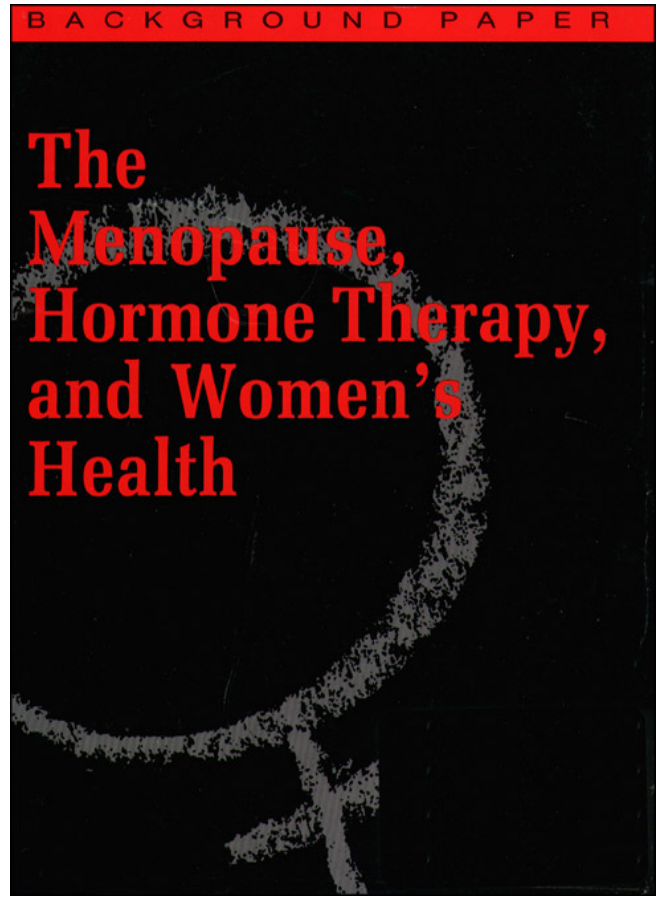
The Menopause, Hormone Therapy, and Women's Health

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Foreword

Few topics in women's medicine today are as fraught with confusion and controversy as the question of appropriate treatments for menopausal symptoms and the prevention of negative long-term health outcomes common to postmenopausal women—such as osteoporosis and cardiovascular disease. A better understanding of the natural history of the menopause is critical to providing better care. Despite its universality as an event in human female aging, the menopause and its biology are incompletely understood. Researchers are becoming increasingly convinced, however, that the loss of ovarian hormones plays a significant role in the development of age-related problems in women.

If women and their physicians had a better understanding of predictors of risk, they could make more informed decisions about interventions related to menopausal symptoms, cardiovascular disease, osteoporosis, and gynecologic and breast cancer. Few other recently introduced medical interventions have as great a potential for affecting morbidity and mortality as does hormone therapy, which maintains estrogen levels in postmenopausal women to near those of premenopausal women. Hormone therapy has pronounced effects on health risks: Some are reduced, some are increased, and some remain uncertain, and these data are interpreted differently by various scientific, medical, and consumer groups. The debate over hormone therapy focuses on whether it should be used to treat menopausal symptoms for a short period of time, thereby reducing any risks associated with long-term treatment, or whether it should also be used to prevent future disease, thereby requiring longer treatment that could increase the risk of cancer. Convincing research into alternatives to hormone therapy is limited. In addition, the true contributions to cardiovascular disease and osteoporosis of such factors as lifestyle-e. g., diet, exercise, smoking-socioeconomic status, race, and genetic predisposition deserve further investigation.

An October 1990 letter to the Office of Technology Assessment (OTA) from Representatives Patricia Schroeder and Olympia Snowe, cochairs of the Congressional Caucus for Women's Issues, and Senator Brock Adams questioned whether current research programs at the National Institutes of Health (NIH) and other public health service agencies adequately address the menopause. Senator Adams and the Caucus requested that OTA study the current state of knowledge regarding the menopause and its management, assess the scope and depth of existing research, and identify those areas in need of further attention. Specifically, Congress was interested in hormone therapy, the most common medical treatment for menopausal symptoms. In June 1991, Senator Barbara Mikulski and Representative Henry Waxman endorsed the project and requested that OTA investigate as well the comparative effectiveness of alternatives to hormone therapy for the treatment of menopausal symptoms and postmenopausal disease.

This Background Paper describes what is known about the natural progression of the menopause and its effect on women's health, hormone treatment and prescribing practices, alternative approaches, and research needs. Managing diseases and disorders among middle-aged women requires more information to help practitioners differentiate those disorders whose causes stem from a cessation of ovarian hormone production (and that are thus potentially treatable by hormone therapy) from those that do not. Only then can misdiagnosis-or dismissal-of the medical complaints of midlife women be prevented.



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Chapter 1
Introduction

At the turn of the century, fewer than 5 million American women were older than 50, the average age at which the menopause occurs in this country. In the first decade of the 21st century, more than 21 million women from the baby boom generation will reach the age of 50 and become menopausal. In 1991 alone, 1.3 million women turned 50, marking the end of reproductive fertility for those who have not already been rendered sterile as a result of hysterectomy; they join the 35 million other women who have reached the menopause-either surgically or naturally-and who constitute more than one-third of the total female population of the United States (18). With a current life expectancy approaching 80 years, these women can expect to spend more than a third of their life with reduced ovarian hormone levels.

This increasing longevity and the changing demographics noted above will require dramatic changes in the delivery of preventive and clinical health care for women. Women already constitute a significant portion of the practices of many physicians. Indeed, more than 58 percent of the approximately 1.32 billion physician-patient contacts in 1989 were with female patients, and women over the age of 44 accounted for more than 41 percent of these contacts (19).

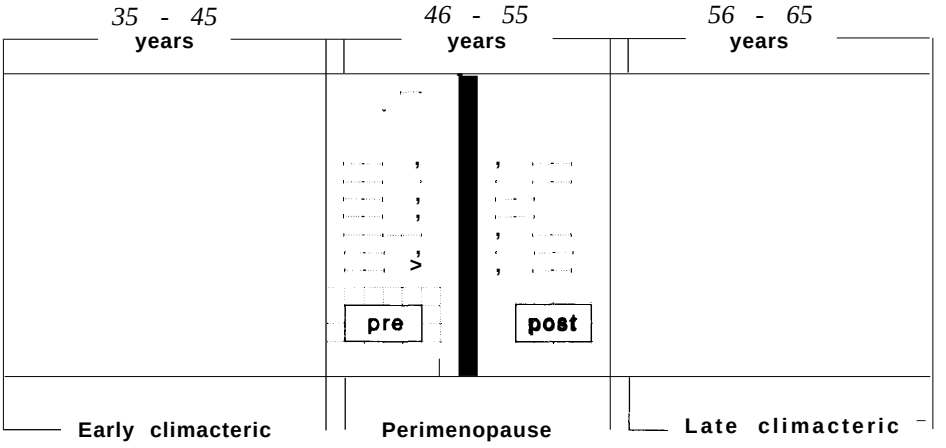
Furthermore, growing awareness of the role of gender in differential patterns of disease and disability in later life underscores a critical need for gender-specific perspectives in developing research agendas and methodologies. Women constitute approximately 59 percent of the U.S. population aged 65 and older, and about 72 percent of the population aged 85 and older (20). Substantive progress in understanding the etiology and clinical picture of age-related disease among women will require increased sensitivity to their inherent biological and psychosociocultural differences. Such progress is fundamental to accurate diagnosis and effective treatment to reduce morbidity and mortality and maintain the independence of the rapidly growing population of postmenopausal women.

A better understanding of the natural history of the menopause is critical to providing better care. Despite its universality as an event in human female aging, the menopause and its biology are incompletely understood. Researchers are becoming increasingly convinced, however, that the loss of ovarian hormones plays a significant role in the etiology of age-related pathology in women. Managing diseases and disorders among middle-aged women requires more information to help practitioners differentiate those disorders whose etiologies stem from a cessation of ovarian hormone production (and that are thus potentially treatable by hormone therapy) from those that do not. Only then can misdiagnosis-or dismissal--of the medical complaints of midlife women be prevented.

As the average woman approaches age 50, her ovaries-the primary source of the female hormone estrogen-gradually cease to function as they have since menarche. As follicle depletion occurs in the ovaries, ovarian hormone production slows, and the menstrual cycle typically becomes irregular and finally ceases. For the purposes of this report, the term ***menopause*** is defined as the final menstrual period that a woman experiences, although ***menopause*** colloquially describes the transition from the reproductive to the nonreproductive state. The date of the menopause can be accurately pinpointed: It is retrospectively diagnosed after a year with no menstrual periods (9,21). The less frequently used term ***climacteric*** refers to the phase during which a woman passes from the reproductive to the nonreproductive state. The last few years of the climacteric and the first year after the menopause are the ***perimenopause. The*** menopause, a single event, is easy to define; the climacteric and perimenopausal periods are much more difficult to quantify and evaluate, particularly from the patient's perspective. The terms ***premenopausal*** and ***postmenopausal*** describe, respectively, the state of active ovarian estrogen production and the state of absent ovarian estrogen production (see figure l-l).

Women whose menses are stopped surgically by removing the ovaries have a sudden and atypical postmenopausal experience. Nevertheless, in studies of the menopause, this group of women is often mistakenly included with those who experience a natural menopause (2,9,12). This report makes an effort to clarify the distinction between natural and surgical menopausal issues whenever they arise.

Figure I-l—The Transition from Reproductive to Nonreproductive Life



NOTE: In this report the perimenopause is defined to be the last few years of the earlyclimacteric and the first year after the menopause.

SOURCE: Adapted from M. Notelovitz, 'The Non-Hormonal Management of the Menopause," J.W.W Studd and MI. Whitehead (eds.), The *Menopause* (Oxford, UK: Blackwell Scientific Publications, 1988).

Few topics in women's medicine today are as fraught with confusion and controversy as the question of appropriate treatments for menopausal symptoms and the prevention of the long-term health outcomes associated with postmenopausal women-osteoporosis and cardiovascular disease. Because decreased estrogen appears to underlie the disturbing symptoms of the menopausal period as well as the susceptibility to bone loss that often leads to osteoporosis, it is not surprising that the administration of estrogen relieves some of these problems.

Since 1937, practitioners have known that estrogen therapy[1] prevents the occurrence of such menopausal symptoms as hot flashes and vaginal dryness (6). The 1960s and early 1970s saw a dramatic increase in retail prescriptions for noncontraceptive estrogens for the treatment of these symptoms. Some attribute the rise in use to the best-selling book ***Feminine Forever*** by Robert Wilson (22), who claimed that the menopause could be averted and aging allayed with estrogen therapy.

In 1975, however, two case-control studies produced risk estimates that women who used estrogen therapy were four to seven times more likely to develop endometrial cancer than women who did not (8). After further reports of a possible association between estrogen use and endometrial cancer, sales of estrogen dropped by almost 30 percent (8). The subsequent decline in estrogen prescriptions was followed by a decline in the rate of endometrial cancer.

Women and the medical establishment consequently became more conservative in their use of estrogen. An additional factor in this trend was the fear of increased risk of breast cancer resulting from estrogen use, a fear that has never been satisfactorily resolved. Breast cancer strikes one of every nine women in the United States; it is the second most frequent malignancy among women, constituting 26 percent of all cancers (lung cancer is the most frequent) (l). About 50 percent of breast tumors require estrogen for growth. For some women, increasing the odds of developing breast cancer in any way is unacceptable, and they either refuse estrogen therapy altogether or refuse to comply with prescribed treatment regimens.

In trying to determine the extent of the risk of endometrial cancer associated with estrogen use, researchers found that adding a progestin to estrogen could protect women against endometrial cancer by opposing the effects of the estrogen (hence the terms

[1] The use of estrogen for the relief of hot flashes is commonly referred to as estrogen replacement therapy, or ERT. Because some consumer groups oppose the notion that the menopause causes an estrogen deficiency tbat requires replacement, OTA uses the term *estrogen therapy,* or ET, to describe this practice.



Photo credit: National Cancer Institute

Women are living as much as a third of their life postmenopausally. Decisions about hormone treatment and its effect on subsequent health are based on uncertainty for many women.

opposed and ***unopposed estrogen).***[2] ***Estrogen stimu-*** lates the growth of endometrial tissue (the lining of the uterus) while progestins cause shedding of the estrogen-thickened endometrium, lessening the chances that cancer will develop. Progestins have side effects, however, that lead many women to cease therapy. Nevertheless, it has become increasingly more common to prescribe both estrogen and a progestin, or combined hormone therapy, for menopausal women who still have an intact uterus.

Recent studies have shown that estrogen may play a role in preventing cardiovascular disease (3,4,7, 11), which adds a new incentive for prescribing hormones. The effect of progestin on cardiovascular disease prevention, however, is unknown. Since progestins at least partially reverse the favorable effects of estrogen on circulating cholesterol levels, the addition of a progestin might diminish or completely eradicate the protective effect against cardiovascular disease provided by unopposed estrogen (10).

The debate over hormone therapy—in particular unopposed estrogen—focuses on whether it should be used to treat menopausal symptoms for a short period of time, thereby reducing any risks associated with long-term treatment, or whether it should also be used to prevent future disease, thereby requiring longer treatment that could increase the risk of cancer. For most women, the short-term use of hormones has known benefits (e.g., relief of hot flashes) and some known risks (e.g., endometrial cancer); long-term use has known risks (e.g., endometrial cancer) and benefits (e.g., prevention of osteoporosis and cardiovascular disease), as well as unknown outcomes (e.g., risk of breast cancer). The Nurses' Health Study, the largest longitudinal study of women in the world, found an increased risk of breast cancer associated with "current use" of estrogen (5). As with any form of medication, the benefit of relief of symptoms must be weighed against adverse side effects or complications.

ORIGINS AND ORGANIZATION OF THE REPORT

Congressional interest in matters related to the health of women has mounted in the past 5 years. Numerous bills have been introduced (see table l-l) to address the apparent lack of attention to women's health issues by agencies of the Public Health Service (PHS), in particular, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA). An October 1990 letter to the Office of Technology Assessment (OTA) from Representatives Patricia Schroeder and Olympia Snowe, co-chairs of the Congressional Caucus for Women's Issues, and Senator Brock Ada.ms questioned whether current research programs at NIH and other PHS agencies adequately addressed the menopause. Senator Adams and the caucus requested that OTA study the current state of knowledge regarding the menopause and its management, assess the scope and depth of existing research, and identify those areas

[2] The addition of a progestin t. the estrogen regimen is a practice commonly referred to as hormone replacement therapy, or HRT. For the reasons cited in footnote 1, OTA refers to this form of treatment as ***combined hormone therapy,*** or C'HT. Collectively and generally, the term hormone ***therapy*** describes either estrogen therapy or combined hormone therapy, when a distinction is not necessary.

Table l-l—Women's Health Legislation Introduced in the 102d Congress

Title l-Research
Women's Health Research Act
Clinical Trials Fairness Act
Women's Mental Health Research Act
Women and Alcohol Research Equity Act
Breast Cancer Basic Research Act
Contraception and Infertility Research Centers Act
Sense of Congress Resolution Regarding Contraceptive Research
Women and AIDS Research Initiative Amendments
Ovarian Cancer Research Act
Osteoporosis and Related Bone Disorders Research, Education, and Health Services Act
Title I/-Services
Breast Cancer Treatment Informed Consent Act
Women's Health Care Coverage Expansion Act
The Mickey Leland Adolescent Pregnancy Prevention and Parenthood Act
Adolescent Health Demonstration Projects
COBRA (Consolidated Omnibus Budget Reconciliation Act of 1985) Displaced Family Amendments
Federal Employee Family Building Act
Title I//-Prevention
Medicaid Infant Mortality Amendments
Medicaid Women's Basic Health Coverage Act
Breast Cancer Screening Safety Act of 1991
Medicare Bone Mass Measurement Coverage Act
Women and AIDS Outreach and Prevention Act
Infertility y Prevention Act

SOURCE: Congressional Caucus for Women's Issues, 1992.

in need of further attention. Specifically, Congress was interested in hormone therapy-both opposed and unopposed estrogen use-the most common medical treatments for menopausal symptoms. In June 1991, Senator Barbara Mikulski and Representative Henry Waxman endorsed the project and requested that OTA investigate as well the comparative effectiveness of alternatives to hormone therapy for the treatment of menopausal symptoms and postmenopausal disease.

Clearly, widespread interest in understanding sex differences in disease morbidity and mortality exists and could lead to improvements in prevention, treatment, and care for women. Pressure from Congress for action has led to a new NIH initiative to study the effects on women's disease risk of changes in diet and exercise patterns, the use of hormones, and smoking cessation; the study focuses specifically on the risks of cancer, cardiovascular disease, and osteoporosis. Many experts believe that the menopause and the physiological changes that accompany reduced ovarian function play a significant role in the etiology of these diseases.

This report focuses on the menopause as a delineating point in the life of women. Chapter 2 addresses what is known about the factors leading up to and causing the diminishment of ovarian production of estrogen, and how these changes immediately affect the health and well-being of women; it also discusses the long-term health consequences of reduced ovarian estrogen production. Chapter 3 describes the risks and benefits of estrogen therapy (ET) and combined hormone therapy (CHT), the most common treatments for menopausal symptoms. The chapter also presents information about nonhormonal approaches to management of menopausal symptoms and why women choose the treatments they do. The marketing and regulation of the hormones prescribed for menopausal symptoms and prevention of osteoporosis and cardiovascular disease are described in chapter 4, together with what is known about prescribing practices. Chapter 5 sets forth the areas in which research is needed and discusses the role of the Federal Government in addressing those needs. Also included are data on the current Federal investment in research in those areas. Chapter 6 provides a summary and conclusions.

Previous OTA reports on women's health are ***Costs*** *and Effectiveness of Screening for Cervical Cancer in the Elderly (15), Infertility: Medical and Social Choices (16), Breast Cancer Screening for Medicare Beneficiaries (14),* and *Adolescent Health (13). An* additional forthcoming OTA report is an assessment of ***Policy Issues in the Prevention and Treatment*** *of Osteoporosis (17).* That report addresses the costs and effectiveness of the use of estrogen for the treatment of osteoporosis.

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Chapter 2

Understanding the Menopause

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Chapter 2
Understanding the Menopause

Medical science has yet to provide systematic, objective information about the biological and medical implications of the transition women make from a reproductive to a nonreproductive status. For centuries, women have viewed the cessation of the menses at the least with misinformation and at the worst with alarm and dread. But in recent years, 'the change of life' has begun to elicit greater attention from biomedical science. That interest, coupled with women's greater awareness about their own health and their willingness to ask questions, has led to more and better research on the etiology, symptomatology, and sequelae of the menopausal period. Still, as chapter 5 of this report indicates, such research is nowhere near complete.

Most descriptions of the menopausal process rely on clinical impressions (with little or no data) or on small samples of women selected from patient populations rather than from the general public. This pattern of investigation was true 20 years ago and has not changed appreciably (56). As a result, the extent to which women suffer from the symptoms of menopause is unclear. Some women are uncomfortably symptomatic; others report little or no discomfort. This clinical variability has contributed to the debate about the appropriate management of a natural process of aging in women. Women who suffer, and the doctors who treat them, are more likely to advocate a treatment approach, while those who report few symptoms are more sympathetic to the avoidance of medical interventions. A discussion of the most common treatments for menopausal symptoms, estrogen therapy (ET) and combined hormone therapy (CHT), appears in chapter 3. Also discussed in chapter 3 are the uses of ET and CHT for prevention of disease in later life.

The next section presents a brief historical and cultural perspective on the menopause. The sections that follow it discuss the biology and symptomatology of the perimenopause and the long-term health consequences faced by some postmenopausal women.

THE MENOPAUSE: HISTORICAL, SOCIAL, AND CULTURAL PERSPECTIVES

Throughout Western medical history, physicians have sought to understand and explain the menopause. Prior to the 20th century, the medical profession saw it as a physiological crisis that could result, under certain circumstances, in the development of disease (11). It has also been called a disease in and of itself. As early as A.D. 600, medical writings described the cessation of menstruation between the ages of 35 and 50 and linked it to a woman's lifestyle, attributing menopause to the "excesses of society" (91). Throughout history, social norms and attitudes, as well as the degree of understanding of menstruation and female physiology attained by the medical profession (see box 2-A), have influenced the evolution of medical thought regarding the menopause.

The menopause elicits a variety of societal responses, the specifics of which depend on a woman's particular cultural milieu. Thus, in addition to variations in the type and incidence of symptoms reported by menopausal women, there exists a wide range of cultural reactions to and repercussions accompanying the end of the childbearing years. In some Eastern cultures, for exarnple, the community may recognize the occurrence of the menopause through a ritual. Alternatively, as in the Papago culture, it may be completely ignored, to the extent that the language affords it no name (30,44). Besides variation in cultural cognizance and recognition of the menopause, anthropologists have observed different effects on the role of the woman ranging from an increase in freedom and status (see box 2-B) to the complete loss of role (see box 2-C). In fact, however, cross-cultural studies of the menopause are sparse, and some researchers ascribe the meagerness of anthropological offerings in this area to a historical lack of attention to the experience of women by the formerly male-dominated field of ethnography (30).

