skeletal response to estrogen. Hybrid compounds may be useful agents, but have been inadequately studied as yet.

Conclusions

Estrogens remain the major therapy for prevention of osteoporosis in postmenopausal women. While other potential candidates for use in prevention of bone loss exist, insufficient data are as yet available on efficacy, compliance, and side effects. Indeed, none of the available compounds has the overall effects of estrogen on the general health of the postmenopausal woman. For the high-risk woman who does not wish to take estrogen treatment, other possible therapies include calcitonin and progestogens, with a recognition of the risk factors.

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Panel Session: Prevention/Treatment

Hormonal Therapy in Climacteric Women: Compliance and Its Socioeconomic Impact

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This article is based on his presentation at the FDA Special Topic Conference on Osteoporosis, sponsored by the Food and drug Administration, held at Bethesda, MD, October 30, 1987.

Synopsis

Hormonal therapy can effectively enhance the quality of life for postmenopausal women, and prevent climacteric-related conditions such as osteoporosis. Since long-term therapy is often required, compliance becomes an important issue. This can best be achieved by measurement, documenting the reason for hormone therapy, and by repeated measurement, demonstrating a response to the treatment. Case histories documenting this principle are described.

THE MENOPAUSE is still regarded as a "gynecologic condition" to be treated solely by estrogen replacement therapy. There are four reasons why this approach is no longer tenable: (*a*) the menopause, the last natural menstrual period, is merely one event in the broader continuum of changes associated with reproductive senescence. Menopause occurs during a 30-year period from ages 35 to 65. This span is known as the climacteric; (*b*) two sex steroids, estrogen and progesterone, are affected by failing hormonal synthesis by aging ovaries; (*c*) since all naturally postmenopausal women are deficient in estrogen and progesterone, their treatment with hormones is accurately referred to as "additive" rather than "replacement" therapy. This terminology is not merely an issue of semantics; the term points out the reality of the pharmacologic treatment of postmenopausal women, rather than the assumed physiologic approach implied by the term "replacement". The term "replacement" is correctly applied when referring to the restoration of an estrogen-progesterone milieu with exogenous estrogens in women who have experienced surgical or premature menopause; and (*d*) the "total" woman needs to be considered; this ensures that as much consideration is given to monitoring the health of the postmenopausal woman's skeleton and cardiovascular system, for example, as is given to monitoring the traditional gynecological problems of the menopause—hot flashes and atrophic vaginitis.

Given the information above, the use of hormonal therapy should be judged in the broader context of benefits that accrue to women during their climacteric years, and which can enhance both their immediate quality of life and serve as insurance for good health in their geriatric years.

Socioeconomic Benefit

The selective and judicious use of hormone additive therapy has a definite and positive impact on society; this can be seen in both the short- and long-term benefits that individual women derive from hormone additive therapy, and its subsequent influence on other individuals in her environment, both at home and at work.

Short-term benefit. According to the U.S. Chamber of Commerce, in 1984, 54 percent of women between the ages of 35 and 65 were in the labor force. Of these 20.3 million women, 1.1 million were older than 65 (*1*). Circumstances that would impair the well-being of this labor force would obviously have a serious negative impact on the productivity and quality of work. Although they are not as yet quantified in scientific sociological terms, at least three sets of hormone-dependent symptoms could influence work performance: hot flashes, insomnia, and the mood disorders associated with menopause, impaired memory, lack of concentration, depression, and irritability.

After decades of clinical and anecdotal descriptions, the menopausal hot flash has been objectively characterized as a real event with elevations in the cutaneous temperature that vary from 2 to 5 degrees C., and which may last about 3 minutes. The mean duration of the measured temperature change, however, is about 30 minutes. About 48.5 percent of women with hot flashes have acute physical discomfort with or without embarrassment, while an additional 20.5 percent report embarrassment without physical discomfort. An infrequently reported fact is that about 18 percent of regularly menstruating women in the immediate premenopausal period (ages 45–54 years) also experience clinically significant hot flashes. A large body of scientific data has documented the efficacy of estrogens, administered orally or parenterally (*2*), or progestin therapy (*3*) in alleviating or controlling this troublesome complaint.

