Chapter 3

Treatment of Menopausal Symptoms and Prevention of Future Disease

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As the previous chapter notes, the state of knowledge concerning the role of estrogen in the development of menopausal symptoms and the development of age-related disorders is deficient. This knowledge gap leads to uncertainty about the most appropriate treatments for symptoms during the perimenopause and about preventive measures for disease occurring in the postmenopausal years. Estrogen has been proven effective in the amelioration of hot flashes and in slowing the rate of bone loss, and it plays a role in protection against cardiovascular disease, although the causal explanation remains speculative. Yet it can simultaneously increase the risks of endometial and breast cancer. These competing risks and benefits create a clinical conundrum. As the population ages, with more women facing the decision of whether to make use of this drug, calls for more complete and better formulated information are likely to increase in volume. This chapter explores the basis for and use of hormones to treat perimenopausal symptoms and postmenopausal disease, and describes what is known about nonhormonal interventions such as other therapeutics, nutrition, and exercise. It also describes the menopause clinic, a new setting for addressing the health needs of midlife and older women. Last, it presents what is known about the reasons women seek the treatments they do.

ESTROGEN THERAPY

Hormone therapy that uses estrogen alone (ET) is by far the single most efficacious treatment strategy in the management of acute perimenopausal symptoms. Orally administered ET is 95 percent effective in reducing the severity and frequency of hot flashes and is frequently prescribed for the relief of insomnia resulting from vasomotor changes (59). In vaginal cream form it is prescribed to reverse atrophic urogenital changes (87). Symptom relief may not occur until at least 2 weeks of treatment have been administered. Side effects of estrogen use may include headache, breast tenderness, bloating, and water retention.

Estrogen therapy uses both conjugated (derived from the urine of pregnant mares) and synthetic estrogens; synthetic agents, however, are used at much higher doses and more frequently for contraception than for treatment of menopausal symptoms. Both conjugated and synthetic hormones control symptoms at equivalent doses (11).

The restoration of a sense of well-being, termed a ‘‘mental tonic’ effect (109,1 10), has also been attributed to estrogen use, although there is no evidence documenting such an effect (see ch. 2). Recent data on the biobehavioral aspects of the menopause (see ch. 2) suggest that physicians need to look more deeply into the root causes of emotional distress in menopausal women before prescribing estrogen. Although evidence shows that estrogen may affect the central nervous system, anxiety and depression in menopausal women often have other causes that deserve investigation. Estrogen’s documented relief of hot flashes alone may improve the general mood of women who have been uncomfortable. Estrogen therapy may also alleviate depression in some women, although routine use of estrogens to treat postmenopausal women for depressive symptoms may be inappropriate (95). On balance, when standardized tests are used, estrogens do not appear to improve emotional well-being (50).

In terms of metabolic effects, oral estrogen therapy maintains higher serum high-density lipoprotein (HDL) cholesterol levels (“good cholesterol”) and lower serum low-density lipoprotein (LDL) cholesterol levels (’’bad cholesterol’ (27,93). Daily administration of the routine dose of estrogen (0.625 milligram [mg]) slightly lowers LDL cholesterol levels and raises HDL levels by about 15 percent (114). Estrogen therapy thus brings these levels to a point that is comparable to premenopausal values and that also is associated with a lower incidence of cardiovascular disease (15,66,70,114).

Estrogen has other metabolic effects as well. For example, it increases serum triglycerides-the storage form of lipids-by as much as 20 percent; the significance of this action, however, is unknown (78,93). For the most part, this level of triglyceride elevation does not produce any increased risk of atherosclerosis or pancreatitis (60). The transdermal use of estrogen, on the other hand, does not affect

triglycerides at all and also is not associated with the same increase in HDL that is seen with oral therapy. This difference in effect from the two types of administration has important clinical consequences. Physicians should prescribe oral estrogens for patients with low HDL; they should prescribe transdermal estrogen therapy for those patients whose initial clinical profile includes hypertriglyceridemia (78,1 14).

Estrogens may also affect the prostaglandin-thromboxane system, causing vascular dilatation and reduced platelet aggregation (71,85). In addition, estrogen therapy reduces serum calcium and phosphorus levels, and decreases urinary excretion of calcium; these changes (with others) restore a metabolic profile characteristic of a reduced rate of accelerated bone loss—and thus a reduced risk of development of osteoporosis (63).

Estrogens can be taken in a variety of different preparations, by various routes of administration, and in different dosages. Oral preparations are most often prescribed; other, less common routes of administration are subcutaneous implants (not approved for use in the United States), transdermal skin patches, or percutaneous (cream) applications (also not available in the United States). Nonoral applications deliver estrogen directly into the systemic circulation; as a result, they can be given in lower doses to achieve the appropriate physiological levels because they avoid the 'first-pass' effect that occurs in the liver, where a substantial proportion of ingested estrogens of greater potency are converted into estrogens of reduced potency (e.g., estrone sulfate) (75).

However, nonoral estrogen preparations may have negative aspects that should be balanced against their favorable qualities. For example, the potential cardiovascular benefits of nonoral preparations are uncertain because they do not produce lipoprotein profiles as rapidly as oral formulations (35,52,103). Where oral estrogen will increase HDL cholesterol in 4 to 8 weeks, nonoral estrogen may take 12 to 24 weeks (34). Additional drawbacks in the use of the transdermal patch are its greater cost compared with oral administration and the tendency of the adhesive to produce skin irritations (erythema) in approximately 17 to 30 percent of users (24,98).

Historically, contraindications to the use of estrogen include reproductive and especially estrogen-sensitive tumors, thromboembolitic disease, and acute liver disease. Previously, a recent myocardial infarction or cerebrovascular accident (see table 3-1) were also considered contraindications, but with the knowledge now available, more patients who have experienced previous thromboembolic disease, myocardial infarction, and cerebrovascular disease are being placed on hormonal therapy (78).

One of the well-known effects of estrogen alone (i.e., unopposed estrogen) is its stimulation of endometrial proliferation, which can lead to hyperplasia (uncontrolled growth) and sometimes to endometrial cancer (for further discussion, see the later section on the cancer risks of hormone therapy). Since the end of the 1970s, scientists have consistently reported an excess incidence of endometrial cancer in nonhysterectomized users of unopposed estrogen (46). These data have resulted in important changes in estrogen administration. First, lower doses of estrogen, commonly 0.625 mg per day of conjugated estrogens, are being prescribed; second, as discussed later, cyclic therapy using a combination of estrogen and a progestin is generally recommended.

COMBINED HORMONE THERAPY

Some clinicians and medical groups recommend adding a progestin (also known as a progestogen) to estrogen therapy because progestins oppose some of the actions of estrogen and prevent endometrial overgrowth, irregular bleeding, and excess risk of endometrial cancer. When a progestin is added to estrogen therapy, the treatment is considered to be ''combined' and is often referred to as hormone replacement therapy, or HRT. As previously noted, for the purposes of this report, an estrogen/progestin regimen is referred to as combined hormone therapy, or CHT. Cyclic (also known as sequential) use of a progestin for at least 10 to 12 days during a 25-day schedule of estrogen (or during a schedule of continuous estrogen use) reduces the risk of endometrial cancer by inhibiting continued proliferation of the endometrium and inducing its maturation and complete shedding (116).

The progestins that were initially used in CHT were derivatives of testosterone and 19-nortestosterone. Thus, in addition to their progestogenic properties, they also had androgenic (masculinizing) effects. The most widely used progestin in the United States is medroxyprogesterone. More recently, natural progesterone in the form of micronized progesterone has become available, although it is not yet

Table 3-l-Contraindications to Estrogen Use

Absolute contraindications	Relative contraindications	Subjective complaints
Stroke	Cigarette smoking/significant nicotine abuse	Nausea/gastrointestinal irritation
Recent myocardial infarction	Fibrocystic breast disease	Headaches
Breast cancer	Familial hyperlipidemias	Breakthrough bleeding
Endometrial adenocarcinoma	Hypertension aggravated by estrogen therapy	Depression
Other estrogen-dependent tumors	Pancreatitis	fluid retention
Acute liver disease	Hepatic porphyria	
Pancreatic disease	Endometrial hyperplasia	
Gallbladder disease	Leiomyomata uteri	
Chronic impaired liver function	Endometriosis	
Recent venous thromboembolic event	Migraine headache	
Chronic thrombophlebitis		
Undiagnosed vaginal bleeding		

SOURCE: R.L. Young, N.S. Kumar, and J.W. Goldzieher, "Management of Menopause When Estrogen Cannot Be Used," Drugs 40(2):220-230, 1990.

approved for use in this country. The Food and Drug Administration (FDA) has approved the use of progestins for the treatment of amenorrhea, abnormal uterine bleeding, and endometriosis. No progestin has been approved for use in CHT, but physicians continue to prescribe them for this purpose (see ch. 4). Progestins alone are effective in treating hot flashes and can be used when estrogen is contraindicated. However, most progestin use related to CHT occurs in conjunction with estrogen.

Physicians most often prescribe combination therapy for women with intact uteri **to** counteract the increased risk of endometrial cancer associated with estrogen therapy. There is no official standard or protocol for administering or prescribing combination therapy and no conclusive studies **to** indicate which regimen is most beneficial. In addition, studies that meet adequate design, duration, and sample-size requirements have yet to be performed to deterrnine conclusively the risks and benefits of long-term use (more than 10 years) of combined therapy (9).