Box 2-A—Evolution of Medical Thought Concerning the Menopause

1777—John Leake, in his book Chronic or Stow Diseases Peculiar to Women, proposed **a** *link* between menopause "at this critical time of life, around age 50," and the development of "various diseases of the chronic kind." He proceeded to delineate the effects of the cessation of the menses: "pain and giddiness of the head, hysteric disorders, colic pains, and a mid-life female weakness . . . intolerable itching at the neck of the bladder and contiguous parts are often very troubling. " In addition, he described possible psychological effects inasmuch as "women are sometimes affected with low spirits and melancholy." Such repercussions, as well as the peculiarity of the menopause to human beings, were attributed by Leake to the "many excesses introduced by luxury, and the irregularities of the passions." Leake accounted for the lack of a corollary occurrence in other species by stating that "quadrupeds and other animals are entirely exempt [from such disease] by living comfortable to their natural feelings."

1845-Columbat de l'Isere, in his ***Treatise of the Diseases of Females, included*** a chapter on the menopause that contained the fallowing: "Compelled to yield to the power of time, women now cease to exist for the species and hence forward live only for themselves. Their features are stamped with the impress of age and their genital organs are sealed with the signet of sterility.. . It is the dictate of prudence to avoid all such circumstances as might tend to awaken any erotic thoughts in the mind and reanimate a sentiment that ought rather to become extinct, . . in fact, everything calculated to cause regret for charms lost and enjoyments that are ended now forever." Previously, he had offered an analogy to describe a woman at the menopause: She "now resembles a de-throned queen, or rather a goddess whose adorers no longer frequent her shrine. Should she stall retain a few courtiers, she can only attract them by the charm of her wit and the force of her talents. "

1876-Merson asserted that the menopause is "always a time of trial, often of suffering and danger."

1882-Tilt determined that the menopause was an event bearing "evil effects."

1887—Borner proclaimed the insufficiency of medical knowledge regarding the menopause and encouraged further study, asserting that "the climacteric, or so-called change of life in women, presents, without question, one of the most interesting subjects offered to the physician, and especially to the gynecologist in the practice of his profession. The phenomena of this period are various and changeable, that he must certainly have had a wide experience who has observed and learned to estimate them all. So ill-defined are the boundaries between the physiological and the pathological in this field of study, that it is highly desirable in the interest of our patients of the other sex, that the greatest possible light should be thrown on this question."

1887—Farnham Summarized the relationship between the menopause and psychiatric disorders as "the ovaries, after long years of service, have not the ability of retiring in graceful old age, but become irritate& transmit their imitation to the abdominal ganglia, which in turn transmit the irritation to the brain, Producing disturbances in the cerebral tissue exhibiting themselves in extreme nervousness or in an outburst of actual insanity."

1897-Currier produced a historical evaluation of the importance of menstruation indifferent cultures in The Menopause. In addition to observations concerning the dearth of scientific attention to the subject and the lack of a known corollary event in animals, Currier examined the variation in the appearance of symptoms, noting that the menopause was uneventful for the majority of women. Comparisons were made in regard to variation in women's experience of the menopause both between societies, contrasting Eskimos and American Indians with the French and Irish and within a society, postulating that "highly bred," "civilized" women and "those with many troubles and ills" appeared to be the main sufferers, Furthermore, the assertion was made that ***predisposing*** factors were evident in women with severe menopausal symptoms.

1963--Physician Robert A. Wilson offered a disparaging depiction of the psychological state of the menopausal woman when they state&in *Feminine Forever,* that "a large percentage of women.. . acquire a vapid cow-like feeling called a 'negative state.' . . . It is a strange endogenous misery. . . **the world appears as** though through a gray veil and they live as docile, harmless creatures, missing most of life's values." In addition, in an article in ***Look magazine,*** Wilson listed 26 "symptoms of menopause": nervousness, irritability, anxiety, apprehension, hot flashes, night sweats, joint pains, melancholia, palpitations, crying spells, weakness, dizziness, severe headache, poor concentration, loss of memory, chronic indigestion insomnia, frequent urination, itching of the skin, dryness of the eye, nose, and mouth, backache, neuroses, and a tendency to take alcohol and sleeping pills or even to contemplate suicide.

1966R&ert A. Wilson concluded that, "in the course of my work, spanning four decades and involving hundreds of carefully documented clinical cases, it became evident that menopause . . . is in fact **a deficiency** disease.. . . To cure diabetes, we supply the lacking substance in the form of insulin. A similar logic can be applied to menopause-the missing hormones can be replaced."

1967—Phillip Rhoades painted the situation as a calamity, asserting that "many women are leading an active and productive life when this tragedy strikes. They remain attractive and mentally alert. They deeply resent, what to them, is a catastrophic attack on their ability to earn a living and to enjoy life."

1967—Brewer and de Costa, in their textbook on gynecology, wrote as follows: "Emotional instability is another outstanding symptom of this phase of life. Nervousness and anxiety are extremely frequent. The patient may feel that the end of her useful life has come, that now she is old, that she has lost her appeal as a woman, and that nothing is left to her. She cries easily; she flares up at her family and friends; she is irritable and may have difficulty in composing her thoughts or her reactions. Often the patient maybe extremely depressed. A person who has been extremely emotional most of her life will without much doubt have severe emotional disturbances during the climacteric.'

1968--Dunlop proclaimed that the menopause "is the trigger for the powder keg of emotions slowly smoldering somewhere in the hypothalamus. "

1970--K. Achte, in "Menopause From the Psychiatrist's Point of View," reported that "the assumption has been put forward that women's ability to work reduces to a quarter of the normal by menopause."

1970-Howard Osofsky and Robert Seidenberg, in the ***American Journal of Obstetrics and Gynecology,*** **perpetuated** misconceptions about the psychological repercussions of the menopause and reinforced the image that reproductive organs and capacity constitute the sum total of the female. They asserted that "it is no wonder that . . . women become depressed around the time of menopause; professionals and society have helped to ensure this reaction. At an age in life when a man is in the upswing of active social and professional growth, woman's service to the species is over. Professionals, including female experts, define the woman's role as one of mortification and uselessness.'

1986-Lila Nachtigall and Joan Rattner Heilman published Estrogen, ***The Facts Can Change Your Life,*** which **purports to offer "the latest word on ERT [estrogen** replacement therapy]: what the new safe estrogen replacementh can do for great sex, strong bones, good looks, longer life, preventing hot flashes" (cover).

1991—The Massachusetts Women's Health Study reported that "menopause, as a natural event, appears to have no major impact on health or health behavior. Any increase in symptomatology appears to be relatively small and transitory, occurring primarily in the perimenopause. The majority of women barely notice the menopause and health care utilization does not increase during menopause."

SOURCES: Adapted from S.E. Bell, "Sociological Perspectives on the Medicalization 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. 173-178; M.J. Goodman "A Critique of Menopause Research," *Changing Perspectives on Menopause,* A.M. Voda, M. Dinnerstein and S.R. O'Donnell (eds.) (Austin TX: University of Texas Press **1982);** **J.B. McKinlay,** S.M. McKinlay, and D.J. Brambi1la "Health *Status and* Utilization Behavior Associated With Menopause," *American Journal of Epidemiology* 125(1):110-121, 1987; E. Perlmutter and P.B. Bart "Changing Views of 'The Change': A Critical Review and Suggestions for an Attributional Approach," *Changing Perspectives on Menopause,* A.M. Voda, M. Dinnerstein and S.R. O'Donnell (eds.) (Austin, TX: University of Texas Press, 1982); B. Seaman and G. Seaman, *Women and the Crisis in Sex Hormones (New* York NY: Rawson Associates Publishers, Inc., 1977); P.J. Schmidt and D.R. Rubinow, "Menopause-Related Affective Disorders: A Justification for Further Study," *American Journal of Psychiatry* 148(7):844-852, 1991; W.H. Utian, Menopause *in Modern Perspective: A Guide to Clinical Practice (New* York NY: Appleton-Century-Crofts, 1980).

The menopausal experience encompasses a complex interaction of sociocultural, psychological, and environmental factors as well as biological changes relating strictly to altered ovarian hormone status (42). Endocrine changes and the cessation of menses are certainly one way of describing the menopause, but cultural factors also shape it and can strongly influence how particular women define their status (43). For example, a Newfoundland woman, when defining herself as menopausal, includes symptom experience, the menopausal status of women in her peer group, the occurrence of specific life, events, changes in status and role, and her chronological age (43). Japanese women who have not menstruated for more than 12 months might still report themselves as without signs of menopause (see app. A) (43). Thus, the cessation of menstruation is not necessarily the

Box 2-B-Cultural Variations in Positive Perceptions of the Menopause and Aging

Although the relevant data are somewhat limited, there is evidence that in some non-Western cultures, the menopause is considered a positive event in a woman's life, entitling her to certain privileges such as greater mobility, the right to exercise authority over members of the younger generation, and increased status and recogniton beyond the household unit. Many of the benefits of reaching the menopause in these societies come from the removal of constraints and prohibitions imposed on menstruating women; paradoxically, this positive view of the menopause thus reflects a negative cultural disposition toward the menstrual cycle itself. Some instances of positive change, particularly those pertaining to increased authority within the immediate family, may be a repercussion more of the maturation of offspring than of the cessation of menstruation. All of the changes, however, entail the improvement of a woman's life situation in conjunction with aging. Cultural studies of the roles of women in society provide a multitude of positive examples of the role of the postmenopausal female. For example:

. The Yoruba of West Africa allow older women, who are free from childbearing responsibilities, to participate in the long-distance travel required for profitable trade.

- Among Bengali women, who are traditionally confined to the village, older, upper-class women are entitled to make one or two religious pilgrimages every year to distant religious sites.
- In Moroccan society, women are perceived as excessively sexual and damaging to men. As a result, the sexes are separated, for the most part, during a woman's childbearing years. But once a woman reaches the menopause, she is considered to be asexual and is permitted to move freely within the world of the male.
- The Yonomamo of South America, known for their particularly poor treatment of younger women, extend to older women a great deal of kindness and respect, owing to the fact that old women are believed to be somewhat sacred. Warring amongst tribes includes the practice of stealing women; however, older women are considered neutral, and this neutrality extends to protection from enemy sorcery. In addition, older women are the only members of a tribe who are able to travel freely throughout the land.
- A similar freedom to travel unsupervised, usually for the purpose of communication, is permitted postmenopausal women of both the Kanuri, of the Lake Chad region of Africa, and the Tiwi, an aboriginal people from the islands off northern Australia.
- Among the Mandurucu of South America, the oldest woman maintains authority over the household, which may exceed 50 people. In addition, she controls the complex, labor-intensive preparation of food and holds the key to the food storage area. The menopause releases Mandurucu women from societal constraints on demeanor and behavior, and is perceived as graduation of the female to the status and role of a male.

marker by which women define themselves as menopausal. Treating this time in a woman's life as a' 'medical' condition warranting medical attention has raised concerns about the medicalization of a natural life event (18,63).

Popular opinion (and many medical experts) continue to portray the menopause as a major negative life event of the same magnitude as the loss of a spouse or a job (6). It signifies the end of reproduction and the acceleration of aging (both of which are viewed with dread by many members of Western societies that extol the family and youthful sexuality). A common stereotype is that of menopausal women as depressed hypochondriacs, facing the end of usefulness and life and, in Western cultures, finding solace in the doctor's office. Slowly, these images and myths are giving way to different pictures. Women are becoming more assertive and more informed consumers of health care. Open discussion of sexuality and reproduction has led women to become more outspoken about this last reproductive phase of their lives. Much-needed studies of menopausal women have also helped to debunk some of the myths. For example, research has shown that menopausal women do not use health care services at a rate higher than would be expected with increases in age (6,52). Thus, the so-called menopausal syndrome may be more related to personal characteristics than to the menopause per se (6,28, 29,56).

More and more, women are seeing the menopause as a highly individualized experience that deserves openness and discussion, not embarrassing stigmatization. Part of this change in perception maybe due to increasing press and media coverage of the menopause in recent years and its appearance as the subject of public service announcements and television situation comedies. In fact, far from viewing the menopause as something shameful, some women have learned to recognize and announce this impor-

. The position and power of the shaman are available to women only after the menopause in both the Plains Cree and Winnebago Indian cultures. The postmenopausal women of the Winnebago may sit, for the first time, alongside men during ceremonial feasting.
• The Bemba of East Africa reserve many leadership roles, both political and social, for older women. The *Nacimbusa,* are a respected position reserved for an older woman, conducts the intricate initiation rites for young girls and acts as midwife for their deliveries. She also gives permission for a woman to resume intercourse after a waiting period following the birth of a child.
. A belief in supernatural interaction following the menopause is found in Indian villages in Mexico where the ***curandera,*** a ceremonial priestess, is often a woman who is past the menstrual cycle.
. Among the Navajo, menstruating women are constrained by a number of taboos. The high-status role of ***hataalii,*** or ceremonialist, is only available to postmenopausal women. Postmenopausal Navajo women are also able to assume the role of singer, or curer, as well as the diagnostic roles of star-gazer and hand-trembler.

In some cultures, aging is a time for equality between the sexes. Postmenopausal women are viewed as elders and are accorded senior status equal to that of senior men. Examples include the following:

• Among the Nayar of Kerala in southwest **India advancing age is marked** by a rite-of-passage ceremony that involves both men and women. A jubilee is held on the individual's 60th birthday, after which "respectable people are supposed to retire from worldly life."
• Among the Qemant of Ethiopia, a simple rite of passage **called kasa** ushers both men and women into ''the status of a venerated elder . . . who do[es] most of the debating and ha[s] the greatest voice in making decisions." Requirements for ascension to this reserved status, which "signifies marked closeness to Mezgana (God)," are the appearance of gray hairs for the man and the occurrence of the menopause for the woman. The Qemant believe that individuals at this stage of life have reached an age at which they are "too old to sin any longer. " Interestingly, such elevated elders of either sex are prohibited from entering a place where women are menstruating.
• Both the Hare Indians of Canada and the Chinese signal a person's change in status to that of elder with a symbolic change in form of address.

SOURCES: Adapted fromJ.K. Brown "A Cross-Cultural Exploration of the End of the Childbearing Years"; J. Griffen "Cultural Models for Coping With Menopause"; and A.L. Wright, "Variation in Navajo Menopause: Toward an Explanation" *Changing Perspectives on Menopause,* A.M. Voda, M. Dinnerstein and S.R. O'Donnell (eds.) (Austin, TX: University of Texas Press, 1982).

tant change and to see it as the natural event it is (see box 2-D) (79) .

Yet although women are beginning to change their attitudes about the menopause, the biological sequelae and consequences of this event are nevertheless a dramatic change in the physiological profile of a woman. The short- and long-term consequences of reduced ovarian estrogen production vary widely and have only recently been documented. Physicians may understand the hormonal changes of this period in physiological terms, but they still lack good estimates of the percentages of women who will have symptoms and who will not. One reason for this gap in knowledge is that acquiring it involves extensive study of cycling women, which is generally avoided because of the complexity of hormonal changes and the wide variability among women (54). What is known about the biological changes that occur during the menopausal period is described in the next section.

BIOLOGY AND SYMPTOMATOLOGY OF THE MENOPAUSE

The menopause is colloquially known as "the change of life" because it signifies the end of reproductive fertility. This event is a completely natural, normal biological phenomenon; it is a significant component of the reproductive cycle and is accompanied by profound hormonal changes.

Natural menopause (as opposed to surgical menopause, which results from removal of the ovaries) is generally believed to be due to exhaustion of the remaining ovarian follicles, the multicellular structures that contain the germ cell, or "egg," and that produce the steroid hormones estrogen and progesterone (see figure 2-l). The actual causes of follicu-

Box 2-C--Cultural Variations in Negative Perceptions of the Menopause and Aging

Anthropological investigation has found that in some cultures the menopause elicits a variety of negative societal responses. In much of the Western world, as well as in some non-Western cultures, the menopause is an event that women are taught to dread through societal myths regarding the psychological effects of the climacteric and of aging in general. Cross-cultural surveys of negative reactions to the menopause reveal that the end of the reproductive years may be accompanied by a loss of role or by the transition to an anomalous role. The former reaction does not preclude the latter in fact, the loss of one's role in the community may result in the adoption of a role that seems abnormal or inconsistent with expectations.

Alternatively, a culture may offer no overt reaction to the menopause whatsoever. Nonresponse may not seem intuitively negative; however, inasmuch as cultural silence limits a woman's knowledge, it may impair her understanding of and ability to discuss her own physiological changes, and result in a sense of anomalous being. For example:

- In the Twi of Ghana, the postmenopausal woman may lose the role of wife because her husband may take younger wives, although the menopause does not precipitate actual divorce. The distress caused by such displacement has sometimes resulted in the menopausal woman's believing that she has become a witch, eliciting confessions of wrongdoing.
- Until recently in Ireland, the belief that no role was possible for women following the end of their reproductive life prompted some rural women to confine themselves to bed until their death years later.
- The cutural perception that death may occur in conjunction with or as a result of the menopause has been found among the Sinkaietk, a southeast group of the Salish Indians from the Pacific Northwest of North America.
- Yoruban women, lacking adquate information about the menopause, believe that menopausal women are actually pregnant but that witchcraft is preventing the pregnancy from continuing to its normal conclusion. The same belief has been found among Twi women.

SOURCES: Adapted from J. Griffen "Cultural Models for Coping With Menopause," and BAR. Kearns, "Perceptions of Menopause by Papago Women," *Changing Perspectives on Menopause*, A.M. Voda M. Dinnerstein, and S.R. O'Donnell (eds.) (Austin, TX: University of Texas Press, 1982).

Box 2-D-Changing Attitudes About "MENOPOZ"

In May 1991, Dorothy Mitchell of Seattle, WA, received a letter from the State's Department of Licensing asking that she return her customized license plates, which read "MENOPOZ." "It has come to our attention that the phrase used on your personalized plate, MENOPOZ, is offensive to good taste and decency," wrote Bob Anderson, the department's assistant directorof vehicle services. After returning the replacement plates and refusing to give up her customized plates, Mitchell was told by a department official that she could be stopped for canceled plates.

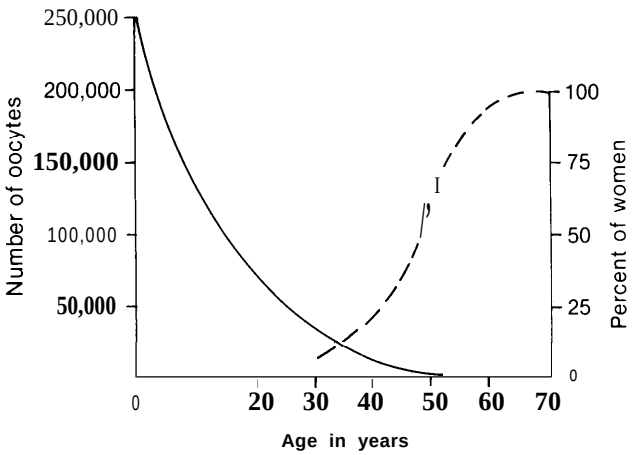
Mitchell said she got the idea for the MENOPOZ plate after she went with her husband to get an oil change for his truck and ended up buying a sporty white Dodge Daytona with an orange stripe. She later told her father that the impulse buy must have been part of a menopausal phase and decided to put that on her license plate. She said the plates had resulted in "a lot of fun I wouldn't have had otherwise." A few days after the story was broadcast by the wire services, Mitchell was notified by licensing director MaryFaulk, aged 50, that she could keep the plates. Faulk said, "I don't think a normal process of aging to be in bad taste."

SOURCE: Adapted from Associated PressWise stories, May 24 and May 26, 1991.

lar depletion, and hence the menopause itself, are unknown and puzzling, considering the finding that the number of follicles that remain in the ovaries in the first half of the fifth decade of a woman's life may range from 350 to 28,000 (91). On the basis of studies in aged rodents and in humans, researchers have postulated that the menopause in humans may be preceded by an accelerated rate of depletion of follicles, which results from changes in the brain leading to altered neuroendocrine stimulation of the ovaries (71).

The natural menopause is due as much to nonresponse by the depleted remaining follicles to follicle-

Figure 2-l—Relation of Age, Oocyte Number, and the Menopause



SOURCE: Adapted from D.R. Mattison, M.S. Nightingale, and K. Shiromizu, "Effects of Toxic Substances on Female Reproduction," *Environmental Health Perspectives 48:43-52, 1983.*

stimulating hormone (FSH) as to the total exhaustion of the remaining ovarian follicles (see box 2-E). Some investigators postulate that if these follicles could be reactivated, the menopause would be delayed (62).

Although age-related changes in the menstrual cycle and its associated hormonal patterns are not well characterized, it is believed (but has not yet been demonstrated) that a gradual decline in overall ovarian function and in the production of estrogen and progesterone begins when a woman is in her 30s (61,86,87). During the middle to late portion of a woman's fifth decade, anovulatory cycles or cycle irregularities and, not uncommonly, episodic bouts of heavy uterine bleeding of unpredictable frequency and duration begin to increase. These changes mark the start of the perimenopausal, or transitional, phase. The perimenopause is frequently accompanied by symptoms of varying intensity that are believed to reflect marked fluctuations in levels of estrogen and progesterone or outright deficiency (see box 2-E for a discussion of estrogen and progesterone) (87). The tissues that are most affected by reduced estrogen are the ovaries, uterus, vagina, breast, and urinary tract. Tissues such as the hypothalamus (part of the neuroendocrine system), skin, cardiovascular tissue, and bone may also be affected (90).