Many menopausal women experience insomnia, characterized by early awakening and difficulty in falling asleep again. In an appropriately designed double-blind, cross-over study, exogenous estrogen was associated with a shorter mean sleep latency, a longer period of rapid eye movement sleep (which results in sound and refreshing sleep), and a positive correlation with the psychologic attitude and well-being of the estrogen-treated (versus placebo) subjects (*4*).

Earlier studies have shown that 29 percent of women between 40 and 55 years in the general population (*5*) and 57 percent of similarly aged women attending a gynecologic clinic (*6*) had psychologic disturbances. The highest incidence of depression in midlife appears to occur just before the last menstrual period, suggesting that an alteration in hormonal levels, rather than an absolutely low concentration of estrogen, may be responsible for this particular symptom. Whatever the actual pathogenesis, placebo-controlled studies with both oral and parenteral estrogens have shown that a battery of psychological symptoms—depression, anxiety, impaired memory, and mood change—respond rapidly and well to estrogen additive therapy (*7,8*).

The author is unaware of any study that has attempted to scientifically quantify the loss of pro-

Table 1. Change (percent) in life-style following an education and bone density screening program[1]

Behavior	Subjects screened		
	Normopenic[2]	Osteopenic[3]	Nonscreened[4]
Overall	68.7	86.4	53.8
Exercise	39.6	53.6	21.2
Diet	69.0	85.5	49.2
Smoking (decrease)	3.0	6.4	2.3

[1]Data from Reference *18*.
[2]N = 268.
[3]N = 110.
[4]N = 132.

'The selective and judicious use of hormone additive therapy has a definite and positive impact on society; this can be seen in both the short- and long-term benefits. . .'

ductivity, or time off from work, due to hormone-dependent symptoms. However, the observation of an individual's positive response to hormone additive therapy in clinical practice justifies the contention that appropriately chosen women will indeed benefit from exogenous hormone use, and that this will result in a socioeconomic benefit to both the individual and her community.

Long-term benefit. In his address to the 1984 annual meeting of the American College of Obstetrics and Gynecology, the incoming President noted that only 11 percent of the population of the United States were above 65 years of age, but they were responsible for 20 percent of office visits, 23 percent of acute care discharges, 36 percent of patient-day acute care, and 95 percent of long-term care patient days. Two conditions that have a negative impact on the health of aging women and that are directly related to the change in hormonal levels during the climacteric are cardiovascular disease and osteoporosis.

Given the multifactorial etiology of coronary heart disease, it is generally agreed that a premature menopause—whether spontaneous or surgical—substantially increases the risk of angina pectoris and myocardial infarction (*9*); conversely, epidemologic studies—both case-control and cohort—have shown, with two notable exceptions, that long-term estrogen therapy has a protective effect and significantly reduces the risk of coronary heart disease by between 20 and 70 percent (*10*). It has been estimated that, if the risk of ischemic heart disease were reduced by as little as 20 percent, there would be an 18 percent net reduction in mortality of women on moderate doses of estrogen replacement; if the protective effort of estrogen reduced risk by 50 percent, the reduction in mortality due to coronary heart disease would be more than 41 percent (*10*). The reason for the potential protective effect of estrogens has not been established, but results in part from the suppressant effect of exogenous postmenopausal estrogens on total cholesterol and low-density lipoprotein cholesterol, as well as from the stimulation of the cardioprotective lipoprotein, high-density lipoprotein cholesterol. Unfortuanately, the concomitant use of progestins (to prevent endometrial hyperplasia) may negate this beneficial effect, and needs to be considered when prescribing hormone therapy.