Frequently, the use of a progestin in combination with estrogen therapy is associated with unpleasant side effects, both physical (breast tenderness, bloating, edema, abdominal cramping, weight gain) and psychological (anxiety, irritability, depression). Cyclical progestin use (see below) also results in withdrawal bleeding; this is frequently perceived as a major source of inconvenience and is one of the principal reasons for lack of compliance with prescribed regimens among older women. Clinicians are experimenting with various regimens that will either make bleeding more predictable or eliminate it entirely (69). The most commonly prescribed regimens are cyclic administration of estrogen and progestin, continuous administration of estrogen plus intermittent progestin, and, increasingly, continuous/combined administration of estrogen and progestin (see table 3-2). Cyclic administration typically uses estrogen for the first 25 days of the calendar month and adds progestin on days 14 to 25. Both hormones are stopped for the last days of the month at which point withdrawal bleeding occurs. Another cyclic method involves daily use of both estrogen and progestin for 21 days, followed by 7 days of no use of either hormone. A regimen of continuous use of estrogen with intermittent progestin involves administration of estrogen every day and administration of progestin for the first 12 days of the calendar month. Withdrawal bleeding typically occurs for several days after progestin use is stopped. Under the continuous/combined regimen, estrogen and progestin are both administered daily, and withdrawal bleeding is diminished or eliminated.

The side effects of progestins vary according to the type used and the dosage. For example, depression is reported more often in patients for whom Provera is prescribed than in those receiving the 19-nortestosterone derivatives such as Norlutate (78). By reducing the dose or by prescribing natural progesterone, some of these side effects can be avoided (78).

Short-term studies have shown that the addition of a progestin may attenuate the cardioprotective lipid profile of higher levels of HDL cholesterol produced by unopposed estrogen (116). Longer studies (6 to 12 months or more) have shown no adverse effects (33,35,52,53,99,103). Regardless of these uncertainties, most physicians recommend the use of combination therapy, perhaps because the long-

Table 3-2—Estrogen and Progestin Regimens

Common Doses Used

Estrogens

0.3 mg conjugated estrogen
0.625 mg conjugated estrogen
0.9 mg conjugated estrogen
1.25 mg conjugated estrogen
0.05 mg transdermal estrogen
0.10 mg transdermal estrogen

Progestins

5 mg medroxyprogesterone acetate
10 mg medroxyprogesterone acetate
2.5 mg medroxyprogesterone acetate
5 mg norethindrone acetate
5 mg norethindrone

Typical Regimens

Cyclic estrogen plus progestin

Estrogen: days 1 to 25 (0.625 mg or transdermal patch changed two times/week)
Progestin: days 14 to 25 (5 or 10 mg)
Stop both: days 26 to end of the month

OR

Estrogen and progestin: days 1 to 21 (estrogen-0.625 mg or transdermal patch changed two times/week; progestin-5 or 10 mg)
Stop both: last 7 days of the month

Continuous estrogen with intermittent progestin

Estrogen: 365 days/year (0.625 mg or transdermal patch changed two times/week)
Progestin: days 1 to 12 of the month (5 or 10 mg)

Continuous/combined

Estrogen and progestin daily (estrogen+O.625 mg or transdermal patch changed two times/week; progestin—2.5 mg)

SOURCE: W. Utian, *Managing Your Menopause (New York, NY:* Prentice Hall Press, 1990).

term risks associated with the addition of a progestin are not well defined, while those of endometrial cancer from unopposed estrogens are well established. Unfortunately, studies designed to define risks and benefits more clearly have met with a number of problems. High dropout rates (up to 30 percent) have plagued most of these efforts, in large part because at least within the first 3 months, not only may it be difficult to establish amenorrhea but regular withdrawal bleeding may be supplanted by more bothersome chronic and irregular bleeding patterns (116). Consequently, no data are available on the long-term effects on the endometrium of combination therapy. In addition, it has yet to be proved that this treatment maintains or increases the benefits of unopposed estrogen on the skeletal or cardiovascular systems, or improves compliance among users. In general, clinical researchers in the field consider unopposed estrogen acceptable as long as there is adequate monitoring for endometrial cancer with yearly biopsies (13).

USE OF HORMONES TO PREVENT BONE LOSS AND PROTECT AGAINST OSTEOPOROSIS

Researchers have long recognized the extreme sensitivity of the skeleton to the loss of ovarian hormones as a result of natural and especially surgical (oophorectomy) menopause; they have also documented the profound effect of exogenous estrogen (externally administered) on the maintenance of bone mass and skeletal integrity (38). In addition, studies have shown that long-term use of estrogen protects against postmenopausal bone loss (74) and osteoporosis (30,38,65) for as long as 10 years-and possibly longer. Although the specific mechanisms of the protective effects of estrogen are unknown, it is generally accepted that estrogen suppresses the enhanced rate of bone breakdown characteristic of acute ovarian hormone deficiency in oophorectomized and perimenopausal women (38,43). At the same time, it conserves stores of skeletal calcium by promoting more efficient absorption and utilization of dietary calcium (44), restores serum calcium and phosphorus (critical to healthy bone), and increases alkaline phosphatase (a useful biological marker of the bone remodeling cycle) to levels comparable to those in premenopausal women (64). Once estrogen replacement stops, however, bone loss resumes, and at a rate faster than normal. For this reason, some physicians advocate extended estrogen therapy (10 to 15 years), and some even advocate lifelong use.

The treatment of established postmenopausal osteoporosis remains unsatisfactory, because available therapies can do little more than slow the progression of bone loss. Prevention of the disorder is still the best strategy (notwithstanding a recent

report that showed that therapy with estrogen and calcium could retard bone loss in the hip and even promote increased vertebral density in postmenopausal osteoporotics) (64). Currently, there is no acceptable therapy that can restore lost interconnections of architectural elements of bone (which serve structurally to provide biomechanical stability) or prevent further fractures in patients who have osteoporosis. However, some researchers have speculated that estrogen used for 5 years after the menopause--when bone loss is the most accelerated—can decrease by 50 percent a woman's chances of suffering a hip fracture later in life (81). This claim has been the subject of some controversy (17).

Other factors that are believed to be important in maintaining g skeletal integrity include dietary calcium and physical exercise. Inadequate dietary calcium is known to exacerbate bone loss (45), and women who are beyond the acute menopausal phase (or at least 5 yearn postmenopause) may realize benefits in bone mineral conservation from increased dietary intake of calcium (25). Yet even megadoses of calcium cannot compare with the effectiveness of estrogen therapy in successfully preventing the accelerated bone loss that may occur during the perimenopause ***(89).*** Interestingly, several reports have shown that combining high-calcium supplements with a hormone regimen increases the efficacy of estrogen in skeletal conservation (31,86). This finding suggests the possibility of using lower doses of estrogen, which could reduce the side effects of CHT and increase compliance with the regimen.

Physical exercise has a positive effect on muscle and skeletal mass and strength, whereas immobilization is known to promote bone loss. But no studies are available to show that the estrogen reduction component of the perimenopause can be successfully overcome by exercise. Preliminary data from one study show that within the first 5 years of the perimenopause, women can slow down the rate of bone loss with aerobic exercise three times a week (78). However, no controlled trials have been able to demonstrate a decrease in the incidence of fracture after either dietary or exercise interventions, although weight-bearing exercise is frequently recommended for women.

USE OF ESTROGENS TO PREVENT CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is by far the leading cause of death in the United States. Thus, even minor changes in risk as a result of estrogen therapy could improve the Nation's collective health. Initially, concerns were raised about the safety of exogenous estrogens and their effect on the heart; these concerns stemmed from the serious adverse effects attributable to the use of oral contraceptives. For example, the high-dose, high-potency estrogen preparations used in oral contraceptives in the 1960s brought an increased occurrence of thrombosis, severe hypertensive episodes, and massive hypertriglyceridemia with pancreatitis or overt diabetes (55). In addition, some more recent studies of noncontraceptive estrogen preparations have shown an increased risk of cardiovascular morbidity and mortality in users of postmenopausal estrogens compared with nonusers (117). Nevertheless, the preponderance of the evidence suggests that estrogen therapy is associated with very substantial reductions-greater than ***50*** percent—in the risk of cardiovascular disease and associated mortality (12,21,42,47,66,102).

In one meta-analysis of 19 studies, 15 show a reduction in risk among estrogen users, 2 show no effect, and 2 report an increased risk (29). A more recent meta-analysis looked at the results of 16 prospective studies and found decreased risks in 15 of them (101). A recent report has shown that the risk of death from stroke, myocardial infarction, and cardiovascular death in current estrogen users has been reduced by almost 50 percent, with a reduction in overall mortality of 40 percent after 15 years of use (47). Furthermore, estrogen use has been associated with enhanced survival in women with angiographic evidence of coronary artery disease (105); it has also been associated with a reduced risk of stroke in the presence of other, concurrent risk factors such as hypertension, obesity, and previous myocardial infarction (79).