The age of onset of the menopause varies greatly among women. Although the average age of women at the menopause is between 50 and 51 (12,23,57,95),



Photo credit: National Cancer Institute

More and more, women are seeing the menopause as a highly individualized experience that deserves openness and discussion, not embarrassing stigmatization.

some women may stop menstruating much earlier. There is no evidence that this median age has tended to increase (92). Although the average age of onset of puberty has decreased over time, there is no indication of a relationship between a woman's age at menarche and the timing of the menopause (91). Moreover, age at menopause does not appear to depend on race, marital status, or geography. Early menopause has been consistently associated with smoking, but the exact nature of this effect remains speculative (12). Smokers, on average, experience the menopause nearly 2 years earlier than nonsmokers (12). Women who have never had children also tend to experience an earlier menopause (58). If the menopause occurs before age 40, as it does in roughly 8 percent of women, it is considered "premature" ovarian failure, not menopause (17,20). There is some evidence that the age at which women experience the menopause is in part

Box 243—The Production of Estrogen and Progesterone in the Reproductive Cycle

Hormones are chemical messengers that are produced by specialized glands and released into the bloodstream. Three groups of hormones are relevant to female reproductive status: releasing factors, pituitary gonadotropin, and sex steroids. Their actions are explained below.

- Gonadotropin-releasing hormone (GnRH), produced in the hypothalamus, induces the pituitary gland to release the pituitary gonadotropin: follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
- FSH stimulates the maturation of the ovarian follicle, or egg, and induces the synthesis of the sex steroid estradiol, the most potent naturally occurring estrogen in humans. The ovary accounts for more than 90 percent of total body production of estradiol. other forms of estrogen, such as estrone, are produced by other glands, such as the adrenal, and by peripheral conversion of circulating hormones, such as testosterone. These other sources account for 10 percent of premenopausal estrogen production. The first detectable endocrine manifestation of reproductive aging is a gradual increase in plasma FSH levels. This rise becomes apparent almost a decade before the menopause, despite apparently normal ovulatory cycles. Significantly elevated levels of FSH are in themselves a diagnostic criterion of the approach of the menopause.
- LH stimulates egg release and formation of the corpus luteum. The corpus luteum also synthesizes another sex steroid, progesterone, as well as estradiol. Sometime after the FSH level increases, there is a concomitant increase in serum LH levels, usually around ages 45 to 50.

Immediately after estradiol and progesterone are produced, they are released into the bloodstream and transported throughout the body. As noted in the text, many kinds of tissue located throughout the body can have receptors for estradiol, for progesterone, for both, or for neither of these hormones.

The synthesis and release of hormones vary from moment to moment and from day to day; their cycling nature produces the menstrual cycle. The ovarian reproductive cycle each month is a repetitive, self-cycling mechanism that continues for as long as the ovary is capable of response, that is, for as long as there are functional ovarian follicles present. Once the ovary becomes depleted, as it does gradually during the climacteric, the ability to reproduce will end. Following the menopause, levels of estradiol and estrone drop, but, as might be expected, the level of estrone falls to a relatively lesser extent than that of estradiol because it continues to be produced by other glands (e.g., adrenal). Estrone, therefore, becomes the major free estrogen in the circulation, and progesterone production ceases. The plasma levels of the sex steroid androgen increase, relative to the reduction in estrogen. The postmenopausal ovary is a potential source of androstenedione and testosterone, which are then available for conversion to estrone.

SOURCE: Adapted from W.H. Utian, *Menopause in Modern Perspective:A Guide to Clinical Practice (New York, NY:* Appleton-Century-Crofts, **1980).**

genetically determined, but smoking seems to be the best predictor of when the menopause occurs.

The transition from a reproductive to a nonreproductive state is gradual for women who undergo natural menopause; consequently, as a woman approaches the menopause, her menstrual function may change gradually rather than ceasing abruptly. Clinical studies of women have shown that approximately 10 percent will have sudden amenorrhea—i.e., sudden stoppage of menstrual periods (58); 70 percent report oligomenorrhea, or abnormal menstrual periods (intervals of 36 to 90 days between periods) or hypomenorrhea (regular menses but decreased in amount); and 18 percent report menorrhagia (bleeding of excess duration), metrorraghia (bleeding irregularly between cycles), and hypermenorrhea (excessive bleeding) (78). Given these variations, it is not surprising that some studies indicate that women often have little idea of the alterations to expect in their menstrual cycles as they become perimenopausal (78). Data show that the severity of most menopausal symptomatology is related to the length of time since the last period. That is, symptoms decline in severity as time passes. This is not true of all symptoms, however. Genital symptoms, such as vaginal atrophy, which can affect between 20 to 40 percent of women (62), appear to worsen with time (91).

In the United States and in Western countries, the most common menopausal symptom is the vasomotor "hot flash," which is estimated to occur in at least 50 percent of U.S. women at some point during the menopausal years (58). Estimates of the incidence of hot flashes from population studies in the United States and worldwide have ranged from 25 to 85 percent, depending on the geographic region (47).

The vasomotor symptoms of the hot flash (which may persist from 5 to 10 years or longer tier the permanent cessation of menstruation) have been described as "recurrent, transient periods of flushing, sweating, and a sensation of heat, often accompanied by palpitations, feelings of anxiety, and sometimes followed by chills" (see box 2-F) (47). The majority of women may experience only a sensation of warmth and minor discomfort; 15 to 25 percent of women, however, experience severe or frequent hot flashes (as many as 10, or even more, per day) and often find them to be associated with repeated episodes of interrupted sleep, fatigue, nervousness, anxiety, irritability, depression, and memory loss (90). Night sweats, the nocturnal version of the hot flash, are usually conceded to be worse than hot flashes (17). Of those women who have hot flashes, 80 percent complain of them for more than 1 year, and 25 to 50 percent experience them for longer than 5 years (3).

For most women, symptoms subside within the first 3 to 5 years (or sooner) after the menopause; for other women, particularly those who undergo surgical menopause as a result of bilateral oophorectomy (bilateral removal of the ovaries), symptoms may be more severe and long-lasting (47). Within 4 to 5 years after the cessation of menstruation, some women who are not using hormonal therapy begin to experience signs of atrophy in the vagina, urethra, and bladder base. Consequences of atrophic changes include dyspareunia (difficult or painful intercourse), repeated vaginal infections, urinary tract infections, and dysuria (painful or difficult urination) (60). These women may also experience urinary stress incontinence (the inability to refrain from discharging urine under such stresses as jogging, exercising, sneezing, or even laughing). Studies indicate that incontinence is more common in women who have undergone vaginal hysterectomies than in women who experience a natural menopause (17). Additional physical complaints among menopausal women are pain in muscles and joints, headaches, and increased weight (5).

Women who have had both ovaries removed before the onset of the menopause experience more severe menopausal symptoms than women who experience a natural menopause (18). Past studies of menopausal symptoms have mistakenly combined women who experience a natural menopause with those who have had a surgical menopause. This error has resulted in problematic and, in some cases, erroneous characterizations of the progression of the perimenopause; it may also be responsible for overstatements about common symptomatology.

Box 2-F—The Hot Flash

The hot flashes experienced by many women during their menopausal years, although quite variable across women, are generally characterized by a sudden feeling of intense warmth throughout the upper part of the body, often accompanied by flushing of the neck and face and sweating. A cold, clammy sensation or chills may follow. Flashes vary in intensity, frequency, and duration within one person and among different individuals. They may cause discomfort, embarrassment, and loss of sleep. Sometimes an aura precedes the hot flash by several seconds. During this period, heart rate and finger blood flow begin to increase (finger blood flow and temperature are easily measured indicators). Then there is a sensation that the flash is about to occur, which is followed immediately by an increase in finger temperature of up to 6 'C and sweating, a drop in skin temperature in areas of sweating such as the forehead and chest, and a subsequent drop in internal temperature of 0.1 to 0.6 'C. Hot flashes are associated with a sharp rise in blood levels of the hormone epinephrine (a potent stimulator of heart function that increases heart rate, cardiac output, and systolic blood pressure) and a simultaneous decline in the hormone norepinephrine (which increases blood pressure dramatically). An increase in circulating luteinizing hormone is also associated with most hot flashes, as is an elevation of blood neurotensin-like reactivity.

SOURCES: Adapted from National Institute on Aging, *Research Advances in Aging, 1984-1986, NIH Publication No. 87-2862, March 1987,* and V. Ravnikar, "Physiology and Treatment of Hot Flushes," *Obstetrics and Gynecology 75(4,* Suppl.), 1990, PP. 3S-8S.

Hysterectomy or Surgical Menopause

Currently, hysterectomy is one of the most commonly performed inpatient surgical procedures in the United States, with more than 650,000 performed each year. Of all surgical procedures performed annually on men or women, only the number of caesarean sections exceeds this figure (66).

More than 18 million women living in the United States have had a hysterectomy. This figure translates to 19 percent of all women over the age of 18.

Table 2-l—Rates of Hysterectomies (per thousand) by Age and Geographic Region, United States, 1972-87

Age and region	1972	1975	1980	1981	1982	1983	1984	1985	1986	1987
15 and older										
United States	8.3	8.8	7.1	7.3	6.9	7.1	6.9	6.9	6.6	6.6
Northeast	6.7	6.6	5.3	4.7	4.7	5.4	4.8	4.3	4.4	4.1
Midwest	7.9	9.0	7.5	7.2	7.1	6.8	6.6	6.6	6.8	6.5
South	9.6	9.9	8.7	8.7	8.5	8.5	8.3	8.3	7.6	7.4
West	8.9	9.6	6.4	7.9	6.6	6.9	7.2	7.8	7.0	8.1
15 to 44 years										
United States	8.9	9.3	7.6	7.9	7.5	8.0	7.4	7.4	6.9	7.0
Northeast	6.4	5.8	4.9	4.3	4.2	5.0	3.8	3.7	3.6	3.5
Midwest	7.8	9.1	7.7	7.2	7.1	7.5	6.7	6.5	7.0	6.7
South	11.7	12.0	10.3	10.7	10.5	10.8	10.0	9.9	8.9	8.4
West	9.0	9.0	5.9	7.9	6.7	6.9	7.9	8.2	6.8	8.7
45 to 64 years										
United States	10.0	11.0	8.8	8.3	7.8	7.7	8.1	8.1	8.1	8.0
Northeast	9.3	10.2	7.6	6.9	6.6	7.9	8.4	6.5	7.3	6.2
Midwest	10.8	12.4	9.2	9.5	9.1	8.3	8.7	8.8	8.9	8.5
South	9.0	9.1	8.8	7.5	7.8	7.0	8.0	8.4	7.5	7.9
West	11.5	13.7	9.6	9.7	7.6	8.0	7.0	8.6	9.3	9.7
65 and older										
United States	2.7	3.2	3.1	3.7	3.7	3.2	3.6	3.5	3.3	3.4
Northeast	2.7	3.0	2.9	2.9	3.4	3.0	2.9	3.2	2.7	3.3
Midwest	2.8	2.5	4.5	3.6	4.2	2.6	3.8	4.1	3.3	3.5
South	2.5	3.4	2.2	3.5	3.1	3.0	3.2	2.3	3.2	3.4
West	2.9	4.3	2.9	5.2	4.4	5.1	4.9	5.2	4.1	3.7

SOURCE: National Center for Health Statistics, "National Hospital Discharge Surveys," 1987.

At present rates, 37 percent of all women will be hysterectomized before they reach 60 years of age (9). The widespread prevalence of this procedure and the sizable regional variations seen in the rates of its performance (see table 2-1) have generated much controversy regarding the risks and benefits of hysterectomy to the continuing health of American women (see box 2-G).

Hysterectomy performed in conjunction with the removal of both ovaries and the fallopian tubes has become increasingly more comrnon (see figure 2-2). According to the National Center for Health Statistics, between 1965 and 1984, the rate of performance of this procedure (known *as total hysterectomy and* ***bilateral salpingo-oophorectomy)*** increased ***from 25*** percent of all women undergoing hysterectomy to 41 percent. The bulk of this increase was in women 45 to 64 years of age.

Prior to the 1970s, one commonly reported—and controversial-reason for performing a bilateral oophorectomy in conjunction with a hysterectomy in the absence of any obvious pathology was to prevent ovarian cancer, which occurs at a rate of 1 in every 70 women (2,94). It was widely believed that the only function of the ovaries after childbearing was to produce estrogen and progesterone, and because these hormones could be adequately replaced, the ovaries were considered expendable (94).

It has long been documented that hysterectomy alone in the premenopausal patient is associated with increased risk—perhaps three times greater than among nonhysterectomized women--of coronary artery disease (16,75). Recent evidence also supports the concept that bilateral oophorectomy increases the risk of coronary heart disease (19), possibly as a result of altered lipoprotein profiles. In addition, the incidence of osteoporosis is higher in young women who undergo bilateral oophorectomy than in women who experience a natural menopause (38). Hysterectomized women have a greater loss of bone density and a higher incidence of osteoporotic fractures than women of an equivalent age with intact uteri.

Some studies have suggested that even women whose ovaries have been retained after hysterectomy have undergone some changes that are sufficient to cause menopausal symptoms and adverse alterations in lipid levels and bone metabolism (38,94). These changes occur at a reduced rate compared with

Box 2-G—Hysterectomy: An Overview

The term hysterectomy refers to the surgical removal of the uterus. The first hysterectomy was allegedly performed more than 16 centuries ago by Soranus in the Greek city of Ephesus, and the practice was continued with little success throughout the 16th and 17th centuries. Hysterectomy was not developed further until the 18th century, when university-trained physicians entered the field of midwifery. At that time, medical technology had not advanced sufficiently to allow hysterectomy to become a practical procedure. The mortality rate of the operation continued to approach 90 percent and was thus limited to obvious, life-threatening gynecological conditions. Indications for the surgery remain controversial. Some estimates show that 10 percent of all hysterectomies are performed for life-threatening conditions. The remaining 90 percent are classified as *elective* hysterectomy and are performed for quality-of-life considerations or for the prevention of pregnancy or disease.

The notion that a woman who has completed her family no longer has a specific need for her uterus is often referred to as the useless uterus syndrome. Prevention of pregnancy or disease as an indication for hysterectomy is becoming less common and is no longer viewed as sufficient cause for the procedure without evidence of further pathology. One study has shown that only 1.3 percent of all women would be helped by hystereetomy as a preventive procedure to guard against cervical or endometrial cancer. A woman undergoing an elective hystectomy at the age of 35 could increase total life expectancy by only 2.4 months.

The most common diagnostic indication for hysterectomy in women of all ages is uterine fibroids, benign fibromuscular growths that can be found in more than 25 percent of women over the age of 35. From 1985 to 1987, this diagnosis accounted for 30 percent of all hysterectomies. During the same period, endometriosis accounted for 19 percent of all hysterectomies, followed by uterine prolapse at 16 percent, cancer at 10 percent, and endometrial hyperplasia as an additional 6 percent. Diagnoses also differ between age groups. Nineteen percent of hysterectomies are concentrated in the youngest age group and are performed for such indications as menstrual disorders, pelvic peritoneum, and diseases of the parametrium.

Although quality-of-life considerations are of the utmost importance to women experiencing the pain of uterine prolapse, endometriosis, or other non-life-threatening conditions, many argue that hysterectomy is not necessarily the treatment of choice. As with any major surgery, there is a substantial risk of complications that must be balanced against the benefits. The morbidity rate for hysterectomy is between 25 and 50 percent for all operations performed.

Despite the risks of possible complications, hysterectomy remains the second most commonly performed surgical procedure in the United States. There are vast regional differences in the rates of the procedure, suggesting professional disagreement about the appropriateness of hysterectomy for some indications. Within the United States, hysterectomy rates are highest in the south and lowest in the Northeast. The high rates in the South are mainly the result of an increased number of younger women-between the ages of 15 and 44-undergoing the operation.

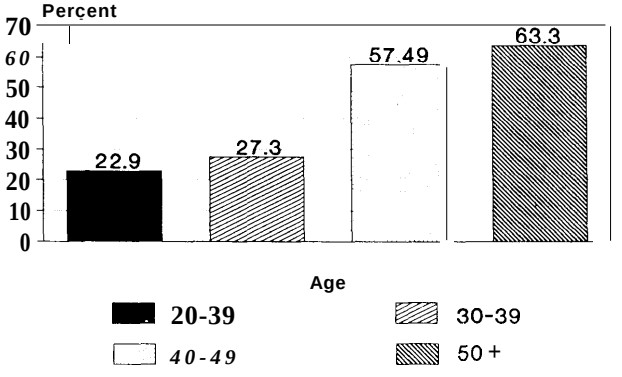
Other factors that affect the rate of hysterectomies are race and income. The only racially relevant data available focus on black versus white women: The rate of hysterectomies performed on black women is higher than for white women, although the absolute number performed on white women is greater. With regard to income levels, indications are that women with very low incomes and women with very high incomes are most likely to have a hysterectomy. This finding could be explained by the availability of Medicaid and health insurance at the extremes. Physicians who are reimbursed on a fee-for-service basis perform up to 25 percent more hysterectomies than do physicians who are salaried or reimbursed on a cavitation basis. The implications of such statistics are that a combination of patient and physician characteristics, including monetary compensation, age, race, and income, rather than a narrowly defined medical need, explain much of the variation in regional hysterectomy rates.

SOURCES: American College of Obstetricians and Gynecologists, *Understanding Hysterectomy (Washington, DC: 1987); G.A. Bachman* "Hysterectomy: A Critical Review," *Journal of Reproductive Medicine 35(9):839-862, 1990; C.L.* Easterday, DA. Grimes, and J.A. Riggs, "Hysterectomy in the United States," *Obstetrics and Gynecology 62(2):203-212, 1983;* A.S. Kasper, "Hysterectomy as a Social process," *Heath and Public Policy* 10(1):109-127, 1985; C.J. Mackety, "Alternative to Hysterectomy," Today's OR Nurse 8(4):10-14, 1986; R. Pokras, "Hysterectomy: Past, Present and Future," *Statistical Bulletin 70(4):12-21, 1989* N.P. Roos, "Hysterectomy: Variations in Rates Across Small Areas and Physicians' ***Practices," American Journal of Public Health*** **74(4):327-335, 1984.**

women who have had both ovaries removed. Current recommended practice is to perform an oophorectomy on a premenopausal woman only if it is detrimental to the woman's health to conserve her ovaries. In the postmenopausal patient, the ovaries are usually removed if there is no increased surgical risk to the patient (94).

The vast majority of women who undergo hysterectomy do so between the ages of 35 and 44 (see table 2-2). The average age for this procedure is 42.7

Figure 2-2—Percentage of Hysterectomies With Bilateral Oophorectomy, United States, 1985-87



SOURCE: National Center for Health Statistics, "National Hospital Discharge Surveys," 1987.

and has remained fairly constant over the years. The concentration of hysterectomies in this middle age range means that even if the overall rate remains constant, the absolute number of hysterectomies performed will increase substantially as the baby boomers move into this age bracket. The effects of the surgery can be extensive; loss of ovarian hormones is but one, albeit a significant, consequence.

Changes in Mood, Behavior, and Sexuality

For centuries, disturbances of mood and behavior have been associated with reproductive endocrine system change (77). Psychiatric syndromes linked to reproductive function in women have included postpartum (puerperal) psychosis and depression, premenstrual syndrome (PMS), posthysterectomy depression, and menopausal psychiatric syndromes (24). Much of the current understanding of these disorders is based on myths, unwarranted assumptions, and conclusions derived from outdated, poorly constructed studies (24). As a result, substantial controversy remains.

Mood and behavioral changes associated with cessation of a woman's reproductive function 'have been poorly characterized, if not dismissed" (77). Researchers know that estrogen-sensitive cells lie throughout the peripheral and central nervous systems (76). In addition, the cardiovascular system is replete with cells that are sensitive to estradiol (the most potent naturally occurring estrogen in humans) and progesterone; their receptor activity is localized in smooth muscle in the walls of arteries and in endothelial cells throughout the vascular tree. Estrogens increase arterial blood flow (70); investigators thus suspect that decreases in blood flow combined with cell atrophy resulting from estrogen depletion may play a role in the somatic changes (e.g., vaginal dryness) that are often attributed to changes in sexual function during the years immediately before and after the menopause.

For many years, doctors believed that menopausal depression (referred to previously as involutional melancholia) was a syndrome characterized by agitated psychotic depression and somatic (bodily) preoccupation. Despite the fact that 25 percent of all cases of involutional melancholia were diagnosed in men, the syndrome was attributed to physiological and psychological effects of the perimenopause. In the past 25 years, little evidence has been found to

Table 2-2—Number of Hysterectomies (in thousands) by Age and Diagnosis, United States, 1985-87

	Diagnosis						
Age	Total	Cancer	Endometrial hyperplasia	Fibroids	Endometriosis	Prolapse	Other
Total	1,967	198	114	593	372	318	372
15 to 24 years	37	5	z	z	8	4	18
25 to 34 years	424	37	10	63	111	58	145
35 to 44 years	760	29	26	302	179	90	134
45 to 54 years	421	27	42	188	64	58	42
55 to 64 years	148	39	21	23	8	43	14
65 vears and older	176	60	14	15	z	65	20

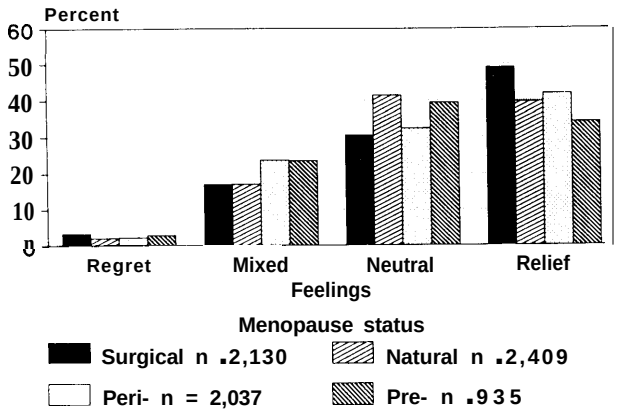
NOTE: Estimates under 10,000 are not considered reliable and should be used with caution.
Z—Too few records sampled to produce an estimate.

