lipoprotein cholesterol. *N. Engl. J. Med.* 304:1396–98
80. Petitti DB, Perlman JA, Sideny S. 1987. Noncontraceptive estrogens and mortality: long-term follow-up of women in the Walnut Creek Study. *Obstet. Gynecol.* 70(3 Pt. 1):289–93
81. Petitti DB, Sidney S, Perlman JA. 1988. Increased risk of cholecystectomy in users of supplemental estrogen. *Gastroenterology* 94:91–95
82. Pfeffer R, Whipple G, Kurosaki T, Chapman J. 1978. Coronary risk and estrogen use in postmenopausal women. *Am. J. Epidemiol.* 107:479–87
83. Pike MC, Peters RK, Cozen W, Probst-Hensch NM, Felix JC, et al. 1997. Estrogen-progestin replacement therapy and endometrial cancer. *J. Natl. Cancer Inst.* 89:1110–16
84. Posthuma WF, Westendorp RG, Vandenbroucke JP. 1994. Cardioprotective effect of hormone replacement therapy in postmenopausal women: Is the evidence biased? *Br. Med. J.* 308:1268–69
85. Psaty B, Heckbert S, Atkins D, Lemaitre R, Koepsell T, et al. 1994. The risk of myocardial infarction associated with the combined use of estrogens and progestins in postmenopausal women. *Arch. Intern. Med.* 154:13333–39
86. Reis SE, Gloth ST, Blumenthal RS, Resar JR, Zacur HA, et al. 1994. Ethinyl estradiol acutely attenuates abnormal coronary vasomotor responses to acetylcholine in postmenopausal women. *Circulation* 89:52–60
87. Rifici VA, Khachadurian AK. 1992. The inhibition of low-density lipoprotein oxidation by 17-beta estradiol. *Metabolism* 41:1110–14
88. Rosenberg L, Armstrong B, Jick H. 1976. Myocardial infarction and estrogen therapy in postmenopausal women. *N. Engl. J. Med.* 294:1256–59
89. Rosenberg L, Palmer JR, Shapiro S. 1993. A case-control study of myocardial infarction in relation to use of estrogen supplements. *Am. J. Epidemiol.* 137:54–63
90. Rosenberg L, Slone D, Shapiro S, Kaufman D, Stolley PD, et al. 1980. Noncontraceptive estrogens and myocardial infarction in young women. *JAMA* 244:339–42
91. Ross RK, Paganini-Hill A, Mack T, Arthur M, Henderson B. 1981. Menopausal oestrogen therapy and protection from death from ischaemic heart disease. *Lancet* 1:858–60
92. Saftlas AF, Hoover RN, Brinton LA, Szklo M, Olson DR, et al. 1991. Mammographic densities and risk of breast cancer. *Cancer* 67:2833–38
93. Schairer C, Byrne C, Keyl P, Brinton L, Sturgeon S, et al. 1994. Menopausal estrogen and estrogen-progestin replacement therapy and risk of breast cancer (United States). *Cancer Causes Control* 5:491–500
94. Speroff L, Rowan J, Symons J, Genant H, Walborn W. 1996. The comparative effect on bone density, endometrium and lipids of continuous hormones as replacement therapy (CHART Study). *JAMA* 276:1397–403
95. Spyridopoulos I, Sullivan AB, Kearney M, Isner JM, Losordo DW. 1997. Estrogen-receptor-mediated inhibition of human endothelial cell apoptosis. Estradiol as a survival factor. *Circulation* 95:1505–14
96. Stampfer MJ, Colditz GA. 1991. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev. Med.* 20:47–63
97. Stanford J, Weiss N, Voigt L, Daling J, Habel L, et al. 1995. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. *JAMA* 274:137–42
98. Steinberg K, Thacker S, Smith S, Stroup D, Zack M, et al. 1991. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. *JAMA* 265:1985–90
99. Sullivan J, Vander Zwaag R, Lemp G, Hughes J, Maddock V, et al. 1988. Postmenopausal estrogen use and coronary artherosclerosis. *Ann. Intern. Med.* 108:358–63
100. Sullivan JM, Vander Zwaag R, Hughes JP, Maddock V, Kroetz FW, et al. 1990. Estrogen replacement and coronary artery disease. Effect on survival in postmenopausal women. *Arch. Intern. Med.* 150: 2557–62
101. Szklo M, Tonascia J, Goris L, Bloom I. 1984. Estrogen use and myocardial infarction risk: a case-control study. *Prev. Med.* 13:510–16
102. Talbott E, Kuller L, Detre K, Perper J. 1977. Biologic and psychosocial risk factors of sudden death from coronary disease in white women. *Am. J. Cardiol.* 39:858–64

103. Thompson SG, Meade TW, Greenberg G. 1989. The use of hormonal replacement therapy and the risk of stroke and myocardial infarction in women. *J. Epidemiol. Commun. Health* 43:173–78
104. Tikkanen MJ. 1993. Mechanisms of cardiovascular protection by postmenopausal hormone replacement therapy. *Cardiovasc. Risk Factors* 3:138–43
105. Vandenbroucke JP. 1991. Postmenopausal oestrogen and cardioprotection. *Lancet* 337:833–34
106. Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. 1991. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. *N. Engl. J. Med.* 325:1196–204
107. Warner E, Lockwood G, Tritchler D, Boyd NF. 1992. The risk of breast cancer associated with mammographic parenchymal patterns. A meta-analysis of the published literature to examine the effect of method of classification. *Cancer Detect. Prevent.* 16:67–72
108. Weiss NS, Ure CL, Ballard JH. 1980. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen. *N. Engl. J. Med.* 303:1195–98
109. Whitehead M, Fraser D. 1987. The effects of estrogens and progestogens on the endometrium. *Obstet. Gynecol. Clin. North Am.* 14:299–320
110. WHO Scientific Group on Research on the Menopause. 1994. *Research on the Menopause in the 1990s. WHO Tech. Rep. #866*. Rep. WHO Sci. Group, Geneva, June 14–17
111. Williams JK, Honore EK, Washburn SA, Clarkson TB. 1994. Effects of hormone replacement therapy on reactivity of atherosclerotic coronary arteries in cynomolgus monkeys. *J. Am. Coll. Cardiol.* 24:1757–61
112. Wilson PW, Garrison RJ, Castelli WPL. 1985. Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50. The Framingham Study. *N. Engl. J. Med.* 313:1038–43
113. Wingo P, Layde P, Lee N, Rubin G, Ory H. 1987. The risk of breast cancer in postmenopausal women who have used estrogen replacement therapy. *JAMA* 257:209–15
114. Wolf PH, Madans JH, Finucane FF, Higgins M, Kleinman JC. 1991. Reduction of cardiovascular disease-related mortality among postmenopausal women who use hormones: evidence from a national cohort. *Am. J. Obstetr. Gynecol.* 164:489–94
115. Writing Group for the PEPI Trial. 1995. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. *JAMA* 273:199–208
116. Writing Group for the PEPI Trial. 1996. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. *JAMA* 275:370–75
117. Writing Group for the PEPI Trial. 1996. Effects of hormone therapy on bone mineral density. *JAMA* 276:1389–96
118. Wysowski DK, Golden L, Burke L. 1995. Use of menopausal estrogens and medroxyprogesterone in the United States, 1982–1992. *Obstet. Gynecol.* 85:6–10