The mechanisms of the cardioprotective effect of exogenous estrogen are unclear. Recent work has shown that in newly menopausal women, oral estrogens may confer a protective effect by maintaining levels of HDL and LDL cholesterol at premenopausal values (27). Data from the Lipid

Research Clinics show a 65 percent reduction in CVD mortality, which suggests that a large proportion of the beneficial effects of estrogen on CVD endpoints may be mediated by the elevation of HDL cholesterol levels (14). It also appears that the reduction in LDL cholesterol that occurs with estrogen therapy (although less consistently observed) may play a cardioprotective role (9). In one study, estrogen users had LDL levels approximately 7 percent lower than those of nonusers. Such a difference would correspond theoretically to about a 14 percent reduction in CVD risk (60,100). In fact, it now appears that oophorectomy alone in the premenopausal patient may be associated with increased risk of coronary heart disease as well as with osteoporosis (115).

As is the case in assessing the risk of endometrial cancer, one finds little information on the long-term effects of hormone therapy on endpoints of CVD when regimens other than unopposed oral estrogens are involved. Some data on the short-term effects of combination therapy suggest that progestins may oppose the favorable HDL and LDL profiles, achieved by estrogen alone (66); others show few, if any, adverse effects on lipid profiles, especially with the use of medroxyprogesterone acetate, an oral progestin that is modestly androgenic (9,27).

Nonhormonal, behavioral interventions, such as smoking cessation, dietary modification, exercise, and weight reduction (or control), may also have beneficial effects on risk factors for osteoporosis and CVD, but, again, there are few available data. The use of such interventions, in addition to or in lieu of hormone therapy (particularly in asymptomatic women without an enhanced risk of osteoporosis), deserves study, especially since these approaches pose potentially fewer risks than replacement therapy ***(76).***

Until recently, many researchers have seen the use of postmenopausal estrogen as a marker for socioeconomic, clinical, constitutional, or lifestyle variables that *a priori* place postmenopausal estrogen users at lower risk for cardiovascular disease (21). This belief has prevailed because women for whom estrogen is prescribed are generally healthier, leaner, and of higher socioeconomic status than women who are not so treated. In addition, most of the women evaluated in previous studies were treated with conjugated equine estrogen, usually administered without a progestin and probably prescribed in higher doses than would be recommended today. Therefore, any conclusions about the cardioprotective effects of estrogen cannot necessarily be extrapolated to other estrogens, to lower doses, or to estrogen used in combination with progestin (8). In 1991, however, results from the Nurses' Health Study virtually eliminated the biases in selection (and recall) that have plagued other studies and eliminated the confounding variables usually attributed to studies of estrogen therapy and CVD, such as the contribution of age, access to medical care, and risk factors (e.g., cigarette smoking, diabetes, hypertension, hypercholesterolemia) (102). The results of this study suggest a causal association between the use of estrogen and a reduced risk of coronary disease, although the causal effect was not established. The study also did not consider the effects of added progestins on CVD. Until carefully controlled clinical trials are completed, the contribution of estrogen to reduction of CVD cannot be fully understood.

CANCER RISKS OF HORMONE THERAPY

Estrogens and progesterones, although naturally occurring substances, are drugs whose administration carries some risks. The risk of endometrial cancer associated with the use of unopposed estrogen is well documented (29). The association of estrogen use and breast cancer remains speculative, but there is evidence that long-term use (for 10 years or more) can increase risk. Of more than 44 studies on estrogen therapy and breast cancer, some found significant increases in some subgroups of women while others found significant decreases in other subgroups (26,34). The cancer risks posed by progestins remain speculative as well; their effect on the breast in particular is a matter of controversy and has not been the subject of adequate investigation.

Endometrial Cancer

Early studies of estrogen therapy without the addition of progestin found increases in the risk of endometrial cancer of two- to twentyfold in postmenopausal women (54). More recent studies evaluating the use of unopposed estrogen at the current lower doses show that such administration carries at least a fivefold increased risk of endometrial cancer (7). This kind of cancer is relatively rare and is not

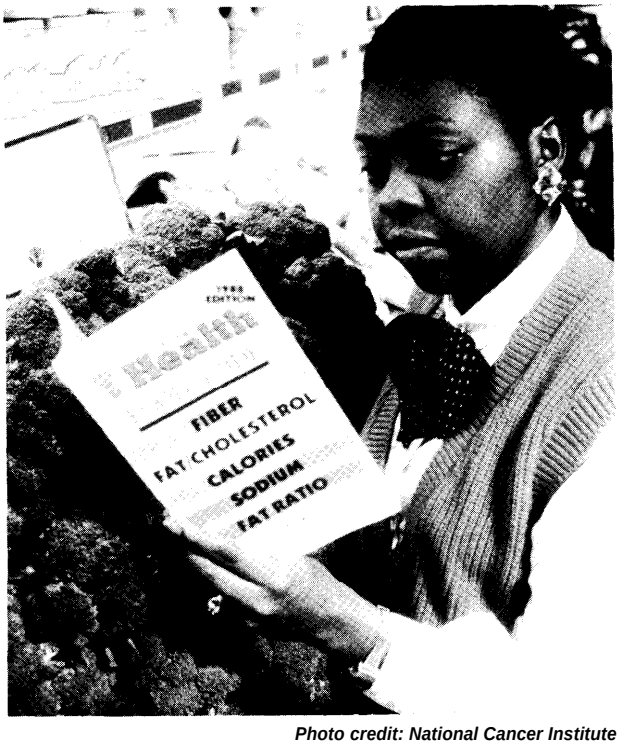


Photo credit: National Cancer Institute

Regular exercise, a healthy diet, moderate alcohol consumption, and a smoke-free environment contribute to reductions in heart disease and cancer.

fatal in the vast majority of cases associated with estrogen use (29). In addition, the endometrial cancer that appears to be caused by estrogen use is of a lower grade and becomes apparent at an earlier stage than endometrial cancer that arises in nonusers (100). Advocates of the use of estrogen to prevent osteoporosis and CVD argue that any increased risk of endometrial cancer pales in comparison to the benefits gained from preventing these diseases (18,102). In addition, they claim, endometrial cancer is easily detected by routine, periodic endometrial biopsy; if cancer is found, a hysterectomy can be performed. However, the assumption that physicians 'will prescribe, or that women will make use of, endometrial biopsies is problematic.

Breast Cancer

After lung cancer, breast cancer is the second leading cause of death from cancer in women. In 1991, an estimated 175,000 women will be diagnosed as having breast cancer, and the lifetime risk of this disease for U.S. women has risen to one in nine. Furtherrnore, 44,500 American women will die of this disease in 1991 (2). **Any adverse effect** of **exogenous estrogens on the risk** of **breast cancer, even if small, would be highly significant, given the high baseline risk, as well as the high cost to society, of this illness.**

A woman's cumulative lifetime exposure to estrogen is strongly related to her risk of developing breast cancer. The earlier a woman begins to menstruate, and the greater the number of ovulatory cycles (an index of cumulative estrogen and progesterone exposure), the greater her risk of breast cancer. Artificial menopause, brought about by oophorectomy, has been shown to markedly reduce the risk of breast cancer, possibly because it lowers a woman's lifetime exposure to estrogen (90,107). Thus, risk is inversely related to age at either artificial or natural menopause. Recently, **some** doctors have begun prescribing an experimental synthetic hormone, tamoxifen, for the treatment of breast cancer, along with surgery (see box 3-A).

The relationship between the use of estrogen and breast cancer is far more controversial than the link between estrogen and endometrial cancer. Evidence from experimental and clinical studies supports the concept that overstimulation of a target tissue by hormones involved in the regulation of that tissue may play an important role in causing cancers, particularly those of the breast and reproductive tract (46). It is generally accepted that ***endogenous*** (naturally occurring) estrogens play an important role in the causation of breast cancer (56). Despite a wealth of epidemiologic studies (26,104), it has been difficult to prove that ***exogenous*** estrogens, given at the time of the menopause, have a similar effect. The often conflicting results of these studies stem from the complexity of the biological issues addressed, the heterogeneity of the populations studied, inherent biases arising from the study methodologies, and the variety of approaches chosen, including the assessment of subgroup populations.

In particular, the nature of the treatment and control populations that are being studied, and variations in the dose, duration, and type of estrogen used may be responsible for the substantial differences in the estimated increase in risk to be found among many of the studies (26,104). A recent meta-analysis summarizing the literature suggests that conjugated estrogens at dosages less than or equal to 0.625 mg per day probably do not pose a substantially increased risk of breast cancer, particu-

Box 3-A—Tamoxifen and Breast Cancer

Tamoxifen is a synthetic hormone that is widely used as an adjuvant to surgery for the treatment of breast cancer. Its use leads to a demonstrably lower risk of the occurrence of new breast tumors and in the recurrence of **breast cancer. In studies thus** far, tamoxifen has demonstrated both estrogenic and antiestrogenic effects, but **it is** not well characterized It has an antiestrogenic effect on the breast and an apparently estrogenic effect **on the** endometrium, vaginal mucosa, lower urinary tract, and (possibly) cholesterol and bone. The side effects also are not well understood but are known to include menopausal-like symptoms (especially hot flashes), depression, increased risk of blood clots, and increased risk of endometrial cancer.