SOURCE: National Center for Health Statistics, "National Hospital Discharge Surveys," 1987.

support the idea of separate depressive disorders occurring in the menopausal years (24,36,77). Studies associate the psychiatric symptoms with age but not with reproductive status (10). In addition, physical symptoms of the menopausal period do not correlate with the psychiatric symptoms that have been seen; psychosocial and psychological variables such as life events, relationships with children, and marital status show a stronger correlation (10). A further point is that physical symptoms occur in some women without psychiatric symptoms and vice versa. Women who experience an artificial menopause as a result of surgery are an atypical subgroup that physicians tend to see more frequently and from whom they may derive a distorted image of the typical menopausal woman (53,55). Even for hysterectomized women, however, the evidence is contradictory regarding a higher rate of psychopathology or depression following hysterectomy (18, 24,58).

Studies of the attitudes of North American women about the menopause are consistent with the lack of evidence of an absolute relationship between it and depression. Of a cohort of 7,500 women participating in the Massachusetts Women's Health Study, 70 percent reported relief or neutral feelings about the cessation of their menses (see figure 2-3) (6). In addition, although rates of depression were slightly higher for perimenopausal women, this trend was largely explained by discomfort with menopausal symptoms (e.g., sleep loss, hot flashes) and appeared to be transitory. In fact, women who were already depressed were more likely to report menopausal symptoms; a change in menopausal status was not a significant predictor of becoming depressed. Factors correlating with depression included stress from interpersonal relationships, decline in physical health, and change in marital status (53,58). Studies based in southeast England report similar findings (58). Some studies have concluded that the women who experience the most distress at the menopause are those who have relied on their childbearing and child-rearing roles for status and esteem (59). (In fact, studies have demonstrated that women of childbearing age, particularly those with young children at home, tend to report more emotional problems than women of other ages (36).) For the majority of women, the natural menopause is not a major crisis and does not influence their opinion of their general health (36).

Figure 2-3—Percentage of Women Reporting Feelings About Menopause by Menopause Status, 1981-82



SOURCE: N.E. Avis and S.M. McKinlay, "A Longitudinal Analysis of Women's Attitudes Toward the Menopause: Results From the Massachusetts Women's Health Study," *Maturitas 13:71,* 1991.

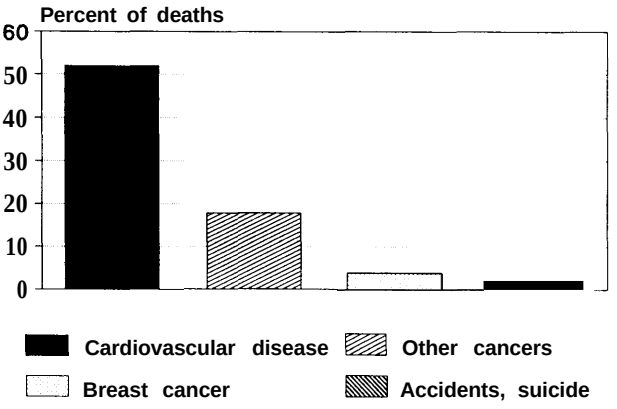
Some women report decreased sexual desire during the perimenopausal and postmenopausal periods. Most evidence, however, shows that sexual pleasure among older women is not compromised over time, although not much is known about their sexuality (8). Researchers thus attribute the decline in sexual satisfaction reported by some women to hot flashes and a decrease in vaginal lubrication and flexibility (17).

In summary, understanding of the relationships among aging, the menopause, and behavioral change is incomplete. Many studies have relied on small samples of self-selected women seeking treatment for symptoms. As a result, the actual prevalence of minor psychological and somatic symptoms directly related to lowered levels of ovarian estrogen remains speculative at best.

LONG-TERM CONSEQUENCES OF CHANGES IN OVARIAN HORMONE LEVELS

In addition to the acute symptoms associated with the menopause, the lack of ovarian estrogens appears to contribute to the onset of other postmenopausal diseases such as osteoporosis and cardiovascular disease, two leading causes of morbidity and mortality in older women (see figure 2-4). Diseases associated with aging in women, such as osteoporosis and cardiovascular disease, are difficult to correlate explicitly with estrogen deficiency be-

Figure 2-4-Percentage of Deaths From Specific Conditions Among U.S. Women Over 50 Years of Age



SOURCE: T.L. Bush, "The Epidemiology of Cardiovascular Disease in Postmenopausal Women," *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), p. 264.

cause aging and genetics are also important influences on the development of these diseases. A number of studies, however, indicate the profound effects of estrogen deficiency in these syndromes (35,46,68,82).

Research has identified estrogen receptors in the uterus, hypothalamus, pituitary, vagina, urethra, breast, and liver. Preliminary studies have also found estrogen receptors in bone. Before the menopause, the ovary secretes 50 to 300 micrograms of estradiol per day directly into the systemic circulation. After the menopause, ovarian estradiol production nearly ceases, but 5 to 20 micrograms per day are produced from estrone in the liver and fatty tissue. Studies have shown that this drop in estrogen correlates with rapid bone loss, which predisposes a woman to osteoporosis, and a loss of protection against coronary heart disease (22,34,37,82,83). Each of these long-term consequences of ovarian estrogen reduction is discussed below.

I

Osteoporosis

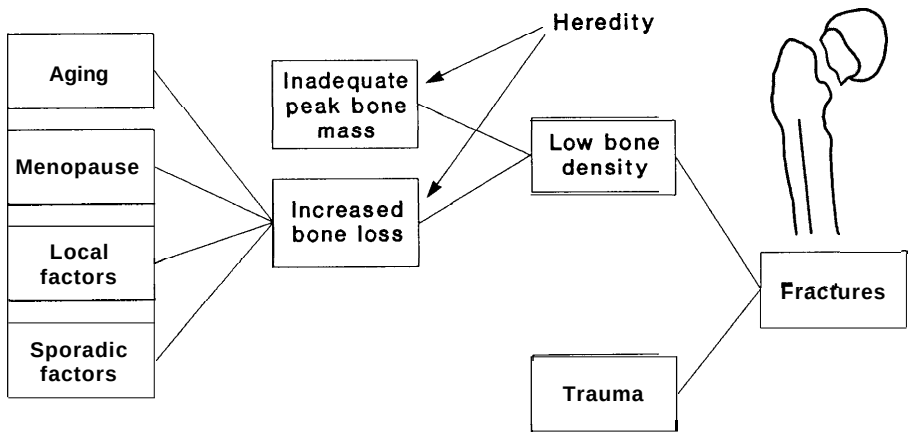
The first report of a link between ovarian hormone insufficiency and increased bone loss came in 1940, when studies by Albright and colleagues revealed that almost all of a cohort of patients with osteoporotic fractures were also postmenopausal and that women who had had their ovaries removed were disproportionately represented (l). Today, an. impressive body of literature has accumulated on this linkage, and the Office of Technology Assessment is conducting a major assessment of Policy ***Issues in the Prevention and Treatment of Osteoporosis (88).***

Osteoporosis is a syndrome composed of a complex, heterogeneous group of disorders with multifactorial determinants attributable to variables of age, sex, race, heredity, and environment (see figure 2-5). Although there is considerable confusion about the exact definition of osteoporosis, a clinically appropriate meaning is that the loss of bone (or osteopenia) has progressed to the point that specific parts of the skeleton are so fragile that they have an enhanced susceptibility to, or the actual presence of, fractures (41). One of the most common sites of bone loss is the vertebrae, where spontaneous crush fractures can lead to curvature of the spine, frequently manifested as a "dowager's hump," loss of height, and pain. Fractures of the hip (especially at the neck of the femur) and the radius are also frequently occurring manifestations of this disorder (74).

Although age-related bone loss is a universal phenomenon and the problems of bone loss and osteoporosis are shared by aging men, osteoporosis is considered primarily a disorder of women in Western societies because the impact of the disease on Caucasian women is much more profound and pervasive. As for men, age is a major factor in the etiology of this condition; but in middle-aged women, bone mass and osteoporosis are related more to menopausal status than to chronological age (80). A telling finding illustrates the preeminence of the ovarian hormones in the maintenance of bone mass: the level of bone density in a group of 50-year-old women who had had their ovaries removed 20 years earlier was comparable to that reported in a group of 70-year-old women who had experienced a natural menopause 20 years earlier or contemporaneously with the oophorectomized group (72). Premenopausal women over the age of 30 may lose less than 1 percent of their bone tissue yearly; such losses may reach 3 to 5 percent per year for the 5 to 10 years that follow the cessation of the menses (64). Women who have been hysterectomized are more likely to develop osteoporosis than women who experience a natural menopause (18).

The traumatic and debilitating consequences of osteoporosis, especially in the form of hip fractures, are a major health concern. To the aging woman,

Figure 2-5—Conceptual Model of the Pathogenesis of Fractures Related to Osteoporosis



SOURCE: L.J. Melton, "Epidemiology of Osteoporosis: Predicting Who Is at Risk," *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), p. 295.

such consequences may entail frailty, personal suffering, and loss of independence. The relationship between osteoporosis and fractures is currently a point of debate (54,88). Fractures are often a result of falls; low bone density is neither necessary nor sufficient for hip fracture, although it may be necessary for vertebral fracture (54). Nevertheless, complications arising from hip fractures give rise to a substantial risk of mortality: Between 12 and 20 percent of hip fracture patients die within 3 months of the fracture (73,74). To the Nation, osteoporosis represents burgeoning health care costs within a population that is growing rapidly in size. Direct and indirect costs of osteoporotic fractures in the United States have been estimated at more than $7 billion, with the cost of hip fractures in women alone accounting for more than $5 billion (65).

It has been estimated that 25 percent of Caucasian women over the age of 70 and 50 percent over the age of 80 will have evidence of vertebral fractures. Given present levels of exercise and past dietary habits, by the age of 90, one-third of all Caucasian women will have sustained a hip fracture (69). The marked effect of gender is obvious from the lower incidence of osteoporosis in men: They experience only one-half as many hip fractures per capita as women (73). These projections of incidence have limitations, however, because they are based on women who are presently diagnosed as osteoporotic. It may be accurately inferred that these women have lived different lives from the 40-year-old women of today. Thus, projections of the incidence of osteoporosis would be more valid if they controlled for such factors as smoking, exercise, and diet (17).

Bone mass, bone fragility, and the riskof fractures are all integrally related. The amount of bone in the elderly skeleton, a key determinant in its susceptibility to fractures, is believed to be a function of two major factors: the peak amount of bone mass previously attained and the rate of loss of bone mass thereafter (32). The importance of hereditary factors in peak bone mass is illustrated by the observation that African American women attain greater spinal bone mass than Caucasian women and have a lower incidence of osteoporotic fractures (45,50). Peak bone mass is determined to a large extent by the genetic inheritance of the individual (67); other important factors include dietary calcium (40,51), vitamin D consumption, exposure to sunlight (21), physical activity or exercise (40), small frame, low weight, cigarette smoking, and excess alcohol and caffeine consumption (4).

Many of the factors that affect the attainment of peak bone mass also affect rates of bone loss; other influences include physiologic stresses such as pregnancy, lactation, and immobilization (85). But hormonal status, reflected primarily by estrogen and progesterone levels, exerts the greatest effect on rates of decline in skeletal mass. Because accelerated bone loss is a frequent occurrence during the perimenopause, the change in ovarian function is



Photo credit: National Cancer Institute

Men and women differ dramatically in rates of cardiovascular disease until after the menopause when women begin to catch up.

believed to be pivotal in the pathogenesis of postmenopausal osteoporosis (39,60,80).

Studies have shown that the loss of bone mass in the perimenopausal period is a generalized phenomenon that affects all parts of the skeleton (27). In the first 5 years after cessation of the menses, vertebral bone may be lost at rates ranging from 2 to 8 percent (27,60). During this same period, 20 percent of the lifetime loss in femoral neck bone mass may occur (33).

Osteoporosis is a significant clinical problem related to decreased bone mass. Women at highest risk for osteoporosis are Caucasian or Oriental, postmenopausal or hysterectomized, and thin; they generally have small frames and a family history of osteoporosis. Risk factors associated with lifestyle include low calcium and vitamin D intakes, caffeine and alcohol use, smoking, and lack of exercise. The most effective management for osteoporosis is prevention. Changes in lifestyle can lower a person's risk, as can estrogen therapy. Chapter 3 describes the use of estrogens to prevent accelerated bone loss.

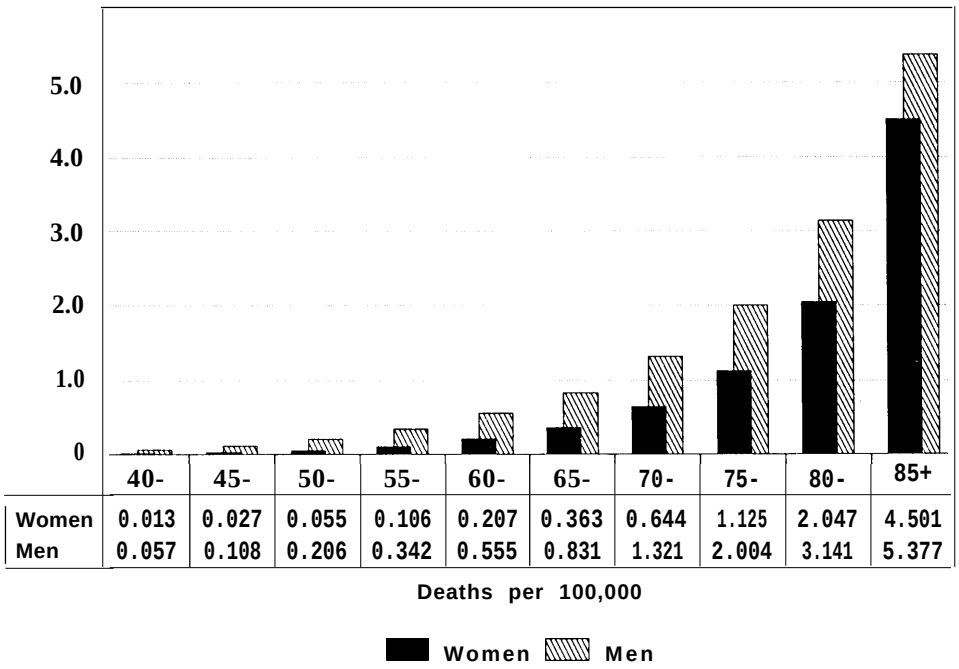
Cardiovascular Disease

Cardiovascular diseases (CVD), which include both heart disease and stroke, are the leading cause of mortality in women, accounting for approximately 50 percent of all deaths in women over the age of 50 (figure 2-4) (13). Mortality rates are low among younger women: e.g., among women aged 30 to 34 years, the rate was 2 per 100,000 in 1986, about ***28*** percent the rate among men the same age. In contrast, among women 55 to 59 years old, the rate was 106 per 100,000 in 1986 (89). As women approach old age, their risk of dying from heart disease approaches that of men of the same age (see figure 2-6). CVD is also one of the foremost causes of serious morbidity and disability. It has been estimated that 37 percent of all hospital days of postmenopausal women are attributable to CVD and that total annual health care costs for CVD in women are in excess of $9 billion (14). Yet despite these dramatic figures, until recently, relatively few studies-either population studies of potential risk factors or clinical studies evaluating the efficacy of treatment regimens for CVD—have included women. This could be due in part to the mistaken belief that the 8- to 10-year lag in the development of CVD morbidity and mortality among women as compared with men means that women are not significantly affected by CVD. Another reason for the relative neglect of women's studies of CVD could be efficiency. Because rates of CVD are higher in men than in women—at every age--a given study will have more endpoints, and hence more precision, by studying men. This preference for using men as the subjects of clinical studies has led to neglect of the uniquely female aspects of some CVD risk factors (81). Sex differences in the management of CVD have also been documented (84): Women tend to receive less aggressive treatment than men for the same symptoms (7).

Available evidence attests to the role of the natural menopause in the loss of apparent protection against CVD, although it does not delineate the precise mechanisms involved (49,81,82,83,93). The incidence of CVD in women increases markedly after the menopause (see figure 2-6) with each year of estrogen reduction and increasing age constituting an enhanced risk (48). The importance of a lack of endogenous ovarian hormones in the development of CVD is further supported by the finding that women who have had a bilateral oophorectomy have a substantially greater risk of CVD than do women with intact ovaries (15,19,26,48).

Evidence clearly shows that high levels of high-density lipoprotein (HDL) cholesterol and low levels of low-density lipoprotein (LDL) cholesterol are protective against the development of atherosclerosis (31,49). Research has also shown that the menopause (both natural and surgical) is associated with changes in serum lipid profiles, such as a

Figure 2-6—Deaths (per **100,000) From Coronary Heart Disease by Age and Sex, United States, 1986**



	40-	45-	50-	55-	60-	65-	70-	75-	80-	85+
Women	0.013	0.027	0.055	0.106	0.207	0.363	0.644	1.125	2.047	4.501
Men	0.057	0.108	0.206	0.342	0.555	0.831	1.321	2.004	3.141	5.377

SOURCE: T.L. Bush, "The Epidemiology of Cardiovascular Disease in Postmenopausal Women." *Anna/s of the New York Academyof Sciences, vol. 592, Multidisciplinary Perspectives on Menopause,* M. Flint, F. Kronenberg, and W. Utian (eds.) (New York, NY: New York Academy of Sciences, 1990), p. 264.

decline in the levels of HDL cholesterol and a rise in the levels of LDL. These changes maybe factors in the development of an increased risk of CVD (14). Estrogen may lower LDL levels by increasing clearance of LDL particles from plasma, a hypothesis that derives from studies showing that estrogen increases the number of hepatic LDL receptors in animals (93). Estrogens may also induce hypertriglyceridemia by increasing the rate of very low density lipoprotein (VLDL) production (93).

Much of the evidence to support the finding of a cardioprotective effect for estrogen has come from prospective studies of women on estrogen therapy (81), which have shown that estrogen users experience half as many cardiovascular events as nonusers (13,14,15,34,49,82,83). In addition, a large number of studies are reasonably consistent in demonstrating that women with early bilateral oophorectomy are at increased risk of CVD (82). Epidemiologic association does not necessarily establish cause and effect, since there is always the lingering possibility that women who choose to take estrogens have other characteristics that explain their lower risk of heart disease (25). Only randomized, controlled clinical trials can demonstrate conclusively that oral estrogen use reduces the incidence of cardiovascular disease (see ch. 5 for a discussion of research needs). In 1991, however, prospective epidemiologic research controlled for confounding risk factors to an extent sufficient to suggest strongly that postmenopausal estrogen therapy has an independent, significant protective effect against CVD. Chapter 3 discusses the use of hormone therapy for prevention of CVD.

SUMMARY

The menopause is a time of normal physiological change in a woman's life that often coincides with changing family or work environments. The transition through the perimenopause varies greatly among women both within and across cultures. Symptomatology varies enormously, with some women reporting few or no symptoms and others reporting extreme discomfort. Hot flashes, the most common complaint of the perimenopause, occur in at least 50 percent of U.S. women at some point during the menopausal years. Women whose ovaries have been

removed experience more severe and more abrupt symptoms.

Debate continues about the effects of reduced ovarian hormones on mood, behavior, and sexuality. In general, however, there is an evolving consensus that no absolute relationship exists between the menopause and depression. Factors that correlate better with depression include stress, decline in physical health, and change in marital status. Methodological difficulties have plagued the untangling of relationships among the menopause, aging, and behavioral change.

The short-term effects of changes in levels of endogenous estrogen, in the form of hot flashes and bodily changes, are but one concern. Possibly of equal or greater consequence are the potential long-term effects of depleted circulating estrogen on bone and the cardiovascular system.

The next chapter describes what is known about the treatment of both short-term and long-term consequences of the menopause, as well as the reasons women or their physicians select particular treatments.

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Chapter 3

Treatment of Menopausal Symptoms and Prevention of Future Disease

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Chapter 3
Treatment of Menopausal Symptoms and Prevention of Future Disease

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

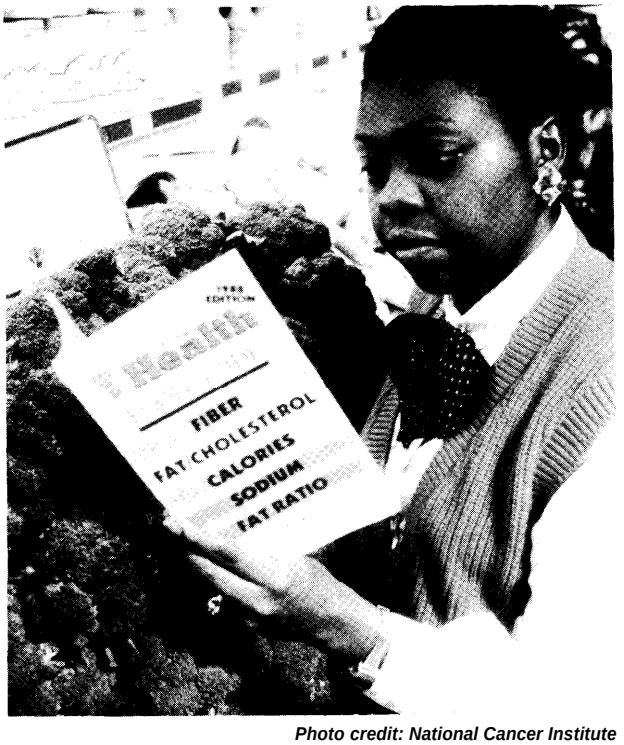


Photo credit: National Cancer Institute

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.