One of the most gratifying results of long-term estrogen additive therapy is the increase in bone mineral content (*11*); studies have associated this observation with a reduction in osteoporosis-related fractures (*12*). A key issue is to decide who should be treated, since the prevention of osteoporosis necessitates long-term hormone usage, certainly until age 65, and thus raises the important question of patient compliance. Densitometers (single and dual photon absorptiometers) can be used to measure the bone mineral content in areas of the skeleton at risk for fracture. Although the precise role of these instruments in clinical practice still needs to be defined, by using them it is now possible to identify women with osteopenia, a precondition to osteoporosis (*13*). In both osteoporosis and osteopenia, the quality of bone is normal, but the bone mineral content is reduced by at least 20 percent below peak bone mass (the bone mineral content at age 35) (*13*). Women with osteoporosis have radiologically demonstrable vertebral deformation indicative of structural failure; the vertebrae of osteopenic women are intact. Conceptually, osteopenia is reversible; osteoporosis is not. To illustrate this point, consider the relationship between blood pressure and cardiovascular accidents (stroke). Individuals with hypertension—defined by a systolic value in excess of 140 millimeters (mm) Hg and a diastolic level of 90 mm Hg—are at greater risk of stroke; the higher the blood pressure, the more likely this possibility. Treatment with hypotensive drugs and other modalities such as exercise and life-style modification reduces this risk. A high blood pressure does not necessarily cause a stroke, nor are

normotensive subjects completely protected from this condition, but since hypertension is asymptomatic in its early stages, the regular measurement of blood pressure will detect persons at risk for cerebral vascular disease, and, with regular monitoring, will allow for early protective measures. The early detection of osteopenia functions in the same way, and in the author's experience has been an essential tool in providing the incentive for patients to take hormones, and to continue taking them.

Long-term usage of estrogen has been associated with a 50 percent reduction in osteoporosis-related hip fractures and, in one study, a 90 percent decrease in vertebral fractures (*14*). The benefit is directly related to the duration of estrogen use and current use. For example, in one study (*15*) the relative risk of hip fracture in women who had taken estrogen for 6–9 years was 0.38 versus 1.0 for nonusers. The relative risk for women currently taking estrogen was 0.43, compared with 0.77 for women who had not had hormone additive therapy for 6 or more years. Interruption of hormone additive therapy results in an immediate and profound decrease in the bone mineral content (*11*) and exposure to the risk of atraumatic fractures.

Prevention and Compliance

Contrary to the opinion of many physicians, most women do not want to take hormones. Some are conceptually opposed to "putting foreign substances in my body"; others are concerned about possible side effects; a majority are unhappy about the resumption of menstruation.

Reducing the negative effects of hormone additive therapy. An unwanted consequence of combination hormonal therapy is withdrawal bleeding, in women with an intact uterus, and the need for endometrial biopsy. Three ways to make these side effects more acceptable are (*a*) reduce withdrawal bleeding to a minimum by continuous combined therapy, such as an estrogen (for example, 0.625 milligram (mg) conjugated equine estrogen) and a progestin (for example, 2.5 mg medroxyprogesterone acetate) every day. A number of studies have been published on the efficacy, safety, and patient acceptability of this approach (*16*); (*b*) chart the bleeding pattern for those who need (or wish) cyclic therapy, to reduce the need for endometrial sampling. If withdrawal bleeding occurs from day 12 or beyond of the progestin course, endometrial hyperplasia will not occur (*17*). A clinically proven regimen is 0.625 mg conjugated equine estrogen (or its equivalent) every day with 5–10 mg medroxyprogesterone acetate daily for the first 2 weeks of each cycle; and (*d*) despite the use of euphemisms such as "discomfort" or "cramplike," the reality is that endometrial biopsies are painful and unpleasant. The procedure can be made psychologically more acceptable by referring to the test as an "endometrial sampling" and by using new techniques, for example, the Pipelle (Unimar). This is a narrow, plastic, manually-operated suction curette which is easily introduced into the uterine cavity with minimal cervical dilatation, and is consequently associated with only a slight degree of pain.