Based on the successful use of tamoxifen in the prevention of new tumors and of recurrence of cancer in breast cancer patients, both the United States and the United Kingdom plan to undertake long-term prevention studies of tarmoxifen in healthy women. Both studies are 5-year, randomized, double-blind placebo-controlled trials in which half the women will receive tamoxifen and half will receive a placebo. The U.S. study will be conducted by the National Surgical Adjuvant Breast and Bowel Project and is jointly sponsored by the National Cancer institute and the National Heart, Lung, and Blood Institute. It is slated to beginin January 1992 and will ultimately involve 16,000 healthy women who are at increased risk for breast cancer, as determined by age or family history. The study will be conducted at 70 centers. The U.K. study will include 10,000 women.

No one disputes the need for research into the prevention of breast cancer, but these studies nonetheless have provoked controversy both within and outside the scientific community. Many argue that healthy women should not be treated with a drug whose side effects are not well understood for the prevention of a disease that they **may** or may not get. These arguments are countered by contentions similar to those made for the use of unopposed estrogens for the treatment of menopausal symptoms and the prevention of osteoporosis and cardiovascular disease: the risks-e.g., the development of endometrial cancer, which is readily treatabl-are outweighed by tamoxifen's potential beneficial effect on the prevention of breast cancer. Some researchers suggest that the increased risk of endometrial cancer seen with tamoxifen can be countered by concurrent use of progestin. The controversy surrounding the planned trials is particularly intense because they constitute the first time that a large number of healthy women will be given a drug for cancer prevention.

SOURCES: *The Wal Street Journal, "Tamoxifen* Helps Prevent New Tumors in Breast Cancer Patients, Study Finds," Sept. 18, 1991; G. Kolata, "A Powerful Hormone To Be Tested in War To Prevent Breast Cancer," The New York *Times,* Sept. 19, 1991, section B, p. 6; 'T. Fornander, B. Cedermark A. Mattson, et al., "Adjuvant Tamoxifen in Early Breast Cancer: Occurrence of New Primary Cancers," *The Lancet,* Jan. **21, 1989,** pp. 117-119; A. Miodrag, P. Eklund, R. Burton, et al., "Tamoxifen and Partial Oestrogen Agonism in postmenopausal Women" *Age and Ageing 20:52-54, 1991;* A. Oakley, "Tamoxifen: In Whose Best Interest?" New *Scientist,* June 22, 1991, p. 12; "Tamoxifen Breast Cancer Prevention Study Should 'Proceed,'" *F-D-C Reports 53(27):T&G4 T&G-5, July 8,* 1991.

larly if the duration of use does not exceed 10 years (26). Some studies, however, have shown an increased risk with increasing duration of use or with daily dosages greater than 1.25 mg per day (90). In June 1991, an advisory committee to the FDA agreed that long-term, unopposed estrogen therapy is associated with a slightly increased incidence of breast cancer, citing an increased risk of 30 percent after 15 years of use. But also in 1991, investigators working on the Nurses' Health Study reported no effect of duration of use of estrogens on the risk of breast cancer. This study found that the risk of breast cancer was significantly elevated among current users (33 percent) but was not increased for past users. The authors speculate that the lack of a duration effect suggests that estrogens may act acutely to increase risk and that this effect is reversible, perhaps within 2 years of cessation of use (19,20). The study did not consider the effect of a woman's age at the menopause. On the one hand, younger age at menopause is associated with a lower risk of breast cancer; on the other hand, women who experience early menopause generally show greater use of hormone therapy (84). Additional contributing risk factors, such as benign breast disease and family history of breast cancer (29), have received inadequate exploration in relation to hormone use. Table 3-3 summarizes the conflicting results of five studies conducted since 1985.

A cautious interpretation of the best available data is that estrogen therapy is associated with an increase in the risk of **breast cancer. This increased risk is on the order of 30 to 80 percent and appears to be no larger than a doubling** of **risk. Moreover, the increased risk appears to be limited to users of more than 15 to 20 years'**

Photo credit: National Cancer Institute

A laboratory technician performing an estrogen receptor assay on breast tissue to assist in the determination of treatment for a breast cancer patient.

duration and may be concentrated among those with other risk factors for the disease. The increased risk may also be restricted to those women who used doses larger than the current dose of 0.625 mg per day of conjugated estrogen—many studies fail to separate the effects of duration of use from those of higher dose (106).

No study of the risk of breast cancer among women using estrogen has found an increase in mortality-but few have addressed this issue directly (26,104). Studies that have examined cancer mortality have found reduced risk of death from breast cancer among estrogen users; other studies have found an increase in the number of smaller, earlier stage tumors (18). These findings suggest that ET (or the patient characteristics associated with its use) may increase the *rate of diagnosis* of breast cancer, rather than its true incidence or mortality from it, reflecting, in part, a detection bias. In **addition, researchers speculate that exogenous estrogen stimulates growth of slow-growing, low-grade tumors that are less aggressive; once estrogen is withdrawn, survival is better than among women who have never used estrogens (18,34,102). In any case, it appears unlikely that progestins will have a protective effect, as they do on the endometrium (13,18,36,49).**

Finally, evidence is lacking to determine the effect on breast cancer of adding progestins to estrogen (49). It has been hypothesized that estrogen plus a progestin would be more carcinogenic than estrogen alone (58). Indeed, some preliminary evidence from European studies suggests that adding a progestin to estrogen may pose higher risks for breast cancer than are found with the use of estrogen alone (10,32) (see table 3-4). One Swedish study reported a tendency toward a fourfold increase in breast cancer in women who used combined therapy for 6 to 9 years (10). The kind of estrogen commonly used in Sweden is estradiol, which is similar in effect to the conjugated estrogen preparations usually prescribed in the United States (11).

Critics of the study claim that because of wide confidence intervals the increased risk is not statistically significant (23,5 1). The possibility of detection bias should also be considered: Swedish physicians may require more frequent physical examinations for women to renew hormone prescriptions (23,28). On the other hand, because the reasons for the prescription or nonprescription of CHT usually are not specified, the role of selection bias is difficult to identify in nonrandomized studies. For example, in the one study citing a protective effect, a reluctance to use estrogens (with or without progestin) among women with potential risk factors—such as family history of breast cancer or a history of late age at first pregnancy or no pregnancy—may have contributed to the finding of a reduced risk of breast cancer (36). In the U.S. studies evaluated for this report, the hormonal regimen consisted of unopposed, conjugated estrogens. Long-term **data on the effect of added progestins on risk for breast cancer are extremely limited, and accumulated knowledge from these studies is inconsistent and controversial (29).** A carefully designed, large-scale study of the potential causal role in breast cancer of exogenous menopausal progestins is needed (see ch. 5).

Hepatobiliary Disease

Another possible risk associated with ET is a greater likelihood of gallbladder disease; it is estimated that 131 out of 100,000 cases of gallblad-

Table 3-3—Recent U.S. Studies of Hormone Therapy and Breast Cancer

Authors, year	Study design	Subjects	Duration of use: Years	Relative risk[a]	95 percent confidence interval	Comments
Brinton et al., 1988	Case control; 29 geographic areas; screening program; volunteers	1,960 cases; 2,258 controls; postmenopausal	5 to 9 10 to 14 15 to 19 20+	1.1 0.8 1.3 1.5	0.9 to 1.3 0.5 to 1.3 0.6 to 2.6 0.9 to 2.3	Significant trend risk by duration
Wingo et al., 1987	Case control; population based; 8 geographic areas; Cancer and Steroid Hormone Study	1,369 cases; 1,645 controls; age less than 55; postmenopausal	5 to 9 10 to 14 15 to 19 20+	1.1 0.8 1.3 1.8	0.8 to 1.5 0.5 to 1.3 0.6 to 2.6 0.6 to 5.8	No significant trend
Buring et al., 987	Prospective; cohort; Nurses' Health Study	33,335 subjects; 221 cases; ages 30 to 55; postmenopausal	[illegible] to 9 10+	1.5 0.9	1.0 to 2.2 0.4 to 1.6	No significant trend
M D d et 1986	Case-control; population based; King County, Washington	183 cases; 531 controls; ages 50 to 74; postmenopausal	6+	0.6		No significant trend
Mills et al., 1989	Prospective; cohort; California; Seventh-Day Adventists	11,468 subjects; number of cases not specified; ages 25 and older; postmenopausal	to [illegible] 1[illegible]+	2.7 1.5	1.6 to 4.6 0.9 to 2.5	Risks increased for all durations; interaction between age at menopause and estrogen use

[a]The referent is never users of hormone therapy.

SOURCE: B. Hulka, "Hormone Replacement Therapy and the Risk of Breast Cancer," *CA-A Cancer Journal for Clinicians* 405:291, 1990.

Table 3-4—European Studies of Hormone Therapy and Breast Cancer

Authors, year	Study design	Subjects	Duration of Use: Years	Duration of Use: Relative risk[a]	Duration of Use: 95 percent confidence interval	Comments
Bergkvist et al., 1989 (Sweden)	Population-based; prospective; cohort	23,244 exposed, 253 cases; ages 35 and older; 6 percent premenopausal	6 to 8 9+	1.3 1.7	0.9 to 1.9 1.1 to 2.7	Six or more years of use; risk= 1.8, conjugated conjugated estrogen: relative risk = 1.3, estrogen + progestin: relative risk = 4.4
Ewertz, 1988 (Denmark)	Population-based; case control	1,486 cases; 1,336 controls	6 to 8 9 to 11	1.8a 1 .3b	1.0 to 3.4[b] 0.7 to 2.5	Risk increased for sequential estrogen + progestin and estrogen; interaction between age at menopause and estrogen use

aThe referent is never users of hormone therapy.
bEsti$_{ma}$t$_{e}$s are for women who experience a natural menopause.