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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).

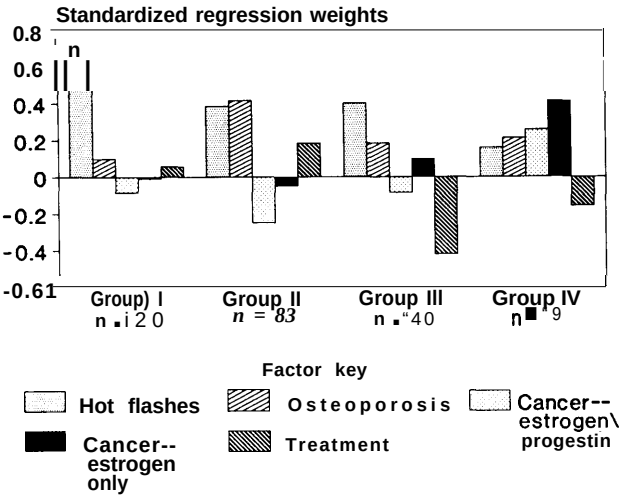
Compliance With Replacement Regimens

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).

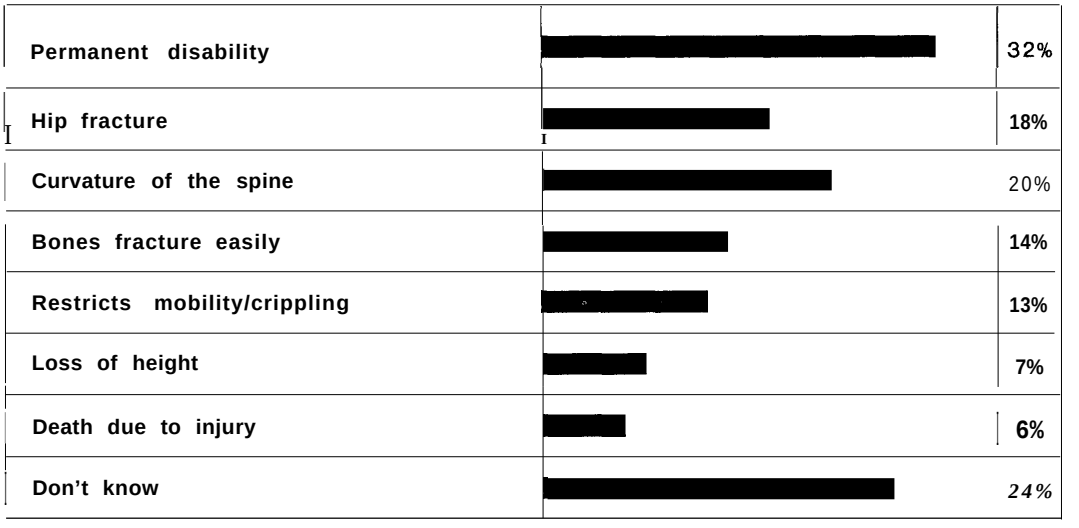
Preventive medicine and wellness approaches, for the most part, are not reimbursed by insurance (88). Many of the services offered at menopause clinics, including most of the advanced-technology bone densitometry tests for osteoporosis, cardiovascular fitness testing, nutrition counseling, and individual 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

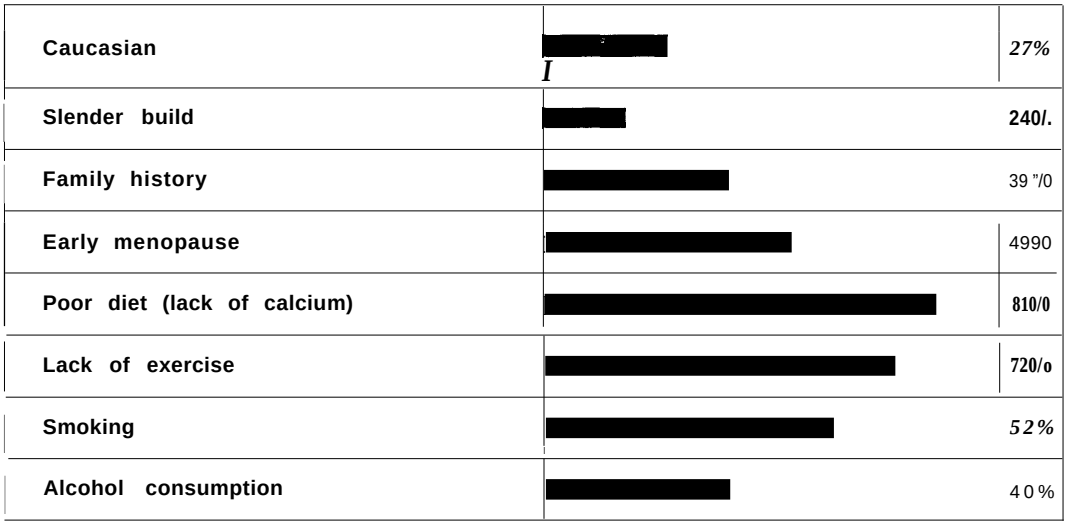
Patients and health care professionals alike tend to know relatively little about the menopause and the risks of conditions that may be associated with it (39,40). Indeed, there is no consensus within the medical community about the definition of the menopause and the risks and benefits associated with 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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Chapter 4

Hormone Products and Prescription

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Chapter 4
Hormone Products and Prescription

INTRODUCTION

Doctors can choose from a variety of different brand-name products, drug formulations and dosages, and possible treatment regimens when they prescribe estrogen therapy (ET) or combined hormone (i.e., estrogen combined with a progestin) therapy (CHT) for postmenopausal women. In the United States, nearly 20 estrogen products are on the market and approved for use in treating menopausal symptoms; two products have the additional indication of prevention of osteoporosis. There are also progestin products that, although not officially approved for use in CHT, are commonly prescribed for it. A number of pharmaceutical manufacturers compete in the estrogen and progestin marketplace and conduct research and development on new formulations, routes of administration, and combination products. Until 1991, when the Food and Drug Administration (FDA) withdrew its approval, several generic formulations of conjugated estrogens were also on the market.

The effects of long-term use of hormone therapy for the prevention of osteoporosis and cardiovascular disease have received much attention in recent years. Drug labeling for estrogen has been changed to include the osteoporosis indication, and the FDA is currently considering adding cardiovascular disease information to estrogen labeling. Doctors employ estrogen and progestin in many different ways; e.g., they may prescribe the use of unopposed estrogen or combination forms (cyclic, sequential, or continuous/combined) of both products. There is little agreement on the optimal prescription for CHT, although for women with intact uteri, some regimen of continuous estrogen combined with progestin is the approach favored by most physicians.

This chapter considers information relevant to the commercial market for hormone therapy, the products that are used, and promotion practices. It addresses the labeling of approved estrogen and progestin products and discusses efforts that have been made to change the labeling to include indications for long-term preventive use. The chapter also describes the attempts to gain approval for generic estrogens and discusses prescribing information.

MARKET INFORMATION

Three classes of estrogens are used for hormone therapy: natural estrogens, conjugated equine estrogens, and synthetic estrogens. Wyeth-Ayerst's Premarin, the most commonly prescribed estrogen product, is a conjugated estrogen derived from the urine of pregnant horses; in 1990 it was the fourth most prescribed drug in the United States (13). Premarin was approved by the FDA in 1942 for the treatment of menopausal symptoms. Because it was approved before the 1962 amendments to the Food, Drug, and Cosmetic Act, Wyeth-Ayerst was required to prove only safety and not efficacy. The product was later evaluated under the Drug Efficacy Study Implementation (DESI) program and judged effective in 1972 (3).

Since the introduction of Premarin the FDA has approved other estrogens, both natural and synthetic, for the treatment of menopausal symptoms, and, in the United States, there are currently 11 manufacturers of estrogen products and 5 manufacturers of progestin products used in hormone therapy (see table 4-l). CIBA's Estraderm transdermal estrogen patch, an alternative to daily oral administration, approved by the FDA in 1986, is the newest estrogen product available. According to senior managers at Wyeth-Ayerst, total sales of estrogen products were close to $460 million in 1990, and Premarin held a 68 percent market share.

Three different progestins are used in CHT: medroxyprogesterone acetate, norethindrone, and norethindrone acetate. Upjohn's Provera, amedroxyprogesterone acetate, is the most commonly prescribed progestin for CHT. Provera has been on the market since 1959, although its use in CHT began much later.

Labeling

Title 21 of the U.S. Code governs drug labeling and defines a label as any display of written, printed, or graphic material on or accompanying a drug, including the actual label, the package insert, and any other material that provides information about the drug (21 U.S.C. Sec. 321 [k][m]). The FDA requires that the following information appear on the package label or package insert: the name and place



Photo credit: National Institutes *of Health*

Conjugated estrogen, the most widely prescribed drug for estrogen therapy, is derived from the urine of pregnant mares.

of business of the manufacturer, packer, or distributor; a description of the drug, including, at a minimum, the proprietary name and other established names of the drug, the type of dosage form and route of administration, qualitative and quantitative ingredient information, pharmacological or therapeutic class of the drug, and chemical name and structural formula. The label or insert must also contain a concise factual summary of the clinical pharmacology and actions of the drug in humans, information on the indications and usage of the drug, contraindications to use, warnings that explain adverse reactions and potential hazards of use, precautions for use and information for patients, an expiration date, an identifying lot or control number, and information about the quantity of the container (21 CFR 201.1, 201.10, 201.17, 201.18, 201.50, 201.56,201.57,21 1.137).

Once a drug is approved by the FDA, doctors can prescribe it for uses other than those named in the labeling, providing the decision is based on sound scientific evidence or medical opinion. The FDA is responsible for ensuring that a drug manufacturer has demonstrated safety and efficacy for its product; it is not within the FDA's jurisdiction to dictate to physicians the proper practice of medicine.

Estrogens

Labeling for all estrogens approved for use in hormone therapy includes a boxed warning stating that estrogens "have been reported to increase the risk of endometrial cancer' and 'should not be used during pregnancy.' The FDA-approved indications for use of estrogen products, which are listed in the 1991 *Physician's Desk Reference* (PDR), are "moderate to severe vasomotor symptoms associated with menopause, female hypogonadism, palliative therapy for advanced prostate cancer, palliative therapy for breast cancer in select circumstances, atrophic vaginitis, kraurosis vulvae, primary ovarian failure, female castration, and atrophic urethritis." Both Premarin and Estraderm are approved for the prevention of osteoporosis, and Premarin is also approved for the treatment of this condition (8).

The PDR explicitly states that "there is no adequate evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions." Several estrogen products, including the Premarin derivatives PMB-200 and PMB-400, and Menrium, contain tranquilizing or antianxiety agents. PMB-200 and PMB-400 are indicated for treatment of vasomotor symptoms and associated tension and anxiety but only when estrogens alone have not alleviated symptoms.

Epidemiologic data have suggested that the use of unopposed conjugated estrogens by women who have undergone hysterectomies results in cardioprotective effects and a reduction in cardiovascular mortality by as much as 50 percent (21). In 1990, the FDA's Fertility and Maternal Health Drugs Advi-

Table 4-l—Estrogens and Progestins Used for Hormone Therapy

Brand name	Generic name	Manufacturer
Estrogens		
Estinyl	Ethinyl estradiol	Schering
Estrace	Micronized estradiol	Mead Johnson Laboratories
Estraderm	Transdermal 17-estradiol	CIBA
Estratab	Esterified estrogen	Reid-Rowell
Estratest	Esterif ied estrogen with methyltestosterone	Reid-Rowell
Estratest H.S.	Half-strength Estratest	Reid- Rowell
Estrovis	Quinestrol	Parke-Davis
Menrium	Esterified estrogen plus chlordiazepoxide (anti-anxiety drug)	Hoffman-La Roche
Ogen	Estropipate	Abbott Laboratories
Premarin	Conjugated equine estrogens	Wyeth-Ayerst
Premarin with methyltestosterone..	Conjugated equine estrogens plus methyltestosterone	Wyeth-Ayerst
PMB-200, PMB-400	Premarin plus meprobomate (tranquilizing agent)	Wyeth-Ayerst
TACE	Chlororianisene	Marion Merrell Dow
Diethylstilbestrol	DES, synthetic estrogen	Eli Lilly
Menest	Esterified estrogen	Smith Kline Beecham
Feminone	Esterified estrogen	Upjohn
Progestins		
Provera	Medroxyprogesterone acetate	Upjohn
Amen	Medroxyprogesterone acetate	Carnick Laboratories, Inc.
Curretab	Norethindrone acetate	Reid-Rowell
Aygestin	Norethindrone acetate	Wyeth-Ayerst
Norlulate	Norethindrone acetate	Parke-Davis
Norlutin	Norethindrone	Parke-Davis

SOURCE: Office of Technology Assessment, 1992.

sory Committee recommended that the labeling for conjugated estrogens be changed to reflect its potential cardiovascular benefits; it also strongly suggested that more studies be conducted, including a secondary intervention trial for women who have experienced cardiovascular disease and a large cohort study to evaluate subgroups of women at particular risk for developing cardiovascular disease. The decision by the advisory committee to recommend the change in the labeling of conjugated estrogens was nearly unanimous, with one committee member abstaining from the vote. Despite several substantial gaps in knowledge (e.g., the lack of long-term data from randomized clinical trials, a lack of consensus on and knowledge about optimal dosages and regimens and which subgroups of women are most likely to benefit from its use), the medical community generally agrees that evidence of unopposed estrogen's cardioprotective effects support general recommendations for its use (20). Wyeth-Ayerst, the manufacturer of Premarin, is actively seeking this labeling change, but the FDA is still evaluating the submitted data to determine Premarin's cardioprotective effects and has yet to make changes in the labeling (7,17).

The PDR lists several absolute contraindications to estrogen use: "known or suspected breast cancer, estrogen-dependent neoplasia, pregnancy, and undiagosed abnormal genital bleeding" (16). Thromboembolitic disorders or a history of such disorders associated with estrogen use has historically been identified as contraindications, but advances in medical knowledge now allow women with these conditions to use estrogen (14). In addition, many relative contraindications and side effects are taken into consideration in the decision to prescribe estrogens.

Progestins

The labeled indications for progestins are "secondary amenorrhea, abnormal uterine bleeding related to hormonal imbalance when there is no organic pathology present (e.g., fibroids or uterine cancer), and endometriosis. " Contraindications are "thrombophlebitis, thromboembolic disorders, cerebral apoplexy (or a past history), markedly impaired liver function, liver disease, breast cancer, undiagnosed vaginal bleeding, missed abortion, and use as a diagnostic pregnancy test. ' No progestin has been approved for use in treating meno-

pausal symptoms or in conjunction with estrogen for such treatment, although it is standard practice to prescribe progestin together with estrogen for women with an intact uterus to protect the endometrium. In addition, progestin is sometimes prescribed alone for the treatment of hot flashes when estrogen cannot be used (see the later section on prescribing practices).

Combined Hormone Therapy

The PDR discusses the use of progestins to counter the increased risk of endometrial hyperplasia associated with the use of unopposed estrogen. Under a section entitled "Precautions" in the labeling for both estrogen and progestin, the PDR addresses concomitant estrogen and progestin use:

> Studies of the addition of a progestin for 7 or more days of a cycle of estrogen administration have reported a lower incidence of endometrial hyperplasia. Morphological and biochemical studies of the endometrium suggest that 12 to 13 days of progestin are needed to provide maximal maturation of the endometrium and to eliminate any hyperplastic changes. Whether this will provide protection from endometrial carcinoma has not been clearly established. There are possible additional risks that may be associated with the inclusion of progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism. The choice of progestin and dosage may be important in minimizing these adverse effects.

A great deal of controversy has arisen over whether to change the labeling to reflect a recommendation for the use of CHT for women with intact uteri. The use of CHT reduces the risk of endometrial hyperplasia that occurs with unopposed estrogen use, but other risk-benefit comparisons-for osteoporosis, breast cancer, and cardiovascular disease--are less conclusive and more controversial. The use of CHT was the subject of an FDA advisory committee (the Fertility and Maternal Health Drugs Advisory Committee) meeting in June 1991. The FDA sought information from the committee on several topics: the associations between the use of estrogens and progestins and the risk of endometrial cancer, breast cancer, osteoporosis, and cardiovascular disease; the effects on those risks of the use of specific estrogens and progestins when given at various dosages and in various regimens; and the risks and benefits of ET compared with CHT. The committee agreed that estrogen labeling should **be changed to more positively endorse the recommended use of CHT for the treatment of menopausal symptoms and the prevention of osteoporosis (when indicated) for women with intact uteri. The committee concluded, however, that the data were inadequate to identify the effect of added progestin on the risk of breast cancer or on cardiovascular protection, or to determine how specific estrogen and progestin compounds, in various dosages and regimens, affect the risk-benefit balance. Despite the lack of data on long-term progestin use, the committee also recommended that the FDA consider new drug applications for** CHT compounds, should they be submitted.

Generics

The FDA, in the spring of 1991, withdrew approval for generic conjugated estrogens on the basis of demonstrated bioinequivalence (5,6). The definition of bioequivalence, which is the basis for approval of generics, requires that the generic product include the same therapeutic ingredient and that its rate and extent of absorption be the same as the innovative product—in this case, Premarin. Information available only after approval of the generic conjugated estrogens showed different rates of absorption for several of them, and concern about the therapeutic significance of these differences led the FDA to reconsider its original approval decision (l). The FDA issued a revised guidance (i.e., guidelines for conducting studies to show bioequivalence) for the approval of generic conjugated estrogens in August 1991 (see box 4-A). Currently, several manufacturers are seeking approval for generic equivalents of Premarin, but the FDA has estimated that it will be several years before any products will be on the market (4).

PRESCRIBING PRACTICES

Obstetricians and gynecologists write the largest percentage of prescriptions for estrogens and progestins used in hormone therapy, but many other specialists care for midlife women and also prescribe these hormones. According to data collected by Wyeth-Ayerst, in terms of percentage of Premarin prescriptions written, obstetricians and gynecologists are followed by family practitioners, internists, general practitioners, and other specialists (see table 4-2).

Box 4-A—Bioequivalence for Generic Conjugated Estrogens

The Food and Drug Administration's (FDA) Generic Drugs Advisory Committee made recommendations in early 1991 concerning bioequivalence testing and approval of generic conjugated estrogen products. The comparison product is Premarin, and part of what makes demonstrating bioequivalence to Premarin so difficult is that Premarin itself is quite complex. Premarin is derived from the urine of pregnant mares and has 10 components: estrone sulfate, equilin sulfate, 17-a dihydroequilin, 17-ß dihydroequilin, ***17-a*** estradiol, 17-ß estradiol, delta (8,9) dehydroestrone, equilenin, ***17-a*** dihydroequilenin, and 17-ß dihydroequilenin. Nine of these components are currently commercially available, but delta (8,9) dehydroestrone is not. Premarin contains about 50 to 60 percent estrone sulfates, 22.5 to 32.5 percent sodium equilin sulfate, and 7.5 to 20 percent unspecified conjugated estrogens.

The United States Pharmacopoeia (USP), the legal standard for drugs in the United States, specifies properties, action, use, dosages, strength, and purity. Conjugated estrogens are derived, either in whole or in part, from equine urine, or they may be produced synthetically using estrone and equilin. Currently, the USP requires only two compounds to be present in a conjugated estrogen product: sodium estrone sulfate and sodium equilin sulfate. Additionally, such products "may contain other conjugated estrogenic substances of the type excreted by pregnant mares." In February 1991, the FDA Generic Drugs Committee recommended that changes be made to the USP monograph for conjugated estrogens to make the required contents more specific, which would result in generic products (when approved) that are closer in composition to Premarin.

The committee recommended that the 10 components of Premarin be divided into several categories:

- therapeutic moieties, which independently demonstrate therapeutic activity and are required components;
- . concomitant components, which are present in a substantial amount in the innovator product but for which independent therapeutic activity has not been established-these components are required to be present in quantities that fall within set upper and lower limits;
- components requiring a limit test, Which allows no more than a specific percentage, which can be zero, to be present; and
- signal impurities, which must not exceed a set upper limit but which may be zero, provided the product is adequately stable.

The committee proposed that the generic product contain two therapeutic moieties present in Premarin--estrone sulfate and equilin sulfate; three concomitant components—***17-a*** dihydroequilin, 17-ß dihydroequilin, and 17-a estradiol; two limit tests for 17-ß estradiol and delta (8,9) dihydroestrone; and signal impurities for equilenin, *17-a* dihydroequilenin, and 17-ß dihydroequilenin. The other five components of Premarin are not required in generic products. The USP is currently revising its monograph for conjugated estrogen tablets and considering a redefinition of content requirements. The FDA issued a revised guidance for bioequivalence studies in August 1991, and several companies are pursuing approval of generic products.

SOURCES: D.B. Burlington Deputy Director, Office of Drug Evaluation II, Center for Drug Evaluation and Research Food and Drug Administratiom , testimony before the Subcommittee on Aging, Committee on Labor and Human Resources, U.S. Senate, Apr. **19,** 1991; Food and Drug Administratiou Guidance, Conjugated Estrogen Tablets, August 1991; transcript of the FDA Generic Drugs Advisory Committee meeting held in February 1991.