Figure 1. Sequential bone mineral density (BMD) change in the radial shaft and far distal radius in a natural menopausal woman before (Sept. 1983) and after (June 1987) combination hormone additive therapy of Cortisone and Synthroid

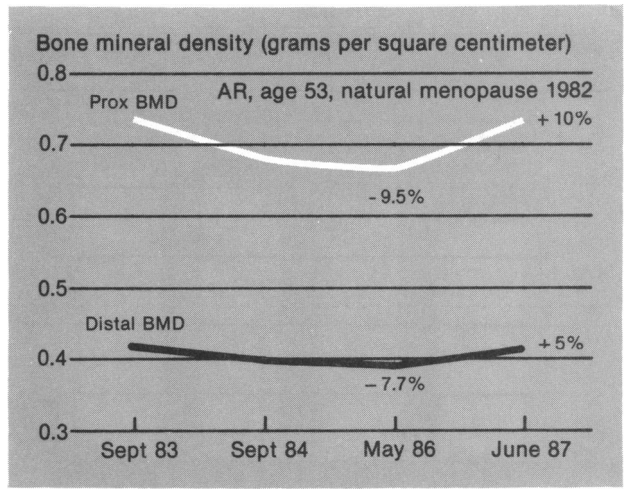


Figure 2. Lumbar bone mineral density (BMD) in a natural menopausal woman before (June 1986) and after (June 1987) treatment with combination hormone additive therapy, showing absolute values and percentage of peak bone mass

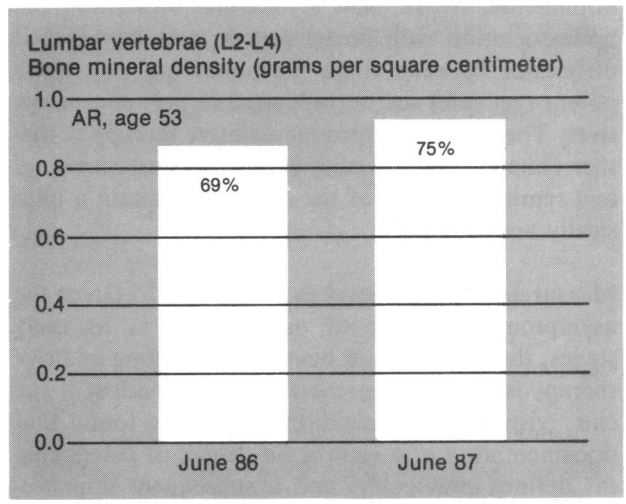
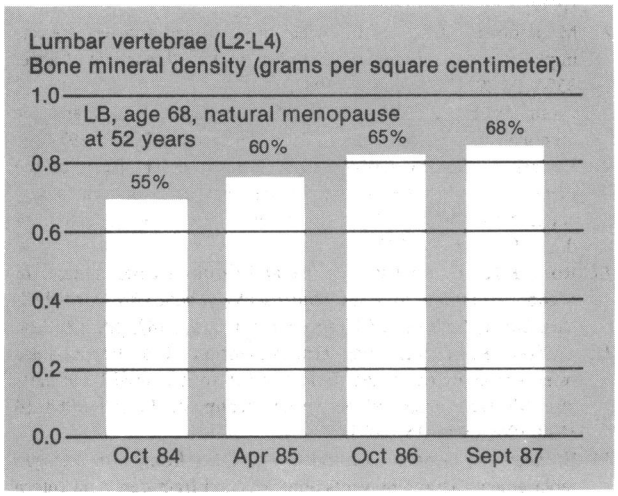


Figure 3. Progressive increase in the lumbar bone mineral density (BMD) in a postmenopausal woman with established osteoporosis receiving continuous hormone additive treatment, showing absolute values and percentage of peak bone mass



Adequate samples for histological examination are usually obtained.

Patients should be told the truth about the proven safety of hormone additive therapy *vis-a-vis* thrombophlebitis, stroke, and myocardial infarction; the nonassociation with breast cancer; and the marked difference between these hormones and the more potent (yet safe) sex steroids used in oral contraceptives. The safety of hormone additive therapy is further enhanced by advising women against smoking, and reminding them of the need to maintain a physically active lifestyle.