SOURCE: B. Hulka, "Hormone Replacement Therapy and the Risk of Breast Cancer," CA-A *Cancer Journal for Clinicians 405:291,* 1990,

der disease can be attributed to estrogen therapy. Orally administered estrogens are absorbed through the small bowel and pass to the liver where they are metabolized before fully entering the circulation. Some investigators have speculated that these hormones might stimulate gallstone formation, but until 1988 the evidence was inconclusive, given that the only available studies were conducted when estrogens were prescribed at higher doses (48). In 1988, researchers found that the risk of gallbladder disease in estrogen users persists after therapy ends, concluding that the effect of estrogen use on the gallbladder should be considered in weighing the net risks and benefits of the use of estrogen (82).

PROFESSIONAL GUIDELINES

It is standard in medical practice for professional associations or societies to issue standards or guidelines for practice regarding drugs and procedures. In the case of hormone therapy, the American College of Obstetrics and Gynecology (ACOG) has been the most active group in issuing such guidance. In June 1986, ACOG published a technical bulletin on estrogen therapy (3). The publication listed indications for use, which include vasomotor effects (hot flashes) and osteogenic, cardiovascular, genitourinary, and gonadal symptoms (this last for use in adolescent girls for treatment of hypogonadism). Other considerations for use include dermatologic and psychological indications. The ACOG publication also listed complications associated with ET including hyperplasia and endometrial cancer, breast cancer, and hepatic effects. Contraindications for use are unexplained vaginal bleeding, acute liver disease, chronic impaired liver function, acute vascular thrombosis, and breast and endometrial cancer. Last, the publication discussed management and prescribing practices for the drug.

More recently, in July 1988, ACOG issued a technical bulletin (4) on osteoporosis, describing the physiology and diagnosis of the disease, dietary and exercise regimens as prevention, and the use of estrogen to slow the rate of bone loss. In February 1990, the college issued a committee opinion (5), which concluded that in women with a history of endometrial carcinoma, estrogens could be used for the same indications as for other women, except that the selection of appropriate candidates for therapy should be based on prognostic indicators and the level of risk that the patient is willing to assume. If the patient is free of tumor, concluded the committee, ET cannot result in recurrence. If she is harboring an estrogen-dependent neoplasm in her body, it will eventually recur; however, ET may result in an earlier recurrence. The report concluded that the need for progestational agents in addition to estrogen is unknown at present.

In 1988, the first International Consensus Conference on progestin use in postmenopausal women concluded that progestins are indicated for opposing the effects of estrogen on the endometrium. The group further concluded that the effect of progestins on breast tissue was unknown, as was its effect on the cardioprotective benefits provided by estrogen (108).

The American College of Physicians is in the process of drafting a position paper on ET, but it is not available at the time of this writing (96).

ALTERNATIVE TREATMENTS FOR MENOPAUSAL SYMPTOMS

Estrogen is the most widely used treatment for menopausal symptoms, specifically, for vasomotor symptoms or hot flashes. But estrogen is contraindicated for a number of women, and consequently they and others seek nonhormonal and nondrug treatments for these symptoms. There is limited research on alternatives to hormone therapy, which consist of the use of other hormones, nonhormonal drugs, and nondrug products, and widespread clinical investigation into most of these treatments is nonexistent. Many small-scale studies have been done, however, and evidence shows that these treatments are somewhat successful in remedying hot flashes (although none are as effective as estrogen). Anecdotally, many women reportedly try ''home remedies' to alleviate menopausal complaints. It is not clear, however, whether these remedies are effective and if they are, for what level of severity of complaints (80).

Progestins

Some physicians prescribe progestins for hot flashes, although no progestin formulation has received FDA approval for this indication. Evidence that progestins are effective in relieving hot flashes includes studies of depomedroxyprogesterone acetate (depo-MPA), medroxyprogesterone acetate (MPA), and megestrol acetate. Depending on the dose, depo-MPA, which was studied among women with endometrial cancer, relieved hot flashes by as

much as 85 percent. Other studies showed that oral administration of MPA, which is the active ingredient in Provera and Amen, reduced hot flashes 15 to 87 percent of the time, again depending on the dose (1,113). These studies also found a strong placebo effect. Women treated with a placebo experienced a 25.9 percent decrease in hot flashes; they had an additional 34.5 percent reduction when they were then given MPA. Women who began treatment with MPA experienced a 73.9 percent decline in symptoms, but their hot flashes worsened when MPA administration stopped and a placebo was given (94). Megestrol acetate decreased hot flashes by as much as 90 percent, but its administration was accompanied by side effects that included bloating, irregular vaginal bleeding, breast tenderness, and mood changes (113). Because of the side effects, **the evidence of placebo effect, and the fact that progestin does not improve vaginal atrophy or protect against osteoporosis, the use of progestin to treat hot flashes is only recommended for women for whom estrogen is contraindicated or undesirable.**

Nonhormonal Drugs

Physicians may also prescribe nonhormonal drugs for hot flashes, and one such drug, Bellergal, has FDA approval for the treatment of menopausal disorders, specitlcally, hot flashes, sweating, restlessness, and insomnia. Bellergal contains phenobarbital, belladonna, and ergotamine tartrate and is potentially addictive (83). It has a 50 percent effectiveness rate for the relief of hot flashes, but its potentially addictive effects warrant careful use (113). No other drugs that have been tested and that are used to treat hot flashes have been approved by the FDA for this use; nonetheless, doctors use many types of drugs to relieve these symptoms, despite the lack of FDA approval and of appropriate labeling for such an indication. These drugs include

- sedatives and tranquilizers,
- nonsteroidal anti-inflammatory agents,
- alpha-adrenergics,
- antidopaminergics,
- beta-blockers,
- opiate receptor antagonists,
- aromatic aminoacid decarboxylase inhibitors, and
- nonsteroidal antiestrogens.

One popular nonhormonal drug treatment is Catapres transdermal patches, which use a form of clonidine, an antihypertensive (75). This treatment is best tolerated by hypertensive patients and can reduce hot flashes by as much as 40 percent. Side effects include dizziness, dry mouth, fatigue, irritability, and nausea (113,1 18). Inderal, another antihypertensive drug (a beta-blocker), has also been used successfully (75). Other alpha-adrenergic drugs that are prescribed for hot flashes include aldomet and lofexidine. Veralipride is an example of an antidopaminergic compound that in many clinical studies has demonstrated a 60 to 80 percent reduction in hot flashes; it is also effective for treating severe flushing (118). Beta-blockers-sotalol, for example reduce hot flashes as well. The mechanisms of action for the different kinds of substances are not well understood, and many of the drugs have been studied only in very small patient populations. In addition, although many of these compounds can be used to treat hot flashes, they are not effective for other menopausal symptoms, including vaginal dryness, atrophy, anxiety, and sleeplessness, and they do not protect against osteoporosis (118). Studies are needed to increase knowledge about alternatives to hormone therapy for women who choose not to undergo long-term treatment or for whom estrogen is contraindicated (67,68).

Nondrug Treatments

Alternative, nondrug therapies for hot flashes exist, but their efficacy and extent of use are largely unknown, and much of what evidence exists is anecdotal. Natural remedies for menopausal symptoms include vitamins, garlic and herbs, ginseng, biofeedback, diet and nutrition, and exercise.

For example, some women claim that vitamin E gives them more energy and an improved sense of well-being, and that it relieves hot flashes and vaginal dryness. In fact, clinical study has demonstrated its effectiveness, both in its elemental form and as derived from the diet. Reports also indicate that other vitamins, including vitamins B and C, help relieve menopausal symptoms (73,97). Garlic and herbs, used in moderation, have been recommended by some to treat symptoms; examples of effective herbs include chamomile, catnip, hops, and passion flower (73).

Ginseng, which is a root and a source of plant estrogen, is the natural remedy most often mentioned for the relief of menopausal symptoms. It can be taken in capsule form; as a tea, powder, or syrup; or in the root form. Clinical research on ginseng is limited, and much of the evidence for its effectiveness is anecdotal and historical in nature. No clinical studies have been done to measure the effectiveness of ginseng compared with a placebo, and its use for the treatment of menopausal symptoms is neither officially endorsed nor regulated by the FDA (97).

Biofeedback has been noted as a treatment for hot flashes, because of its use in treating hypertension, stress, and tension headaches, and its demonstrated effectiveness in regulating body temperature. Little research has been done, however, and little information is available to assess the extent of its use or its effectiveness in relieving hot flashes. There are minimal research data on the effect of exercise on the alleviation of hot flashes, although one study showed positive effects and a decrease in severity with exercise (112). Whatever its effectiveness may be in treating hot flashes, exercise is encouraged for the prevention of bone loss and osteoporosis.

USE OF HORMONE THERAPY AMONG MENOPAUSAL WOMEN

Although natural menopause does not necessarily result in increased use of health care services (6), segments of the medical community continue to view it as a disease or as a disease-causing condition requiring treatment. The belief of some physicians that ET or CHT should always be prescribed at menopause, combined with conflicting information concerning the risks and benefits of hormone therapy, has resulted in fluctuations over the past 30 years in the prescription of noncontraceptive hormonal products. These factors generate a number of research issues pertaining to women's use of hormone therapy. Although examination of the use of hormone therapy among menopausal women is far from complete, investigators have shed some light on several questions:

- How prevalent is the use of hormone therapy at menopause?
- Who uses hormone therapy?
- What factors affect a woman's decision to use hormone therapy?
- Do women comply with prescribed regimens? Why or why not?