Most of the relatively scarce research on physician prescribing practices concentrates on gynecologists and family practitioners. Several studies of the prescribing patterns and strategies of doctors and the indications they follow for use of hormone therapy reveal significant prescription by gynecologists 'of estrogens, and to a lesser extent progestins, for postmenopausal women (9,11,18). Two surveys conducted in California reveal frequent prescription of both estrogens and progestins in this geographic region (see box 4-B).

Most of the available information on the prescription of estrogens and progestins provides data on the number of prescriptions dispensed (both new and refill prescriptions) and the number of times a drug is mentioned during visits to a physician. Some product-specific information is available from pharmaceutical manufacturers, but the more comprehensive information is derived from two pharmaceutical marketing research data bases: the National Prescription Audit (NPA) and the National Disease and Therapeutic Index (NDTI), which are maintained and distributed on a limited basis by a private consulting firm, IMS America, Ltd.

The NPA tracks prescriptions dispensed by a panel of 2,500 retail pharmacies and gives national

Table 4-2—New Prescriptions (Rx) of Premarin (tablets only) by Specialty, 1990

Specialty	New Rxs (000s)	Percent share	Percent[a] change
Obstetricians/gynecologists.....	2,897	43.0	+14
Family practitioners	1,353	20.1	+17
Internal medicine	983	14.6	+19
General practitioners	492	7.3	+ 3
All others	1,010	15.0	+18
Total	6,735	100.0	+15

[a]Compared with 1989.

SOURCE: National Prescription Audit, IMS America, Plymouth Meeting, PA, 1991.

estimates of prescription volume. The data these pharmacies provide for estrogens include all dosage forms and estrogen/androgen combinations. The second data base, the NDTI, collects information from a panel of approximately 2,130 office-based physicians who report on each patient they see or have contact with in any way during a 48-hour period each quarter. All mentions of a drug are reported-whether as a prescription written or dispensed, as the administration of a drug, or as a recommendation (9). Private researchers and the FDA's Division of Epidemiology and Surveillance have also performed several analyses of prescriptions of noncontraceptive estrogen and progestin. The latest available published data from these sources are from 1986.

Estrogens

Until 1990, according to NPA data, 1975 was the peak year for prescriptions containing noncontraceptive estrogen, with 28 million dispensed from retail pharmacies. At about that time, new information became available about the increased risk of endometrial cancer associated with the use of estrogen, and estrogen prescriptions tapered off until 1980, when they began to increase, a trend that has continued. Between 1979 and 1986, the prescription of oral estrogen, the form most often used to treat menopausal symptoms, increased 117 percent (9). In 1990, retail pharmacies in the United States dispensed more than 30 million prescriptions for noncontraceptive estrogens, surpassing the previous peak in 1975 (10).

The vast majority of estrogen prescriptions are for oral preparations, which accounted for 88 percent of all prescriptions in 1986 (9). Conjugated estrogens are most often prescribed, and Premarin is the preparation most commonly used. In 1990, Premarin accounted for 61.9 percent of all prescriptions (both new and refills) for oral and transdermal estrogen (see table 4-3). According to NPA data, in 1981,11 million prescriptions for conjugated estrogens were dispensed, about 95 percent of which were for Premarin. In 1987, 16 million prescriptions were dispensed, of which 75 percent were for Premarin. (Most of this **increase in** prescriptions can be attributed to the prescription of generic conjugated estrogens; as of the spring of 1991, however, these preparations were no longer on the market(5). There is great geographical diversity in estrogen use and prescribing patterns by region within the United States (see table 4-4) (11).

The most common diagnosis mentioned in relation to the prescription of estrogen is menopausal symptoms. In 1990, according **to the** NDTI, diagnosis of menopausal or climacteric states accounted for 47 percent of the prescriptions of noncontraceptive estrogens. The next most common diagnosis was unspecified endocrine disorder, followed by primary ovarian failure/premature menopause, postoperative followup exam, vaginitis/vulvovaginitis, artificial menopause, unknown/unspecified cause of morbidity and mortality (or other), osteoporosis, and malignant neoplasm of the prostate. These diagnoses together accounted for 90 percent of those associated with the use of noncontraceptive estrogen. Although prevention of osteoporosis is an approved indication for Premarin and Estraderm, osteoporosis accounted for only 2 percent of the diagnoses mentioned (10). Other studies show that osteoporosis has rarely been given as a distinctive diagnosis for ET, although mention of this condition is increasing over time. In 1974, prevention or treatment of osteoporosis was mentioned during 1.4 million physician visits; in 1986, this figure had risen to 1.8 million (9).

Progestins and Combined Hormone Therapy

Approved indications for the use of progestins are treatment of amenorrhea, abnormal uterine bleeding, and endometriosis. As noted earlier, no progestin

Table 4-3-Premarin Prescriptions (Rx), 1990

	Number (000s)	Percent of total oral and transdermal estrogen Rx
New Rx	6,735	64.5
Refill Rx	12,105	60.6
Total Rx	18,840	61.9

SOURCE: National Prescription Audit, IMS America, Plymouth Meeting, PA, 1991.

Box 4-B—Prescribing Practices in California

Two studies have been published concerning the prescribing practices of hormone therapy among San Diego and Los Angeles gynecologists. Both studies used mailed surveys to garner responses from the doctors, one group of which was listed under gynecology in the 1985 San Diego telephone directory, while the other was composed of members of the Los Angeles County Obstetrics and Gynecology Society. It is important to remember that regional differences in prescribing practices for hormone therapy have been shown to exist, with the West Coast having a demonstrated higher incidence of use. The results of these studies follow.

A 1985 survey of 166 (108 respondents) San Diego gynecologists showed that between 79 and 83 percent (depending on the length of time as practicing physicians) prescribed estrogens for at least 75 percent of recently postmenopausal women, and that 58 percent prescribed estrogens for virtually all such patients. Seventy-three percent usually prescribed estrogen therapy for 10 years or more, and none reported prescribing estrogen for less than 1 year. The San Diego gynecologists most commonly prescribed 0.625-mg Premarin daily. None of the doctors that had been in practice for less than 10 years at the time of the survey prescribed oral estrogens without a progestin. Menopausal symptoms, followed by the prevention of osteoporosis, were the major indications and reasons cited for hormone therapy.

A 1984/1985 survey of 516 (330 respondents) Los Angeles gynecologists revealed prescribing patterns similar to those found in San Diego. Routine use of hormone therapy was indicated by 94 percent of the respondents for women with intact uteri and by 97 percent for women without uteri. Ninety-seven percent preferred using Premarin for women with and without uteri, and O.625 mg of Premarin daily was the overwhelmingly favored dose (80 percent and 76 percent, respectively). Eighty-six percent routinely prescribed a progestin for women with intact uteri. Ninety-five percent used medroxyprogesterone acetate, with 73 percent prescribing 10 mg daily and 20 percent prescribing 5 mg daily. Surprisingly, 47 percent reported prescribing progestin for women without uteri.

The Los Angeles study compared the 1985 results with data from a 1975 survey of Los Angeles gynecologists. The preferred dosage decreased from 1.25 mg of Premarin daily in 1975 to 0.625 mg in 1985. The use of progestin therapy increased from 17 percent in 1975 to 86 percent in 1985, and the dose and brand remained the same (10 mg daily of medroxyprogesterone acetate). For women without intact uteri, the percentage of doctors prescribing a progestin increased from 11 percent in 1975 to 47 percent in 1985. The use of progestins for women without a uterus was not explained in the study.

SOURCES: E. Barrett-Connor, "Postmenopausal Estrogens--Current Prescribing Patterns of San Diego Gynecologists," *Western Journal of Medicine 144:620-621, 1986;* R.K. Ross, A. Paganini-Hill, S. Roy, et al., "Past and Present Preferred Prescribing Practices of Hormone Replacement Therapy Among Los Angeles Gynecologists: Possible Implications for Public Health," *American Journal of Public Health 78(5) :516-5 19, 1988.*

has been approved for use in CHT, although doctors prescribe it for this purpose, and most progestin use related to hormone therapy is in conjunction with estrogen. Studies have shown that progestin is effective in treating hot flashes, and it is sometimes used for this indication when estrogen is contraindicated. Doctors prescribe CHT most often for women with intact uteri to counteract the increased risk for endometrial cancer associated with ET.

In parallel with estrogen use, progestin use gradually increased through 1976, **at which** point it began to decrease. Like estrogen, however, it began **to rise in** 1981 and has continued **to increase since then. Thus,** 1983 saw the dispensing of 3.2 million prescriptions for progestins, and that number continued to increase rapidly between 1984 and 1986. In 1979,79 percent of progestins were prescribed **to be** used alone, and menopausal problems represented only 18 percent of diagnoses related to progestin prescriptions. In 1986, only 37 percent of prescribed progestins were used alone, and menopausal symptoms represented 59 percent of mentioned diagnoses. Concomitant use of estrogens and progestins has increased over time and was common in 1986. The increase in progestin prescriptions evident after 1982 coincides with the trend toward the use of oral progestin with oral estrogen (9,11).

There is no official standard or protocol for administering or prescribing CHT. Furthermore, no conclusive studies have been performed that indicate which regimen is most beneficial, and there have been no studies that meet design, duration, and sample size requirements for determining conclusively the risks and benefits of long-term use of CHT (2). The current Postmenopausal Estrogen/Progestin Intervention (PEPI) trial

Table 4-4-Estrogen Therapy by Geographic Region, January-December 1991[ab]

Region	States	Percent share	Base (000s)
Total		100	10,626
South Central		34	3,656
South Atlantic	DE, DC, MD, VA WV, NC, SC, GA, FL		
West South Central	LA, AR,TX, OK		
East South Central	TN, AL, MS, KY		
West		28	2,950
Pacific	WA, CA, OR, HI, AK		
Mountain	MT, CO, WY, ID, UT, AZ, NM, NV		
North Central		24	2,503
East North Central	OH, IN, MI, IL, WI		
WestNorth Central	IA, NE, MN, SD, ND, MO, KS		
East		14	1,517
Middle Atlantic	NJ, PA, NY		
New England	MA, RI, NH,VT, ME, CT		

[a]Classes52112 (estrogens oral) and 52114 (estrogens topical) drug occurrences (physician mentions in thousands).
[b]Physician Drug and Diagnosis Audit (PDDA) geographic regions conform to standard U.S. Census regions. PDDA is a nationally projected sample and is not designed to be a subnational database.

SOURCE: Scott-Levin Associates, Physician Drug and Diagnosis Audit, January-Deoember 1991.

being conducted by the National Institutes of Health is investigating the effects on intermediate endpoints of different regimens of CHT used for 3 years each (12). No combination estrogen and progestin products are currently approved in the United States, although some have entered clinical testing; combination products are available in Europe. Many different regimens of CHT are prescribed by physicians; indeed, anecdotal information indicates that as many as 19 different regimens are prescribed in the United States and more than a hundred are prescribed in Europe (21).

One of the main drawbacks to CHT is the incidence of unwanted withdrawal bleeding related to the administration of progestin. Clinicians thus are experimenting with various regimens that will either make bleeding more predictable or eliminate it entirely. 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. Cyclic administration typically prescribes estrogen for the first 25 days of the calendar month and adds progestin on days 14 through 25. Both hormones are stopped for the last several 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 hormone use. This regimen also results in withdrawal bleeding. Continuous use of estrogen with intermittent progestin prescribes estrogen everyday, 365 days of the year, and adds progestin for the first 12 days of each calendar month. Withdrawal bleeding typically occurs for several days after progestin use is stopped, with the length and intensity of the bleeding dependent on the dose and type of progestin used (15). Amenorrhea is often achieved after several months of use of continuous/combined therapy. Increasingly, clinicians are prescribing continuous/combined therapy in an attempt to avoid withdrawal bleeding.

PROMOTION OF HORMONE THERAPY

Pharmaceutical manufacturers market their drugs in several ways: they send sales representatives to meet with individual physicians, place advertisements in medical journals, sponsor symposia and meetings, and fund clinical research on their products. In addition, pharmaceutical companies provide public education about medical conditions and drug use. FDA regulations prohibit companies from promoting drugs for unapproved uses; thus, manufacturers of progestin products may not promote their products for use in treating menopausal symptoms. They do fired research, however, both within their companies and within the medical community, to investigate this use.

Many advertisements for estrogen products feature pictures of attractive women who appear barely old enough to be menopausal. Often the women in the pictures are exercising or vacationing. Even advertisements focusing on osteoporosis (e.g., a recent Wyeth-Ayerst advertisement) feature relatively young-looking women. Many ads focus on femininity, sex appeal, and emotional and marital issues. The captions below have been used in recent advertisements:

- "Menopause Myth No. 1: No man in his right mind would be interested in a menopausal woman,' and "Menopause Myth No. 2: You'd better leave sports to the youngsters." These were both used by CIBA in its promotion of Estraderm, along with the statement, 'Now the change of life doesn't have to change yours. "
- "Calcium every day. Aerobics every week. Bone loss every year. She needs Premarin to help prevent further bone loss," used by Wyeth-Ayerst.
- "I feel more like a woman again," used by Reid-Rowell in its promotion of Estratest, Estratab, and Curretab. This ad also includes the following: "Hormones can make an important difference in a woman's life. These hormones can affect the way a woman feels about herself and those she loves. '

The first ad was directed toward consumers in women's magazines, while the second two ads appeared in professional journals for physicians (6). The implication in these ads is that without hormones, women will experience serious loss (15). Medical information required by the FDA is also part of these ads, and some contain further explanation of the menopause and menopausal symptoms. Many of the ads focus attention on a woman's looks and emotions, however, rather than on the scientific and medical effects of the drugs, and some have been criticized as demeaning, insulting, and degrading to menopausal women (19).

In addition, pharmaceutical companies fund individual and group research teams that conduct studies of their products or perform research in relevant medical areas; they also sponsor clinical trials of their drugs, as well as symposia and conferences that promote the exchange of both scientific and product information. Companies often contribute to commercial exhibitions held at professional meetings and promote their products to the attendees. Many researchers who study the menopause and related fields receive funding from pharmaceutical companies, a not uncommon practice in clinical research.

SUMMARY

There are 11 U.S. manufacturers of estrogen and 5 U.S. manufacturers of progestins. Three classes of estrogens are used for hormone therapy: natural estrogens, conjugated equine estrogens, and synthetic estrogens. Three progestins are used as well: medroxyprogesterone acetate, norethindrone, and norethindrone acetate. In 1990, total sales of estrogen products were close to $460 million. Premarin, the top-selling estrogen and the fourth most prescribed drug in the United States, held a 68-percent market share.

Approved estrogen products have labeled indications for the treatment of the vasomotor symptoms associated with the menopause; Estraderm is approved for the prevention of osteoporosis and Premarin for both the treatment and prevention of this condition. The FDA is considering changes in labeling that would reflect the cardioprotective effect of unopposed estrogen use. None of the progestins used in CHT has been approved by the FDA for the treatment of menopausal symptoms, but this use is common medical practice. FDA is considering labeling changes that reflect a recommendation for the use of CHT for women with intact uteri. The approval of generic conjugated estrogens remains a topic of debate within industry and at the FDA.

Obstetricians and gynecologists write more than 40 percent of estrogen prescriptions and general medicine physicians another 20 percent; all of these physicians most commonly prescribe conjugated oral estrogens. In 1990, more than 30 million prescriptions for noncontraceptive estrogens were dispensed, and the most common diagnosis associated with these prescriptions was relief of menopausal symptoms. Doctors commonly prescribe progestins for use with estrogen in women with intact uteri, but there is no officially approved regimen of CHT. Research continues to explore the long-term effects of CHT and different regimens to reduce side effects, especially withdrawal bleeding.

Many in the field of menopause research and women's health believe that serious gaps exist in the menopause and hormone therapy knowledge base, particularly in the area of long-term effects (see ch.

5). In the absence of sufficient research, especially on long durations of use, doctors are beginning to use CHT for long-term preventive therapy and pharmaceutical companies are pursuing labeling changes for existing estrogen and progestin products. Identifying and then closing these gaps are important tasks that will affect the market for hormone products.

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Chapter 5

Current Research and Future Needs

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Chapter 5
Current Research and Future Needs

Since 1983, the U.S. Public Health Service (PHS) has been working to outline an agenda for women's health. In that year, the Assistant Secretary for Health commissioned the PHS to form the Task Force on Women's Health Issues to "identify those women's health issues that are important in our society today and to lay out a blueprint for meshing those issues with the priorities of the Public Health Service" (60). In the ensuing years, controversy over the adequacy of the Federal response to the health service and health science needs of American women has persisted; debates range from whether enough research dollars are allocated to women's health issues, to whether women are sufficiently represented in clinical trials, to whether treatment of disease varies (inequitably) depending on the sex of the patient.

In response to the controversy about attention to research on women's health, the research activities supported by the National Institutes of Health (NIH) were inventoried by the General Accounting Office (GAO), based on finds expended in 1987, to determine resource allocation according to gender. The inventory used the following criteria to identify health problems:

- diseases or conditions that are ***unique*** **to** women or to some subgroup of women,
- diseases or conditions that are *more* ***prevalent*** among women,
- diseases or conditions that are ***more serious*** for women or for some subgroup of women,
- diseases or conditions for which the *risk factors are* different for women or for some subgroup of women, and
- diseases or conditions for which the ***interventions are*** different for women or for some subgroup of women (30).

The inventory determined that 13.5 percent of the NIH budget for fiscal year 1987—approximately $778 million-was spent on women's health issues (30). Certain groups interpreted this figure to mean that, conversely, 86.5 percent of NIH funds went for research focusing on men's health. NIH responded that 80 percent of all its research funds were allocated "either for studies of diseases which affect both men and women or for fundamental research which has significance for all segments of our population" (30). The inventory did not address whether such research included women in the study populations or used female animal models.

The issue of including women in NIH-funded research study populations has generated growing concern among members of Congress, many of whom regard NIH's response to the matter as inadequate. Congress, therefore, requested GAO to review NIH policy and practices in this area. GAO reported that NIH had "made little progress in implementing its policy to encourage the inclusion of women in research study populations" (58). NIH's response to this criticism was that, "[if] the GAO had done a complete examination of all the data, it would have found that, in the vast majority of research studies, clinical trials and large-scale studies, women are well represented in the study population" (30). On August 24, 1990, in the ***NIH Guide for Grants and Contracts, the*** agency published a revised, strengthened announcement regarding the inclusion of women in clinical studies. This expanded ***Policy Notice*** was republished on February 8, 1991, and will be reprinted twice a year.

In reaction to the controversy and concern produced in Congress by the GAO report, the NIH Office of Research on Women's Health was estab-



Photo credit: National Institutes of Health

Building 1, National Institutes of Health, site of the Office for Women's Health Research.

lished in September 1990 to strengthen and enhance NIH efforts to improve the prevention, diagnosis, and treatment of illness in women and to enhance research related to diseases and conditions that affect women. This office, and the Office of Science of the Alcohol, Drug Abuse, and Mental Health Aministration (ADAMHA), provided the Federal funding figures for research on the menopause and related topics that are presented in this chapter. In addition to presenting these data, the chapter discusses methodologic considerations relevant to studies of the menopause and its treatment, describes completed and ongoing menopause-related studies, and suggests areas for future research.

CURRENT STATE OF RESEARCH ON THE MENOPAUSE AND POSTMENOPAUSAL WOMEN

Previous chapters have referred to the results of studies relevant to the effects of the menopause on the current and future health of women. In addition to these studies, several large-scale investigations with long-term followup involve postmenopausal women. These studies do not necessarily address transmenopausal changes, and hence the impact of the menopause per se, but some of the data they have collected are relevant to these issues. The following section briefly summarizes the objectives and some of the principal findings of these investigations.

The Baltimore Longitudinal Study of Aging

The Baltimore Longitudinal Study of Aging (BLSA), begun in 1958, is an intramural study of the National Institute on Aging to investigate normal human aging. The participants are highly motivated; they are self-recruited, mostly white, educated professionals who return every 2 years for 2 1/2 days of medical, physiological, nutritional, and psychological evaluation (48). The women's cohort was added in 1978. Currently, 441 women, ranging from 20 to 97 years of age, participate in this ongoing observational study. One of its major objectives is to identify and characterize cross-sectional and longitudinal age-related changes among a host of physiological, behavioral, and psychological variables observed in a healthy, community-dwelling population. A second objective is to elucidate risk factors for particular age-related diseases.

Preliminary findings of the BLSA have included the observation that women before the **menopause have a lower incidence of hypertension and heart disease. In addition, diagnoses of cardiovascular disease differ between the sexes: women present for treatment with more angina than men but with fewer myocardial infarctions. More men than women are likely to undergo surgery to remedy their cardiovascular problem.**

Physical fitness, measured as maximal oxygen consumption during treadmill testing, is less in women than in men (in large part because women have a lower level of muscle mass) and declines with age in both sexes. Although women have a greater percentage of body fat than men, they also have a lower waist-to-hip ratio (WHR) in their distribution of fat (which suggests a reduced risk of hypertension, diabetes, cardiovascular disease, and mortality compared with men, who have a higher WHR). Although a surge in WHR occurs in postmenopausal women, at any given age, women still have a lower fat distribution ratio than men. The full significance of the WHR is not understood, however, and the meaning of the difference between men and women on this measure is even less clear (57).

Given its broad-based multidisciplinary approach and capacity for longitudinal followup, the BLSA could conduct highly cost-effective research into the effects of the transition through the menopause on many important biological and environmental factors. Ultimately, these data could be used to generate information about perimenopausal risk factors relevant to morbidity in women. However, the inclusion in the study of only approximately 100 women between the ages of 40 and 60 limits its ability to distinguish the effects of the menopause from longitudinal changes or to describe perimenopausal attributes.