Measurement: the answer to compliance. Given the asymptomatic nature of osteoporosis in its early stages, the need for and benefit of hormone additive therapy is better comprehended by the patient if she can "visualize" her condition. We have found that documentation of a significant degree of osteopenia (as defined previously) and a subsequent improvement in this parameter are the best means of ensuring compliance. Two case histories illustrate this point.

1. Patient A.R. experienced a natural menopause in 1982 at age 49. When first examined a year later, she had specific at-risk factors for osteoporosis: she required frequent courses of corticosteroids to control her asthma, and was taking a thyroid replacement drug. Both medications are known to accelerate bone mineral loss. The patient refused hormone additive therapy because she was reluctant to resume menstruation. Her inital bone mineral content measurement (fig. 1) was in the normal range for her age. Repeated assessments revealed a progressive loss, and by May 1986 she had lost 9.5 percent of her cortical midshaft bone mineral, and 7.7 percent of the distal content. At that time, she consented to dual photon absorptiometry (fig. 2). Her initial value of 0.869 gram (g) per square centimeter (cm^2 of lumbar vertebrae L2–L4) was 69 percent of peak bone mass. The patient was impressed with her fairly rapid peripheral bone loss and her reduced central bone mineral content, and consented to cyclic hormone additive therapy. Assessment a year later revealed an 8 percent increase in her lumbar bone density (0.948 g per cm^2) and a 10 percent increase in her midshaft cortical bone mineral content (from 0.666 to 0.740 g per cm^2). The patient has since adjusted well to the resumption of menstruation and is appreciative of the improvement in her bone mineral status. She remains compliant.

2. Patient L.B. was first seen at age 64 with established osteoporosis and a bone mineral content of her lumbar vertebrae (L2–L4) of 0.694 g per cm^2, only 55 percent of peak bone mass. She was informed that little could be done for her, as she had an advanced disease and was 12 years postmenopausal. This patient was placed on the continuous combined estrogen-progestin regimen discussed previously, plus calcium supplementation and a walking program. Successive evaluations have shown a progressive increase in her spinal bone mineral content; at her last assessment (L2–L4 = 0.854 g per cm^2), it was 20 percent greater than her initial baseline test (figure 3). Although still significantly osteopenic—68 percent of peak bone mass—the patient has been encouraged and complies with her medication regimen.

Primary care physicians deal with individuals: personal experience with patients such as the two described verifies the usefulness of densitometry in selecting patients for hormone additive therapy, monitoring their progress, and ensuring compliance. The demonstration of osteopenia is also useful in population interventions, and can serve as a stimulus to adjust and improve lifestyle practices and habits (*18*). Letters were written to a randomly selected group of women from four medical practices; respondents were sent an educational packet about osteoporosis and were invited, 6 months later, to a free seminar. To evaluate the impact of personal contact, subjects were invited to have a free densitometric examination. Of the original 771 subjects who participated, 378 were screened; a further 132 continued to the final assessment, but declined densitome-

tric testing. As reflected in table 1, 86.4 percent of the women who were screened and found to have a low bone mass altered their lifestyle, compared with 68.7 percent of normopenic screenees and 53.8 percent of the unscreened population. The most obvious changes in all groups were in exercise and diet.

Conclusions

The postmenopausal population of the United States is increasing at a rapid rate, and life expectancy for a woman is now 78 or more years. Since all women will experience menopause, much can be done to ensure that their postmenopausal years will be quality years. A significant minority of these women will be subject to chronic diseases that may be averted by the selective and judicious use of hormone additive therapy. Clinicians and other health care professionals need to be trained in techniques that will help identify women at risk, thereby individualizing the need for hormone therapy. Combined with exercise and other life-style measures, the process of middle-age aging can be altered to ensure greater productivity and health, with an equally important reward of better health, and thus enjoyment, in older age

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Panel Session: Prevention/Treatment

Treatment of Osteoporotic Patients

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Synopsis

The best approach to treatment of osteoporosis is prevention of bone loss as discussed elsewhere in this volume. However, some currently approved therapeutic agents are helpful in the management of the patient who presents with an osteoporotic fracture. These agents include an adequate calcium intake, estrogen replacement therapy, and administration of calcitonin.