The following sections describe what is known.

Prevalence of Use of Hormone Therapy

The lack of good data on the use of hormone therapy is a major problem because it confuses any interpretation of risks and benefits. If it is not clear how many women are actually using such therapy, projections of risks and benefits are bound to be erroneous. There are no definitive figures on the number of women who currently use either ET or CHT; as a result, several studies have employed trends in sales to estimate use. In 1985, for example, it was observed that retail prescriptions of noncontraceptive estrogens had increased steadily between 1966 and 1975 (57). By 1976, however, sales had dropped by about 30 percent after reports of a link between estrogen and increased risk of endometrial carcinoma; sales continued to decline until 1980 (92). After 1980, noncontraceptive estrogen sales began increasing once again with the discovery that adding progestin to estrogen therapy offset the increased risk (92). As of 1980, lower doses apparently were being used, and a trend toward concurrent prescription of progestins was being seen (57).

An analysis of the type of diagnoses associated with the prescriptions dispensed revealed a number of findings. These estimates offer some perspective on the percentage of the population exposed to noncontraceptive estrogen and progestin in 1983; it must be recognized, however, that these figures underestimate actual exposure levels when short-term treatment is taken into consideration (57). Findings include the following:

- The estrogens were used primarily for menopause-related conditions in women.
- Virtually all of the estrogen prescriptions for men were for treating prostate cancer in the elderly (57).

A national picture of hormonal exposure is difficult to piece together inasmuch as the number of noncontraceptive estrogen and progestin prescriptions dispensed per capita varies according to geographic location. For example, by the end of its 5-year project, the Massachusetts Women's Health Study found that 9.2 percent of the study population was being treated with hormonal products (6). By contrast, a study of a California community conducted in 1986-87 generated very different numbers. In a telephone survey of 954 postmenopausal

women between the ages of 50 and 65 years, 32 percent reported estrogen use, and 6 percent of those reporting estrogen use also reported use of progestin (41). This higher usage on the West Coast ties in with data showing that although 21 percent of the U.S. population resides on the East Coast, past studies have shown that only 12 percent of prescriptions for noncontraceptive estrogen are written there (57).

All of these results conflict with findings in recent surveys of physicians, however. These investigations showed that 75 to 95 percent of gynecologists would prescribe estrogen therapy for most of their patients. Estimates from pharmaceutical marketing surveys, on the other hand, found a 43 percent use rate among women living in the western portion of the United States (41).

Users of Hormone Therapy

In addition to geographic variation in the number of women using replacement therapy, researchers have identified other usage trends. The California community study noted earlier found no differences between users and nonusers in their histories of high cholesterol, diabetes, or heart problems. However, women who used estrogen therapy were younger, thinner, lived in smaller household units, and were less likely to be widowed (41). The younger age of hormone users may reflect a greater proportion of recently menopausal women, as well as efforts to control menopausal symptoms and decrease bone density loss (41).

Another study examined the prevalence and determinants of use of estrogen in 9,704 nonblack women 65 years of age or older (mean age, 71.7). These investigators found that 14 percent of the women reported current use of oral estrogen, with 11 percent taking estrogen alone and 2.8 percent taking estrogen with progestin. Hysterectomy was strongly associated with the choice to use estrogen (hysterectomized women were five times more likely to have taken estrogen and two times more likely to continue using it for a long time) (16).

The finding of lower body weights among estrogen users may be partly attributable to increased menopausal symptoms resulting from lower endogenous estrogen levels or to the awareness of physicians of the increased risk for osteoporosis among thinner women. The findings that estrogen users are less likely to be widowed and that they have fewer people living in their households maybe associated with a greater level of health-care-seeking behavior (41).

Women's Decisionmaking About Hormone Therapy

The discrepancy between the stated prescribing philosophies of physicians and the actual use of hormone therapy suggests that menopausal women may be assuming the role of informed consumer rather than accepting without question the treatments prescribed by their doctors. Preliminary 5-year data from the Massachusetts Women's Health Survey found that among patients receiving hormone therapy for the first time, 20 to 30 percent never filled their prescriptions because they were not fully convinced of the benefits and safety of such therapy (87). The participation of patients in decisionmaking has received considerable attention within the medical arena. Not involving women in the decision to take hormones can lead to women carrying unfilled prescriptions (91).

Research to evaluate the decisionmaking of women regarding hormone therapy has sought to identify and systematically assess the factors that affect these judgments (92). One study evaluated 252 women from the general population between 45 and 55 years of age; all had an intact uterus and were not currently receiving hormone therapy (92). Because the study predated the evidence linking the use of estrogen with the possibility of decreased risk of cardiovascular disease, the only decisional factors considered were the occurrence of hot flashes, risk of fractures as a result of osteoporosis, risk of endometrial cancer, and treatment regimen. Investigators discovered that the women fell into three main groups, each of which represented a different approach to the decision to use hormone therapy. The largest group placed the most emphasis on relief of hot flashes and agreed to receive the combined regimen. The decision of women in a second, smaller group incorporated considerations of both hot flashes and the risk of osteoporotic fracture, as well as the risk of endometrial cancer associated with use of the unopposed estrogen regimen but not with use of the opposed regimen. This group was more likely to take the combined therapy. The third and smallest group considered the relief of hot flashes and the risk of osteoporotic fracture in making their decisions; however, in sharp contrast to the other groups, they were less likely to take the combined therapy,

possibly because of negative reactions to the resumption of cyclic bleeding (see figure 3-l).

This study concluded that the women studied gave high priority to the short-term impact of hormone therapy on their lives and did not make their decisions based on the risks of morbidity and mortality (92). In effect, they afforded greater weight to considerations of quality of life over quantity of life. The women in the study also reported that they felt disenfranchised from the health care system; they contended that providers did not listen to them and that they felt they had had inadequate information on which to base a decision concerning hormone therapy (91).

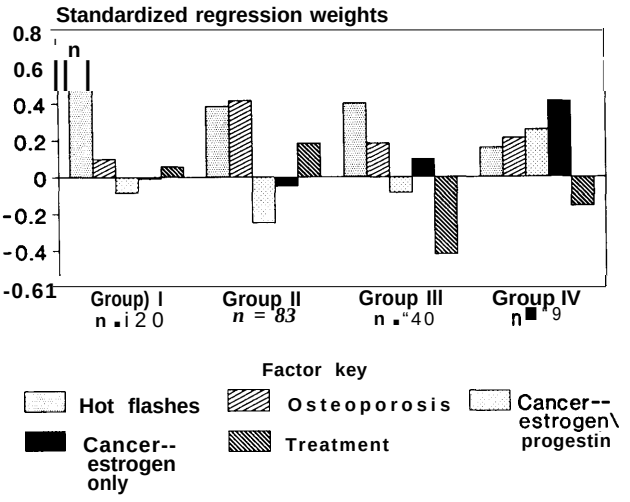
Compliance With Replacement Regimens

Compliance obviously becomes a consideration for those women who have made the decision to use either ET or CHT. **Rates of long-term compliance are difficult to calculate, but at least some studies have shown that most women who are receiving oral therapy take their medication only sporadically. Those who discontinue treatment generally do so because of the fear of endometrial cancer, although unwanted side effects may also play a role in their decision (87).** Data on 301 postmenopausal women receiving various forms of estrogen revealed a compliance rate of only **30 percent, although those who received combined therapy adhered more closely to their regimens over the years than did women who were receiving** other forms. Further research to develop regimens that will decrease side effects, especially bleeding, may aid compliance (87).

MENOPAUSE CLINICS

The terms *women's health center* and ***menopause clinic are*** used to market a wide range of medical facilities and services. Women's health centers, including hospital-based women's health centers, office-based physician practices, government health departments, and independent clinics, serve the medical needs of women, and some target midlife and older women by offering menopause programs. Many centers and clinics specialize in obstetrics and gynecology and provide few services beyond routine care; others are more comprehensive, offering some combination of education, referral services, diagnostic services, support groups, and clinical care, including primary care, and mental health services (61,68); still others additionally conduct research.

Figure 3-l—Women's Use of Information Regarding Hormone Therapy



SOURCE: M. Rothert, D. Rovner, M. Holmes, et al., "Women's Use of Information Regarding Hormone Replacement Therapy," *Research in Nursing and Health 13:355-366, 1990.*

The services vary widely and may be no different from those provided by the same establishment before it was renamed or identified by the words "women's health center' or ''menopause clinic."

In part, the lack of definition of menopause clinics and related services has resulted in many permutations of such facilities in the United States and no reliable source of information to determine the overall number of centers and clinics or to characterize them on the continuum between comprehensive centers offering truly specialized services and centers that are simply using the term as a marketing tool (11 1). Such clinics may be a uniquely Western phenomenon; as box 3-B describes, women in Eastern cultures are less likely to seek treatment for menopausal symptoms. This discussion focuses on the established, better organized menopause clinics that comprise both hospital-based and independent facilities and that provide a multidisciplinary approach to women's health.