The Framingham Study

The Framingham Study began in 1948 as a prospective long-term surveillance study to identify factors related to sex, heredity, and environmental variables (e.g., educational and occupational status, physical activity, smoking) that might be involved in the development of atherosclerotic and hypertensive heart disease. The effort is funded by the National Heart, Lung, and Blood Institute of NIH.

The study recruited two-thirds of the population of Framingham, MA (with the later addition of 740 volunteers), as participants; of these individuals, who were all between the ages of 30 and 59, 2,873

were women. This cohort was offered a physical exam, a standardized cardiovascular exam, and a chest x-ray every 2 years. Medical and family histories were taken, and samples were obtained to determine blood glucose, cholesterol, and hematocrit; urinalysis was performed for other chemistries. Endpoints, or indicators, of coronary artery and cerebrovascular morbidity and associated mortality were evaluated.

The study produced several interesting menopause-related findings. Menopause in this population occurred about a year earlier in smokers (at 49.3 years) than in nonsmokers (50.1 years). Transition through the menopause (naturally or as a result of bilateral oophorectomy) was associated with a rise in levels of hemoglobin and serum cholesterol; it was not associated with changes in body weight, blood pressure, glucose, or vital capacity (22). The study also found an increase in the incidence of coronary heart disease among postmenopausal women compared with premenopausal women, as well as an increase in the severity of the disease when women came to treatment. Surgical menopause was associated with a 2.7-fold increase in the risk of coronary heart disease (19). A particularly important finding was that estrogen users who were also smokers had an increased risk of myocardial infarction (65). Moreover, contrary to most studies of users of estrogen, the Framingham researchers found a 50 percent increase in the risk of cardiovascular disease and a doubling of the risk of cerebrovascular disease in estrogen users compared with nonusers. This result occurred despite the more favorable lipoprotein profiles (higher HDL [high-density lipoprotein] cholesterol and lower LDL [low-density lipoprotein] cholesterol) of estrogen users.

Further consideration of the Framingham findings has produced some reevaluations of these conclusions, however. A reanalysis of the data from the study has revealed that the apparent elevation in risk was not significantly different when only myocardial infarction was considered; in addition, the findings concerning overall elevation in risk were sensitive to the investigator's choice of baseline risk data (52). Moreover, there were only 302 estrogen users in the cohort (51).

In a recent study of offspring of participants in the original Framingham research, postmenopausal estrogen users were shown to have higher levels of the principal protein constituent of HDL, lower LDL cholesterol and glucose levels, and lower diastolic blood pressure than nonusers. Estrogen use was associated with higher levels of HDL cholesterol, but only in women who had undergone oophorectomies (10).

In the original study population, the form of hormone therapy was oral conjugated estrogens (usually Premarin). In the offspring study, Premarin again was the principal therapy used, but 10 percent of hormone users were also taking progestins (which were not identified). Neither study, therefore, provides data regarding the effect of progestins on cardiovascular disease.

The Healthy Women Study

The Healthy Women Study was begun in 1983 and originally consisted of a cohort of 541 Pittsburgh, PA, women who were premenopausal and between the ages of 42 and 50 (36). It was funded, in part, by the National Heart, Lung, and Blood Institute of NIH. The objective of this 5-year prospective longitudinal study was to document normal transmenopausal changes in biological and behavioral characteristics, especially those relating to cardiovascular disease. The study excluded women who had hypertension, thyroid disease, or diabetes mellitus, as well as those who had undergone hysterectomy or bilateral oophorectomy. Medications that might alter the risk factors under investigation were not permitted. Researchers evaluated blood pressure and collected specimens to assess menopausal status, related hormones, and glucose and lipid metabolism. They also assessed medical histories, body size and shape variables, and lifestyle variables such as dietary intake, physical activity, and smoking history.

Although a natural transition through the menopause appeared to have no effect on blood pressure, glucose metabolism, or caloric consumption or expenditure, it was associated with an increase in LDL cholesterol and a decline in HDL cholesterol (36). In addition, declining estrogen levels during the perimenopause were significantly related to the worsening lipid profile (32). Weight gain, a common menopausal occurrence, was significantly associated with a worsening of cardiovascular risk factors such as increases in blood pressure, total and LDL cholesterol, triglycerides, and fasting insulin (66). Compared with

nonusers, postmenopausal women who used estrogen (with or without the progestin medroxyprogesterone acetate) had lipoprotein and cholesterol profiles compatible with a reduced risk of atherogenesis. However, estrogen users also had elevated systolic blood pressure and elevated triglyceride levels (16).

Analyses of the data from this 5-year study are continuing to appear and will provide much needed insight into the natural history of the menopause with respect to the effects of changes in ovarian hormone levels on risk factors for diabetes and cardiovascular disease. Because regimens of hormone therapy are self-selected and not randomized, however, caution is advisable in interpreting the effects of such therapy on measured outcomes. Furthermore, continued followup is critical to ident@ possible links between changes attributable to the menopause and long-term endpoints of morbidity and mortality.

The Leisure World Study

This prospective study of 8,881 postmenopausal female residents of a retirement community in southern California evaluated the use of estrogen in terms of overall mortality (21). The women were almost entirely Caucasian, moderately affluent, and well educated. Their median age at the time of study was 73 years. After 7 1/2 years of following the women, there had been 1,447 deaths. Women with a history of estrogen use had an age-adjusted, all-cause mortality rate that was 20 percent lower than that of lifetime nonusers. Mortality decreased with increasing duration of use and was lower among current users than among women who had used estrogen only in the distant past. Current users with more than 15 years of estrogen use had a 40 percent reduction in overall mortality. Among oral estrogen users, relative risks of death could not be distinguished by specific dosages of the oral estrogen taken for the longest time.

Women who had used estrogen showed reduced mortality from all categories of acute and chronic arteriosclerotic disease and cerebrovascular disease, compared with nonusers. This group of women also had a reduced rate of mortality from cancer, although this reduction was not statistically significant. Mortality from all remaining causes combined was the same for estrogen users and lifetime nonusers.

The Lipid Research Clinic Mortality Followup Study

The Lipid Research Clinics (LRC) Prevalence Study was a cross-sectional study conducted at 10 North American clinics between 1971 and 1976; it was funded, in part, by the National Heart, Lung, and Blood Institute of NIH. Its objective was to describe the distribution of plasma lipids and lipoproteins within populations of American men and women to determine the relationship between hyperlipoproteinemia and cardiovascular disease. A subset of the population was selected for followup in the Lipid Research Clinic Mortality Followup Study, which provided information on the associations between the reported use of estrogen and subsequent cardiovascular and all-cause mortality. The study's female cohort consisted of 2,270 women (40 percent of whom were selected on the basis of elevated lipid levels) aged 40 to 69. The women underwent assessments of blood pressure, blood chemistries including lipid profiles, evaluations of body weight and size variables, electrocardiograms, and 24-hour dietary recalls. To relate environmental and physiological variables to cardiovascular disease, researchers administered questionnaires on lifestyles, menstrual history, reproductive status, and medication use.

After following the cohort for nearly 5 1/2 years, investigators found that overall mortality was lower (60 percent less) among estrogen users compared with nonusers (7). In addition, when they assessed the relationship between mortality from all causes and estrogen use with respect to the status of pelvic surgery, they found that compared with nonusers, estrogen users who were bilaterally oophorectomized had the greatest reduction of risk (nearly 90 percent less) followed by hysterectomized women (66 percent less) and gynecologically intact menopausal women (46 percent less).

In a later LRC report after 8 1/2 years of followup (8), a large portion of the 66 percent reduction in risk of mortality from cardiovascular disease could be explained (statistically) by the elevation levels of HDL cholesterol. In addition to higher HDL cholesterol levels, users of estrogen also had decreased levels of LDL cholesterol.

Additional findings in women (that are not strictly related to the menopause or to hormone therapy) included the absence of a cross-sectional relation-

ship between serum cholesterol and either dietary cholesterol or the ratio of dietary polyunsaturated to saturated fats. The LRC data support the conclusion that high levels of HDL cholesterol constitute a strong, independent protective factor—HDL cholesterol 1evels being an important known lipid-related risk factor for cardiovascular disease in women. Although LDL cholesterol levels in women who experience a natural menopause or bilateral oophorectomy may be elevated compared with levels in premenopausal women, the relationship of this variable to cardiovascular disease in women appears to be less consistent. Among women in the study, LRC findings also showed the well-known positive relationships among smoking, obesity, and cardiovascular disease, and the apparent cardioprotective effect of limited (moderate) alcohol consumption.

Several features of the LRC study warrant careful consideration when interpreting its results. The use of estrogen in the study was self-selected rather than randomly assigned, and reports of the study do not indicate the reasons for its use or nonuse. Although the results of the study addressed the issue of potential selection bias, confounding as a result of self-selection cannot be ruled out. Because most of the women were taking oral estrogens, the findings do not apply to nonoral estrogens or to estrogens combined with progestins. Moreover, dose-response relationships were not evaluated, nor was the effect of duration of estrogen use assessed. Although the use of estrogen is associated with an overall favorable lipoprotein pattern, estrogen users in the study had substantially elevated triglyceride levels, implications of which for cardiovascular disease are unclear. Finally, the study did not address the effect of longitudinal changes on biochemical or physiological variables as women traversed the menopause.

The Massachusetts Women's Health Study, Part 2

Part 2 of the Massachusetts Women's Health Study is a 5-year prospective followup study of a cohort of 427 pre- and perimenopausal women; the study, Part 1 of which was begun in 1982, is being supported by a grant from the National Institute on Aging (NIA) of NIH. The cohort was assembled from a previously studied, community-based random sample of 2,500 premenopausal Massachusetts women who were believed to be representative of U.S. women in general.

The objectives of this study are to obtain biological, anthropometric, psychosocial, and lifestyle data from women as they traverse the menopause. The study will assess changes in reproductive hormones and related parameters and determine their relationship, if any, to changes in bone mass and cardiovascular risk factors (e.g., lipid and lipoprotein profries). An important goal of the project is to provide valuable basic information on normal changes associated with the transition through the menopause, which are needed to distinguish normal from pathophysiologic changes in reproductive physiology, bone mass, and cardiovascular risk factors. Study designers hope to continue followup beyond the original 5-year term to assess relationships between intermediate outcomes of morbidity and mortality and hypothesized risk factors (37).

The Nurses' Health Study

The Nurses' Health Study is a prospective project based on mailed questionnaires that have been updated at 2-year intervals since 1976 (15). It is supported, in part, by various institutes of NIH. The main objective of the study is to determine the relationships among lifestyle and environmental or exposure variables (e.g., dietary factors, cigarette smoking, use of oral contraceptives and hormone therapy, estrogen in particular) and diabetes, cardiovascular disease, and cancer in women. The initial cohort consisted of approximately 122,000 married female registered nurses who were 30 to 55 years of age and living in 11 States when the study began.

Findings from a recent report on the project show that although postmenopausal women who had used noncontraceptive estrogens in the past had no increased risk of breast cancer, even after more than 10 years of use, the risk of this cancer among current **users increased 40 percent (15). Researchers found no relationship between the risk of breast cancer and dietary fat intake, cigarette smoking, or past use of oral contraceptives; nevertheless, the risk of breast cancer was increased by 50 percent for current users of the**

pill compared with nonusers.[1] A 30 percent greater risk of breast cancer was seen among women who consumed between three and nine drinks of alcohol per week. Family history of breast cancer, early menarche, late age at the birth of a woman's first child, or nulliparity also increased the risk of breast cancer.

With regard to risk deriving from the use of hormones, oral contraceptives were associated with a reduced risk of ovarian and endometial cancer. Not unexpectedly, unopposed postmenopausal estrogens were strongly associated with an increased risk of endometrial cancer.

At the end of the first 4 years of followup, results indicated that the use of estrogen was associated with a reduced risk of cardiovascular morbidity and mortality. **Compared with women who had never used estrogen, women who had used estrogen at least once had an age-adjusted risk of coronary disease that was only 50 percent of the expected risk; current users had a risk that was only 30 percent of that expected (15). In a later report based on 6 years** of followup, researchers noted that in this cohort of women (which now ranged in age from 36 to 61), a natural menopause did not increase the age-adjusted risk of cardiovascular disease. However, the relative risk more than doubled for bilaterally oophorectomized women if they had never used estrogen. The enhanced risk in oophorectomized women was eliminated by estrogen use (14).

Other variables that increased the risk of cardiovascular morbidity and mortality in women were cigarette smoking, obesity, diabetes, and current but not past oral contraceptive use. Moderate alcohol consumption led to reduced risk of heart disease but more than tripled the risk of subarachnoid hemorrhage.

Assessments of the relationships among hormone therapy and morbidity and mortality are limited to those that consider the use of unopposed conjugated oral estrogens; in fact, 74 percent of estrogen users in the study report the use of Premarin. In addition, the use of estrogen therapy is self-selected rather than randomly assigned. Because data in this study are obtained by questionnaire and because the 30,000 blood samples obtained since 1989 have not yet been evaluated (due to a lack of sufficient funds), the study is unable as yet to assess longitudinal transmenopausal changes in physiology (13).

In 1991, **the Nurses'** Health Study reported on 10 years of followup of 48,470 postmenopausal women who did not have a history of cancer or cardiovascular disease when they entered the study. After adjusting for age and other risk factors, the overall risk of major coronary disease in women currently taking estrogen was found to be 44 percent lower than expected (54).

Postmenopausal Estrogen/Progestin Interventions Trial

The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial is a newly begun double-blind, placebo-controlled clinical trial of oral conjugated estrogens (Premarin), either unopposed or combined with one of two types of progestin (either Provera or micronized progesterone), in postmenopausal women. The study will also examine two schedules of combined therapy with Provera: cyclical Provera (10 mg given for days 1 through 12 of a woman's menstrual cycle) or continuous Provera (2.5 mg given daily every day). The National Heart, Lung, and Blood Institute of NIH administers the study and is the primary funder; co-funders include the National Institute of Child Health and Human Development, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, and NIA. The trial is being conducted at seven centers throughout the United States and involves 120 women at each center. Total funding is expected to exceed $10 million.

The primary objective of the trial is to describe the relationships between the various regimens and differences in cardiovascular risk factors related to plasma HDL cholesterol, systolic blood pressure, plasma fibrinogen, and plasma insulin. The project's secondary objective is to assess the effect of these regimens on lipoprotein profiles and metabolism, endometrial changes, bone mass in the lumbar spine and hip, several measures of quality of life, body mass index, renin substrate, plasma renin activity, aldosterone, and a number of factors relating to blood clotting.

[1] The **increased risk in current** users is speculated **to be due to an acceleration in the growth and detection of estrogen-dependent tumors in women at risk.**

This study will provide important interdisciplinary data and fill key gaps in knowledge of the short-term effects of various hormone therapy regimens on risk factors for diabetes, cardiovascular disease, and osteoporosis. But the limited picture provided by a 3-year study needs to be enhanced by continued long-term followup to determine the effect of these regimens on endpoints related to morbidity and mortality from disease within the cardiovascular and skeletal systems. Another limitation of the study arises from the decision to evaluate only hormone regimens that use conjugated oral estrogens. Transdermal and other nonoral routes of administration of estrogen warrant investigation, given their potential value for hormone therapy pharmacodynamics. There is also a need to understand the effects of nonoral estrogen on risk factors for cardiovascular disease and osteoporosis. A further limitation of the study, according to some critics, is that it is too small to measure an adequate number of endpoints in a reasonable amount of time (51).

The Tremin Trust: An Intergenerational Research Program

The Tremin Trust Research program on Women's Health was initiated in 1934 at the University of Minnesota and continues today at the University of Utah as a nonprofit program supported primarily through grant awards and contributions. The project, originally titled the Menstruation and Reproductive History program, initially sought to determine the magnitude of the variability in the menstrual cycle among women. In 1935, the project began with a pilot study in which participating University of Minnesota women students recorded the onset and cessation of menstrual bleeds in an effort to dispel the common myth that all women menstruate according to the same cycle, i.e., every 28 days.

Between 1934 and 1965, three primary groups of women were enrolled in the program: a 1930s panel of 2,350 women, a 1960s panel of 1,367 women, and an Alaskan panel of 1,000 women, including both Alaskan Native and Caucasian residents. Over the years, a fourth group of women, comprising the daughters and granddaughters of women in the original panels, has been developed. At present, 1,316 women—representing all four groups and ranging in age from the early teens to the mid-nineties remain active as recordkeepers. Of these currently active participants, 852 are menstruating and 464 are nonmenstruating. The study employs as main data-gathering instruments a menstrual calendar card, a medical report form, and a health report form.

The Tremin Trust is currently conducting the Menstrual and Reproductive History (MRH) Followup Study in collaboration with the National Institutes of Environmental Health Sciences to gather health data from approximately 1,000 women who participated in the original MRH research program prior to 1940. **The aim of the study is to examine the link between menstrual and reproductive history and a variety of health outcomes, including longevity. The Midlife Women's Health Study, another effort of the Tremin Trust in collaboration with Pennsylvania State University, is evaluating women between the ages of 35 and 50 who are still menstruating to document the physical and emotional changes they experience as they approach the menopause (50).**

METHODOLOGIC CONSIDERATIONS

Epidemiology is the study of the relationships of various factors that determine the frequency and distribution of disease; its aim is to estimate or closely approximate cause and effect. Studies of the menopause and the onset of age-related disease are necessarily epidemiologic in nature because populations must be studied (or observed) to better understand the associations among symptoms, the menopause, declining hormone levels, and disease. Studies of the effects of hormone therapy can be conducted as trials (which are usually randomized) to determine the safety and efficacy of the treatment (46). Randomized intervention trials and observational studies are both epidemiologic research; both are expensive and time-consuming because of the need to conduct studies that are large enough to have adequate statistical power to distinguish among a variety of potential effects.

In randomized trials, participants are randomly assigned either to a group that will be treated with the factor of interest (in this case, either estrogen therapy (ET) or combined hormone therapy (CHT)) or to a group that will receive placebo treatment. (Sometimes this group receives the "standard" treatment rather than a placebo.) The purpose of randomization is to equalize other causes or correlates of the disease across the treatment groups; it is

particularly valuable for equalizing the distribution of causes that are unknown or not readily measured.

Sometimes randomization is infeasible, unethical, or unnecessary. In the absence of randomized trials, cause and effect can often be established by the results of observational studies, which, taken together, rule out explanations other than causality. Some of these 'other explanations' include chance, selection bias, and information bias (46). A number of ongoing investigations have attempted to evaluate the effects of the menopause and treatment. Most of these studies have been observational and have contributed to a greater understanding of the menopause and the health of women.

Understanding the Effects of the Menopause

It is not possible to use randomized trials to assess the effects of the menopause on the occurrence of disease: a researcher cannot assign the age at which natural menopause will occur in a woman, and it would be unethical to randomly assign women to a group that would undergo surgical menopause merely for the sake of a research protocol. Observational studies are adequate research designs in most instances. A key concern in such studies, though, is the possibility of a biased assessment of the effects of surgical menopause, which could result from the ''selection' of women to this procedure; i.e., women who undergo surgical menopause may be at higher or lower risk for certain diseases.

Observational studies, particularly case-control and followup studies, have provided considerable evidence about the effects of the menopause on a woman's risk for a variety of diseases. The data indicate that natural or surgical menopause at an early age reduces the risk of breast cancer (27) and increases the risk of osteoporosis (38), and that surgical menopause at an early age increases the risk of cardiovascular disease (53). Problems posed by differences between natural and surgical menopause and subsequent risks for disease can be overcome by conducting large studies that have **adequate statistical power to distinguish among the different effects.**

Evaluating the Effects of Hormone Therapy

Unlike research on the menopause per se, assessing the health effects of hormone therapy may require more rigorous research than is possible through observational studies (2,62). Bias may be a difficult, even intractable, problem with observational studies because women often 'select' themselves to receive therapy (or their doctors select them). For example, hormone users may differ from nonusers in terms of factors that influence the risk of acquiring cardiovascular disease but that are unknown or difficult to measure. If the selection factors (i.e., factors that would "cause" a woman to use hormones) are strongly related to the risk of the disease in question, it maybe necessary to conduct trials in which women are assigned randomly to receive hormone therapy or placebo to ensure that the selection factors—and their effects-are equalized between hormone users and nonusers.

The confounding action of such factors is known as selection bias. Because factors responsible for a woman's assignment to a group in a nonrandomized trial influence the results of the trial in ways that cannot be quantified or even identified, researchers cannot be certain that the effects being observed are attributable to treatment or to extraneous or accompanying factors (6). For example, many studies do not provide the reasons for prescribing or not prescribing estrogen for a woman. Because physicians prescribe estrogen most frequently for symptomatic relief, users initially may be physiologically different from nonusers in their susceptibility to symptoms, and this may be related, in turn, to susceptibility to subsequent disease. Alternatively, women who are found in the nonuser category in studies may be intolerant to hormone therapy, and are thus different from users by virtue of physiological factors that influence tolerance.

It has long been suspected that selection bias might be contributing to a "healthy user" effect in hormone therapy studies. Doctors may not prescribe hormones, or may discontinue their use, for women with preexisting illness, women with a family history of contraindications (e.g., cancer or liver disease), or women who develop such contraindications during therapy. This kind of confounding effect could result in an apparent excess of morbidity or mortality in nonusers of hormones, compared with users. A healthy user effect can also occur as a result of better medical care: physicians require hormone users to undergo more frequent physical examinations than nonusers to renew their prescriptions.