One of the main benefits that patients and doctors attribute to such clinics is that complete, coordinated medical care is available in one facility. In one appointment, in one place, a woman can expect a complete medical workup, basic diagnostic tests, advice and education about midlife issues (particularly hormone therapy), and, if she desires, nutritional, exercise, and psychological counseling. Many women find the menopause clinic an attractive

Box 3-B-Cultural Variations in the Presentation and Treatment of the Menopause

To date, very little cross-cultural research has been conducted on women's experience of the menopause. Although many gynecologists recognize that the interplay between organic changes and cultural perspective influences a woman's experience, nonmedically oriented research concerning the menopause is severely limited. In 1976, the International Menopause Society was established to provide a forum for dialogue across disciplines, as well as cultures, concerning the menopause. Results from cross-cultural, cross-disciplinary studies provide an interesting comparison for evaluating the experiences of American women. Some of these findings appear below.

- Little variation in age at menopause--around 50 years of age-was found in a study of seven Asian countries: South Korea Taiwan (Republic of China), Hong Kong, the Philippines, Malaysia, Singapore, and Indonesia. Although age at menopause in this study was similar to findings regarding age at menopause in Western cultures, the study reported less severe symptoms than have been found in similar research conducted in the West.
- Of the menopausal Taiwanese women studied, 69 percent reported mild symptoms, only 32 percent consulted doctors regarding menopausal symptoms, and of these doctors, only 12 percent prescribed medication, primarily tranquilizers.
- In Malaysia of 400 menopausal women interviewed, 89 percent rated their health as good, and only 20 percent sought medical care for symptoms. Of those seeking treatment, 84 percent were prescribed medication; however, only 47 percent complied with the prescribed regimen.
- A study in the Philippines interviewed 500 women, aged 40 to 55, and found that 67 percent rated their health as good and 31 percent stated that they were seeking medical treatment for climacteric symptoms, Investigators saw no apparent correlation between health rating or treatment seeking and the individual's ethnic background, income, or education level. Of those seeking medical treatment, 86 percent received prescriptions for medication, primarily tranquilizers; of those, 52 percent complied with the treatment that was prescribed.
- Among Pakistani women, researchers found classical climacteric symptoms at least twice as frequently among affluent women as among poor women. In addition, affluent women were more likely to seek medical care for climacteric symptoms.
- Preliminary data have been reported from research in Thailand concerning the perception of the menopause among psychiatric personnel and middle-aged women. The data indicate that Thais regard any anomalous or inappropriate behavior by women as a sign of the menopause despite the fact that women between the ages of 40 and 55 present for treatment of psychiatric problems less frequently than any other age group.
- Research in Indonesia revealed variations in age and severity of symptoms among educated, uneducated, rural, and urban women. The study was conducted in Central Java and in the less developed, less Westernized Minangkabau culture of West Sumatra. Investigators found that the average age at menopause for urban, educated Central Javanese women was 50.2 years--roughly equivalent to that of American and European women. But rural and less educated Central Javanese women experienced menopause on average between the ages of 46 and 47; Minangkabau women experienced it on average between the ages of 47 and 48. The study also found that urban, educated Central Javanese women underwent "the same types of stresses and had the same health care and diet as European women. " In contrast to the number of women in the United States and Europe who report moderate (75 to 85 percent) or severe (10 percent) vasomotor symptoms (i.e., hot flashes), approximately 32 percent of Minangkabau and 22 percent of Central Javanese women report such symptoms.

SOURCES: Adapted from the proceedings of the Sixth International Congress on the Menopause, Bangkok, Thailand, Oct. 29 to Nov. 2, 1990 (New Jersey: Parthenon **1990). Specifically, M. Boulet, "The Menopause and the Climacteric in Seven Asian Countries"; C.** Chirawatkul "Perception of the Menopause Among Psychiatric Personnel and Middle-Aged Women in KhonKaean"; JR. Jalbuena "Menopause Among Filipino Women"; C.-H. Liu "Medical Care-Seeking Behaviour Among Climacteric Women in Taiwan"; N.M, Nasri Ismail, "A Study on Menaopausea in Seven Far-Eastern Countries-Malaysia"; S. Watsi "Age and Symptoms of **Menopause in** a Pakistan Community"; also M. Flint and R.S. Samil, "Cultural and Subcultural Meanings ***of the*** Menopause," *Annals of the New York Academy of Sciences,* vol. 592, *Multidisciplinary Perspectives on Menopause,* M. *Flint,* F. Kronenberg, and W. Utian (eds.) (New York, NY: New York Academy of Sciences, 1990), pp. 134-148.

option for obtaining comprehensive health care and assessment of health risks. In addition, such clinics can foster continuity of care and might improve patient compliance, especially with recommended diagnostic care (e.g., mammography) (72).

Clinical Care and Referral

Wellness achieved through health promotion and disease prevention is one of the goals of menopause clinics. Doctors who approach the health of women at midlife from a comprehensive perspective speak of treating women in terms of physical, mental, and environmental" health. This kind of treatment is best rendered through a multidisciplinary approach to the problems associated both with menopause and aging (78). Because women's health risks for many conditions-cancer, cardiovascular disease, stroke—increase with age, comprehensive health care, including early screening for disease, is advocated by many doctors.

Menopause clinics usually employ gynecologists or internists (at least on apart-time basis) to provide basic clinical care. Sometimes a woman's primary care physician is on the staff of the clinic; alternatively, a woman maybe sent by her own doctor to a menopause clinic for comprehensive attention and evaluation regarding menopause. The extent of care offered on site varies but usually includes a medical history; a routine physical examination, including pelvic exam, pap smear, and breast exam; diagnostic tests, including blood work, x-rays, mammography, and osteoporosis screening; and a decision on the use of hormone therapy. The comprehensive approach to basic clinical care also involves an assessment of health needs beyond the basic physical exam: nutrition and exercise, cardiovascular fitness, bone densitometry, and mental health, especially psychological care and career counseling. Depending on the findings of the basic exam, clinical care beyond the basic, primary level may be indicated (37,110).

Referral to outside specialists is one of the services offered by menopause clinics. Because many clinics are based in hospitals, patients may have access to a range of specialists, including cardiologists, endocrinologists, surgeons, radiologists, urologists, psychologists, physical therapists, and specialists in cancer and osteoporosis who can be consulted for specific health problems (39,40). In addition, patients may be referred to nutritionists and exercise physiologists who can help establish diet and exercise routines to promote health and wellness. Other common medical offerings available at the clinic or by referral include urodynamics training (to deal with urinary incontinence) and sex therapy (78).

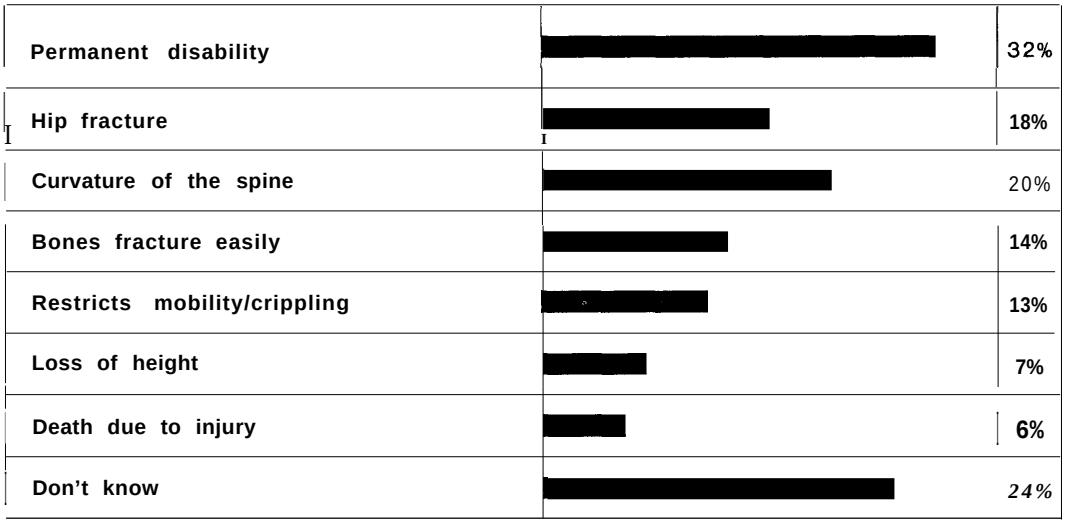
Preventive medicine and wellness approaches, for the most part, are not reimbursed by insurance (88). Many of the services offered at menopause clinics, including most of the advanced-technology bone densitometry tests for osteoporosis, cardiovascular fitness testing, nutrition counseling, and individual counseling and education, often are not covered by insurance plans. These services are optional but are often encouraged. Other services such as mammography, basic blood work, the physical examination, and pap smears may or may not be covered. Despite their apparent benefits, menopause clinics remain inaccessible to a majority of the population because a large proportion of the services they offer are elective in nature and are not reimbursed.

Questions have been raised about the routine use of high-technology equipment and diagnostic tests, especially bone densitometry to determine bone loss, to inform the decision to prescribe long-term hormone therapy. The use of bone densitometry is certainly indicated for women with high risk factors for osteoporosis, and it can be used as part of the decisionmaking process of whether to prescribe estrogen. However, what constitutes normal bone mass and whether bone densitometry can predict future hip fractures are debatable (22).

PATIENT AND PROFESSIONAL EDUCATION

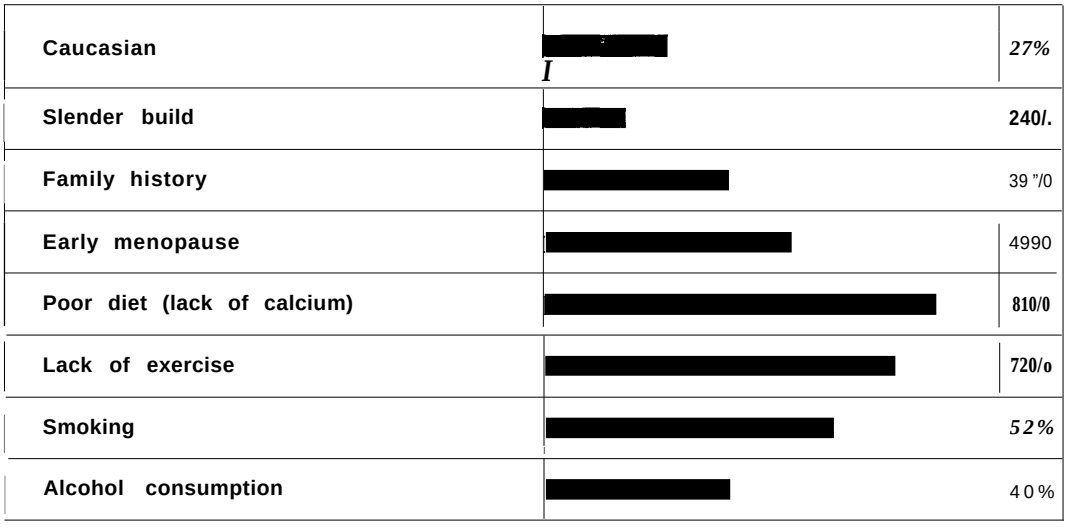
Patients and health care professionals alike tend to know relatively little about the menopause and the risks of conditions that may be associated with it (39,40). Indeed, there is no consensus within the medical community about the definition of the menopause and the risks and benefits associated with hormone therapy, and little information about the natural progression through the menopause and the years that follow. Moreover, there is no agreement on what constitutes a ''normal' menopause and few conclusive research findings on the normal hormonal changes associated with aging.

Figure 3-2-Percentage of Women Who Identified Consequences of Osteoporosis



SOURCE: A Gallup survey of 760 women, aged 45 to 75, sponsored by the National Osteoporosis Foundation. The survey has a margin of error of +/- 4 percentage points.

Figure 3-3-Percentage of Women Who Identified Risk Factors for Osteoporosis



SOURCE: A Gallup survey of 760 women, aged 45 to 75, sponsored by the National Osteoporosis Foundation. The survey has a margin of error of +/– 4 percentage points.

One of the most pressing concerns of many midlife women is that they do not know where to turn for understandable, high-quality menopause counseling. A recent survey revealed that very few women could identify the risk factors for osteoporosis and even fewer could name its consequences (see figures 3-2 and 3-3). Many women do not understand the complex biological changes that are associated with the menopause and find themselves without the basic facts needed to ask questions. The FDA has recently corroborated this perception by acknowledging that patients are reluctant to ask their doctors or pharmacists questions about medication and generally do not receive information unless they explicitly ask for it. The FDA announced that it will begin to address this issue by producing informational materials to be given to patients with their prescriptions and will encourage doctors and **phar-**

macists to inform patients about all aspects of drug use (62).

Education of both patients and doctors is important. Individual practitioners, menopause clinics, community health centers, and hospitals provide a variety of educational materials and programs and often sponsor group sessions and community outreach seminars. Physicians can participate in continuing medical education to learn more about the menopause and hormone therapy. A wide range of topics are included in education campaigns geared toward both midlife women and physicians, including an explanation of the menopause and potential symptoms; changes in the risks of cancer, heart disease, and osteoporosis that occur after the menopause and with increasing age; the pros and cons of hormone therapy; and the role of diet, nutrition, and exercise programs in health promotion and disease prevention (39,40,88).

The menopause clinic at the University of California, San Diego, is an example of a comprehensive education program. Patients attend a one-time, 4-hour clinic that includes group discussions and individual counseling; they also complete a medical history, symptom checklist, and self-assessment instrument, and are given a bibliography of menopause literature, a diary to record symptoms and behavior, a monthly record sheet, and access to the ''Hot Flash' telephone number for further questions and contact with clinic staff. Unfortunately, most women nearing the age of menopause do not have access to such a facility or to this kind of educational program.

The information most readily available to patients is provided by drug manufacturers. Some companies insert educational material in the advertising copy for their products or make it available separately. Such advertising campaigns provide information to consumers about the menopause and estrogen therapy—at the same time that they promote the use of specific products. Two examples include CIBA's advertisements for Estraderm and Wyeth-Ayerst's ads for Premarin. CIBA provides a menopause information packet free of charge to customers, which can be obtained by calling a toll-free number or by mailing in a coupon from the advertisement. The kit includes a letter explaining the menopause and estrogen therapy; a question-and-answer booklet about the Estraderm transdermal system, a patient package insert and a flier detailing the use of Estraderm, a booklet about the changes a woman can expect at midlife, and a placebo Estraderm patch.

Wyeth-Ayerst has mounted an educational advertising campaign for Premarin and osteoporosis. Again, a toll-free number is given in the advertisement for consumers to call for information, which includes a pamphlet entitled "What You Should Know About Estrogen Deficiency and Osteoporosis,' a fact sheet from the National Osteoporosis Foundation, and a personalized letter explaining Premarin's role in preventing osteoporosis. Also included is a form that entitles consumers to a free exercise videotape, courtesy of Wyeth-Ayerst, following a consultation with their doctor. Although this information is accurate, many women choose to seek other sources of information, free from drug company influence (see box 3-C). Consistent and unbiased information about the menopause and the risks and benefits of hormone therapy designed for the layperson needs to be more widely dispersed.

SUMMARY

Estrogen therapy and, increasingly, combined hormone therapy remain the treatments of choice for physicians who treat women seeking relief from the acute symptoms of the menopause, although some women have found relief through nonhormonal and nondrug therapies and, in fact, the majority of women do not seek treatment at all. Estrogen has been found to slow bone loss that could lead to increased risk for osteoporosis and subsequent fractures and appears to have a protective effect against cardiovascular disease. However, even the short-term use of estrogen increases a woman's risk for endometrial cancer and possibly breast cancer; the risk becomes still greater with long-term use, especially when estrogen is used for more than 15 years. The addition of a progestin greatly reduces the risk of endometrial cancer. The effects of progestin on the cardioprotective aspect of estrogen have yet to be determined. In addition, the long-term effects of progestin on the endometrium and breast are unknown. Women who discontinue use of hormone therapy after a few years may experience a "rebound effect,' or return of symptoms, and bone loss again accelerates. These competing risks and benefits pose a dilemma for women and a challenge for their physicians.

Convincing research into alternatives to hormone therapy is limited. The true contributions to cardio-

Box 3-C—Menopause and Hormone Therapy Educational Materials

The most readily available information regarding menopause and hormone therapyis produced and distributed by drug companies, but there are also many other sources of information of which many women and their physicians may be unaware. Educational and informational materials designed for both those in the medical community and laypersons are available from a variety of sources including books, periodicals, private newsletters, and publications from national associations and government agencies.

A search of the Library of Congress's book collection resulted in 148 titles related to the menopause, and the 1991-92 edition of the reference book Books *in Print* lists *22* titles under "menopause" and others under estrogen and hormones. Many books can be found at the public library or in bookstores, often in the health section.

Them are a variety of newsletters written about health and aging issues, some of which include information related to the health of midlife and older women and others that are devoted exclusively to this population. Examples of the latter include *A Friend Indeed (for women in the prime of life),* Box 515, Place du Parc Station, Montreal, Canada, H2W 2P1; ***Menopause News,*** 2074 Union Street, Suite 10, San Francisco, CA 94123; Hot ***Flash (Newsletter for Midlife and Older Women),*** National Action Forum for Midlife Older Women, c/o Dr. Jane Porcino, Box 816, Stony Brook, NY 11790-0609; and *Health Facts,* Center for Medical Consumers, 237 Thompson Street, New York NY 10012.

Government agencies and private associations are other sources of information and educational material related to the menopause, the aging process, and concerns of midlife and older women. The following are some of the groups that provide information either free of charge or for a small fee: National Women's Health Network, American Association of Retired Persons, American College of Obstetrics and Gynecology, National Institute on Aging, National Institutes of Health, National Council on Patient Information and Education, U.S. Pharmacopeial Convention, and the American Medical Association.

Despite the availability of these resources, more unbiased information explaining the menopause and outlining the risks and benefits of hormone therapy needs to be developed and made more widely available.

SOURCE: Office of Technology Assessment 1992.

vascular disease and osteoporosis of such factors as lifestyle, socioeconomic status, race, and genetic predisposition deserve further investigation (see ch. 5). Women are given hormone therapy for a variety of reasons but often do not comply with treatment. Such noncompliance must be considered when risks and benefits are calculated and prescribing policy is determined. Increasingly, menopause clinics and women's health centers provide services to help women make decisions about treatment. The course of treatment, its utility, and its cost ultimately influence not only outcomes but who receives care.

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