In observational studies, selection factors can be taken into account by statistical "control" for

confounding variables such as cigarette smoking, hypertension, and a wide range of other factors that may be related both to hormone use and the risk of disease (54). If statistically controlling for such variables does not alter the results of the study, an absence of bias is assumed. There are circumstances, however, in which statistical control maybe inadequate. Factors generally considered under the headings of "lifestyle" or 'socioeconomic status" may be related to the risk of particular diseases, and they may also be strongly related to the decision to commence or adhere to hormone therapy. But it may be difficult or impossible to control for the effects of these factors because they cannot be measured with adequate precision. In that case, it may be possible to achieve adequate control only by means of randomization.

For many years, these methodological uncertainties have led to doubts about the existence of a relationship between cardiovascular disease and estrogen therapy. In 1991, however, the Nurses' Health Study (54) addressed many of these concerns about the effects of selection bias. The study design controlled for the various confounding variables, and the results of the study demonstrated an association between the use of estrogen and reduced risk of coronary artery disease.

Controlled, randomized prospective trials can overcome the confounding effects of selection bias by randomly assigning participants to experimental groups. This kind of study design can produce an unbiased assessment of the effects of hormone therapy vis-à-vis its risks and benefits, but it cannot provide an understanding of the whole scope of risks and benefits. Some effects are simply too uncommon to be assessed, even in a large, randomized trial. In addition, some effects, such as reduced mortality from hip fracture, take a long time to become manifest (51).

With the exception of the Healthy Women's Study, the Massachusetts Women's Health Study, and future findings from PEPI, the preceding large-scale studies provide, at best, quite limited information on normal hormonal and physiological changes in women as they progress through the menopausal years. Other, smaller-scale studies offer little additional help. Moreover, few ongoing studies include the objective of evaluating longitudinal changes (beginning with premenopausal women) to determine the effect of ovarian hormone **deficiency on the endpoints of other diseases (in addition to cardiovascular conditions) whose clinical presentation may be temporally removed from the menopause.**

Requirements for a Randomized Trial of Hormone Therapy

Randomized trials to assess the health effects of hormone therapy must be large enough to detect protective effects against cardiovascular disease and osteoporosis (or fractures); they must also be of sufficient duration to detect effects that may occur only after relatively long use. Both the use of unopposed estrogen and combination therapy should be assessed. In addition to cardiovascular disease and osteoporosis and fractures, other outcomes of interest are breast cancer, endometrial and other gynecologic cancers, and cerebrovascular disease. Also worth studying (from the risk side of the benefit-risk ratio) is hysterectomy and the morbidity associated with this procedure: concerns have been raised that women receiving hormone therapy are more likely to undergo hysterectomy, possibly because bleeding is a side effect of use (2,62).

Trials should be designed to assess both incidence and mortality. Comparisons of total morbidity and mortality among the treatment groups are important for determining overall risks and benefits, but an ''overall' comparison is insufficient to better understand individual risks. For example, researchers should compare effects among various age groups because the benefit-risk ratio may be different at different ages. For hormone therapy, the major benefits may be seen among older women, whereas the major risks may be borne by younger ones; such an outcome would influence the interpretation of the benefit-risk ratio for hormone therapy. The costs of the drug and medical care for each treatment group should also be considered in the comparison of benefits and risks (45).

It will be desirable to continue following participants after a trial ends because the adverse effects of hormone therapy on the risk of breast cancer may not become apparent for a number of years. Randomized trials of hormone therapy will be neither easy to conduct nor inexpensive. For both cardiovascular disease and osteoporosis, the protective effect of estrogen therapy appears to be related to the duration of use: women may have to take the drugs

for relatively long periods (10 to 15 years) before a protective effect becomes apparent. Hormone therapy, particularly combination therapy, can have unpleasant side effects. To be successful, a trial to detect the effects of long durations of hormone therapy use must include major efforts to encourage adherence to therapeutic regimens (45).

The Women's Health Initiative Trial

The Women's Health Initiative intervention trial, proposed by NIH, includes a randomized trial of hormone therapy, currently in the planning stages. The trial will assess not only hormone therapy but the effects of a low-fat diet and calcium/vitamin D supplements as well. It is fashioned as a '3 x 2 x 2' factorial design in which women who agree to participate will be randomized first to one of three groups: estrogen alone, a progestin and an estrogen, or a placebo. Each of these groups will then be divided into a low-fat diet or a no-diet group (creating six study groups). These six study groups will each be randomized once again-into calcium/vitamin D-supplementation or no-supplementation groups. (The scientific justification for trials of the low-fat diet and of calcium/vitamin D supplements has been questioned by some epidemiologists (45,51). For purposes of the present discussion, however, the assumption is made that these interventions are justified.)

The designers of the trial believe that a factorial design is more "efficient" than separate trials, because fewer women are needed than if each treatment were being tested in a separate trial. This argument would be persuasive if the treatments had few and minor side effects and if they were simple to administer (e.g., a single pill taken daily). For example, in the Physician's Health Study, which used a "2 x 2" factorial design in which men were assigned to aspirin only, beta carotene only, both, or placebo, there was a' 'run-in' phase before the trial to screen out men who had serious side effects; in addition, each of the men took only a single pill per day (55). In the Women's Health Initiative trial, however, one treatment does not meet the requirement of having few and minor side effects, and another is not simple to administer: hormone therapy—particularly combination therapy-has common and serious side effects (e.g., bleeding) that discourage adherence, and the low-fat diet requires major changes in the choice and preparation of foods. Good adherence to these treatments will require a serious commitment on the part of the participants over along period of time (9 years is the planned length of the trial).

No **feasibility studies have been conducted to test whether women will adhere to hormone therapy coupled with any of the other treatment conditions (i.e., low-fat diet, calcium/vitamin D supplementation), nor are there plans to carry out such investigations. Yet several sources suggest that adherence over the long run may be a problem. These include data from observational studies on the proportion of women who have ever used hormone therapy and who use it for long periods (2); experience with adherence problems in the PEPI trial, a randomized trial of hormone therapy (2); and results from a feasibility study of adherence to a low-fat diet (21). It is reasonable to predict that adherence to multiple treatments will be poor, particularly over a period of 9 years. Consequently, the likelihood is high that the trial, as designed, will fail to detect treatment effects, even if they exist (45).**

FILLING THE RESEARCH GAPS

Only in the past few decades have researchers begun to understand the potential effects of ovarian hormone levels on morbidity and mortality, effects that appear to be of even greater import in the light of increasing life expectancies for U.S. women. A hormonal component is now believed to be involved in the etiology of osteoporosis and probably in the cardiovascular diseases as well. Metabolic alterations are possible during the perimenopause and may occur in very different biological systems.

The implications of short-term menopausal symptoms for subsequent pathophysiology, as well as the effects of the symptoms themselves, have never been studied. Undoubtedly, the absence of an understanding of ovarian hormone action and of the effects of ovarian hormone levels on nonreproductive target tissues has severely constrained the generation of hypotheses. A further complicating factor is the marked differences among women with respect to the manifestation of menopausal symptoms and susceptibility to chronic diseases. A major challenge in research to develop strategies to prevent disease and maintain the health of older women lies in exploring the consequences of acute, short-term symptoms, as well as the effect of long-term reductions in ovarian hormones on the development

of disease—particularly conditions that have a long latency period or that are temporally removed from the menopause.

As the proportion of older women in the population continues to grow, the need to focus on the prevention of morbidity and disability in this group increases as well. Prevention will require an understanding of the potential effect of modifying lifestyle variables (e.g., nutrition, exercise, smoking) and the identification and use of appropriate intervention strategies (both hormonal and nonhormonal). Determining appropriate strategies requires substantially improved knowledge of the natural history and sequelae of the menopause, and of the role of exogenous and endogenous estrogens and progestins in the etiology and prevention of disease.

An understanding of the physiological consequences of reduced ovarian hormone levels requires protocols and subject selection procedures that can assess the effects of age and type of menopause (natural or surgically induced by hysterectomy or bilateral oophorectomy) on intermediate biological variables and, ultimately, on the risk of disease. **Sensitivity to the potential roles of age and type of menopause is also important in assessing the effects of hormone therapy because there may be marked differences between younger and older women in tissue-specific responses to therapy and in the benefits to be realized in oophorectomized women compared with those who experience a natural menopause. Other important covariates include the time elapsed since the menopause before commencement of hormone therapy, as well as a woman's history of prior use of hormones.**

Biological Systems That Deserve Special Attention

The Ovary

Normal variations in the cyclical hormone patterns of premenopausal women and age-related changes in the patterns of secretion of the gonadotrophins and of estrogen and progesterone are still incompletely understood. Assessments of postmenopausal ovarian function are needed to compare the risks and benefits of ovarian conservation when hysterectomies are performed. Greater understanding of the reasons for the continued production of estrone (a weaker estrogen), androgens, and testosterone by the ovaries of some postmenopausal women is also required (47). Improved knowledge of the function of the postmenopausal ovary is essential to determine whether the current surgical practice of removing healthy as well as diseased ovaries during a hysterectomy is warranted. Basic research questions include the following:

- What factors differentiate those women with continued ovarian secretory capability from those without such capability?
- What does a fictional postmenopausal ovary secrete, and how long does it remain functional?
- What are the advantages and disadvantages of continued ovarian production of these steroid hormones or precursors?
- Are there fewer or less severe menopausal symptoms among women with continued ovarian secretion?
- Are rates of bone loss lower in these women?
- Do they have an increased risk of reproductive tissue cancer (increased breast, endometrial, or ovarian cancer)?
- Does a more androgenic ovarian output pose increased risk of cardiovascular disease?

The symptoms of reduced ovarian hormone levels (especially the intensity and frequency of hot flashes) are more severe in oophorectomized women than in women who experience a natural menopause (31); oophorectomized women are also more likely to report depression, loss of libido, and dyspareunia (12). Epidemiological studies show that, compared with women who experience the menopause naturally, oophorectomized women have an increased risk of cardiovascular disease (19,14) and significantly greater rates of bone loss (23). Research that controls for or evaluates the role of age at the time of oophorectomy is critical to an objective assessment of the consequences of oophorectomy compared with those of the menopause. For example, the risk of breast cancer is substantially reduced by premenopausal oophorectomy—the degree of protection being related (inversely) to the age of the woman at the time of surgery (57). To better understand the relationship between current medical practice and long-term health outcomes, the following questions need to be answered:

. How widespread is the practice of prophylactic oophorectomy in pre- and postmenopausal women, and why are there regional differences?

- What are the factors that influence judgments by physicians regarding the necessity of removing healthy ovaries?
- What are the risks and benefits of oophorectomy?
- Can women who undergo oophorectomy be assured that they will be able to tolerate hormone therapy and that it will have beneficial effects comparable to those offered by potentially 5 to 10 years of endogenous gonadal hormones?
- Will long-term use of hormone therapy be required for oophorectomized women, and if so, will this increase the risk of (breast) cancer?

In addition to oophorectomies, hysterectomies and tubal ligations are common surgical procedures among U.S. women. Hysterectomies are performed in many pre- as well as postmenopausal women. Tubal ligations may be performed in relatively young, fertile women to prevent conception. Although data are scarce, this procedure may be associated with gonadal hormone deficiency and such symptoms as dysfunctional uterine bleeding and menorrhagia (1 1).

The effects of hysterectomy and tubal ligation on ovarian function are currently unknown, although studies have shown that hysterectomized women experience more severe menopausal symptoms (44, 49). Do these procedures compromise ovarian function and hasten menopause in premenopausal women? Clearly, more research is necessary to understand the consequences of elective pelvic procedures for ovarian function.

The Breast

Some observational studies suggest that the use of unopposed estrogen or of combined hormone therapy, particularly for many years, may result in small increases in the risk of breast cancer (17,56). As is the case for osteoporosis, bias owing to selection factors is less likely to be a problem in these studies than in studies of cardiovascular disease. Women who are more highly educated are at increased risk of breast cancer, whereas thin women are at lower risk. Thus, potential bias from selection factors is not consistently in one direction, as it is in studies of cardiovascular disease.

Randomized trials that are designed to assess whether hormone therapy increases **the risk of breast cancer cannot be carried out because it is unethical to test a drug that is believed to have either a harmful effect or no effect on the occurrence of the disease in question. Therefore, information about breast cancer from randomized trials must come from trials designed to assess possible protection against other diseases. These** data may be sparse because trials designed on the basis of the sample sizes needed to detect protection against cardiovascular disease and osteoporosis may be too small to detect increases in the risk of breast cancer. In addition, such increases may be related to longer durations of use than are required to reduce the risk of cardiovascular disease or osteoporosis. (For this reason, continued followup after the trial is desirable.) Thus, some information will be available from trials, but the most informative data on the influence of hormone therapy on the risk of breast cancer may come from observational studies (45).

Observational studies (case-control and followup studies) of hormone therapy in relation to breast cancer risk must be large enough to detect relatively small increases in risk that may occur after very long durations of use or well after use is completed. It is particularly important to assess combination therapy because the few data currently available on this regimen raise the concern that it may increase the risk of breast cancer more than unopposed estrogen (17,56). It will also be important to control carefully for the age at menopause: because the risk of breast cancer is less for women who experience an early menopause, and because such women are also likely to use hormone therapy for longer periods than women who experience a later menopause, failure to adequately control for age at menopause could mask a harmful effect of hormone therapy on the risk of breast cancer.

Glucose and Lipid Metabolism

The role of declines in ovarian hormones in age-related increases in insulin resistance and the development of adult-onset or type II diabetes is another important issue that deserves study. Insulin resistance has profound adverse effects on glucose and lipoprotein metabolism and may play a prominent role in atherogenesis and cardiovascular and renal diseases. Yet information is limited both on the effects of transmenopausal hormonal changes and on the influence of exogenous estrogen or progestins (4). There is a critical need for an objective evaluation of short- and long-term effects of pro-

gestins on insulin secretion and action because previously progestins have been associated with the development of insulin resistance and compensatory hyperinsulinemia in experimental studies with rhesus monkeys and in studies of oral contraceptive use in women (3). Most important, although short-term use of progestins may not adversely affect glucose metabolism, after 6 months of use, a progressive hyperglycemia and hyperinsulinemia may occur (39). A recent report showed that glucose tolerance and fasting and 2-hour insulin levels were not adversely affectedly the use of a progestin (Provera) in combination with Premarin, compared with unopposed Premarin; however, the study did not consider duration of use of the combination form (3). The PEPI trials will address some of these concerns.

There is considerable evidence that the responsiveness of glucose and lipid metabolism in women, particularly premenopausal women, to diet, weight loss, and exercise is considerably less than the responsiveness in men of the same age (l). In the case of exercise, responsiveness in postmenopausal women may become more like that in men, implying that endogenous estrogen may act as a physiological buffer, dampening the response of lipids to such factors as diet, weight loss, and exercise. This and many other issues related to lipid metabolism and the effects of postmenopausal hormone therapy have yet to be examined (33). Body fat distribution, which is believed to be important in differentiating lipoprotein risk factors in men and women, may be an important risk factor for men that is not present in women (33,42).

A highly atherogenic form of low-density lipoprotein that appears in increasing quantities after menopause (9) also deserves further investigation, as does lipoprotein (a), which increases throughout the menopausal years (33). The effects of estrogen or progestin on the levels of these lipoproteins are unknown (33).

Cardiovascular System

The bulk of research regarding the role of estrogen in cardiovascular disease has focused on changes in lipid and lipoprotein metabolism. Considerable evidence indicates that an important component of the reported cardioprotective effect of exogenous (unopposed) estrogen is mediated by elevated HDL cholesterol and, to some extent, by reduced LDL cholesterol (34). Because of the ongoing development of different estrogen preparations and routes of administration, as well as changes in the formulation and scheduling of progestins (which area necessary component of hormone therapy for women with a uterus), the effects of such therapy on lipid metabolism will continue to be an area of active research.

Important variables in natural history studies of the menopause as well as in controlled randomized trials of the use of estrogen and progestin include effects on blood pressure and blood coagulation factors. Another important area of study is the effect of lipoprotein metabolism changes on the vessel wall and on the atherogenic process itself, including effects on cholesterol uptake, vascular reactivity, plaque formation, oxidation of lipoproteins, and local platelet function (33). The long- and short-term effects of progestins on hemostasis and blood pressure are obviously of great concern because thromboembolic and hypertensive episodes were associated with early use of oral contraceptives. The PEPI trial will address some of these concerns.

Other critical areas of study in humans are the assessment of transmenopausal changes and of changes in coronary perfusion, cardiac output, and physical performance that result from hormone therapy. As discussed in box 5-A, the development of animal models—in particular, studies using ovariectomized monkeys-shows great promise for studies of the direct effect of estrogens and progestins on the production and amelioration of human-like atherosclerosis.

Much of the available evidence from observational studies suggests that estrogen users have a reduced risk of cardiovascular morbidity and mortality (17,54); thus, an important issue to be addressed is whether women with preexisting cardiovascular disease will likewise benefit from hormone therapy and in what ways. Also deserving of study is a determination of the effects of hormone therapy among women with known risk factors (e.g., hypertension, hyperlipoproteinemia) for cardiovascular disease.

Randomized trials are needed to determine what proportion, if any, of the observed reduction in risk is due to a real effect of estrogen and what proportion, if any, is due to selective use of estrogen by women already at reduced risk of cardiovascular disease. Such a trial would, of course, also assess the effect of combination therapy. There is as yet no informative evidence on the effect of this drug regimen; because progestins can affect

Box 5-A—Development of Animal Models for the Menopause

Animal models are useful in understanding basic biological mechanisms, formulating hypotheses, and providing evidence of cause-and-effect relationships. It is generally difficult, expensive, or time-consuming to study risk factors in humans because tissues affected by pathophysiological changes may not be readily (or ethically) available and decades may be required for the manifestation of pathophysiological processes. Furthermore, reproducible outcomes, which are fundamental to establishing direct evidence of cause and effect, may be confounded by the severely limited ability to ensure compliance-that is, to control for lifestyle and environmental variables in free-living populations. An additional problem in securing such outcomes is the difficulties that arise in trying to use randomized designs, which prevent bias in the allocation of subjects to treatment regimens.

Although rats have a strain-dependent 4- or 5-day estrus cycle (rather than a 28-day menstrual cycle) and do not experience a menopause, the ovariectomized rat has been proposed and used as an animal model for human postmenopausal osteoporosis, because the loss of ovarian hormones in rats, as in women, results in decreased bone density and more fragile long bones. As in oophorectomized women, ovariectomized rats also have deficits in intestinal calcium absorption, which contribute to the loss of bone mass.

Although it is commonly believed that the ovariectomized rat is not the best animal model because its skeleton continues to grow, this finding is probably not due to any species-specific anomaly but rather to the use of juvenile animals that have not attained skeletal maturity. The selection of a mature rat (before ovariectomy is performed) is essential as a paradigm, because bone loss in postmenopausal women obviously occurs only after the attainment of skeletal maturity. Although the ovariectornized rat is a convenient, practical animal model of bone loss, significant differences in bone morphology with respect to the organizational pattern of skeletal components, compared with humans, limit its widespread use+

Attempts have been made to overcome this drawback as well as to develop an animal model that has a more relevant reproductive physiology and that is susceptible to atherogenesis. Researchers at the Arteriosclerosis Research Center (ARC) and Comparative Medicine Clinical Research Center at Wake Forest University's Bowman Gray School of Medicine (Winston-Salem, NC) have begun evaluating the utility of cynomolgus monkeys as models for menopause-related pathophysiology.

For the past decade, researchers at the ARC have conducted randomized, controlled intervention trials using cynomolgus monkeys to explore the physiological and cellular mechanisms by which estrogens and progestins affect not only bone metabolism and bone density but also coronary artery atherogenesis and vascular tissue responsivity. Because this species of monkey is susceptible to diet-induced atherogenesis, and because female cynomolgus macaques have a reproductive physiology more comparable to that of humans than the reproductive physiology of other primates, these investigators have been able to study directly and simultaneously the role of ovarian hormones on endpoints of both atherogenic and osteoporotic processes. Their investigations have produced valuable insights that would be impossible to achieve from studies of humans.

Scientists from the ARC have provided substantial evidence that the ovariectomized female cynomolgus macaque is a highly appropriate model for the study of menopause-related pathophysiology. The center has studied the effects of ovariectomy and ovarian hormone treatment on bone histomorphometry, bone density, and biochemical parameters of bone metabolism. Researchers have also observed changes in histomorphometric parameters (indicative of a loss of architectural elements) and biochemical markers of bone breakdown that are similar to those seen in postmenopausal women with osteoporosis.

With regard to cardiovascular disease, ARC studies have shown that coronary artery atherosclerosis in female cynomolgus monkeys appears to be morphologically similar to that in women. Furthermore, ovariectomy in this species results in a doubling of the extent of atherosclerosis. Most important, these investigators observed that ovariectomized monkeys given estrogen or estrogen plus progesterone showed a marked inhibition in the progression of atherosclerosis compared with ovariectomized monkeys receiving placebo. It thus appears that the ovariectomized cynomolgus monkey may be a highly appropriate model to study the pathogenesis of age-related diseases in middle-aged and older women.

SOURCES: **Office of** Technology Assessment adapted **from** C. Gennari, D. Agnusdei, P. Nardi, et al., "Estrogen Preserves a Normal Intestinal Responsiveness to 1,25-Dihydroxyvitamin D_3 in Oophorectomized Women" *Journal of Clinical Endocrinology and Metabolism 71(5):1288-1293, 1990;* R.P. Heaney, R.R. Reeker, and P.D. Saville, "Menopausal Changes in Bone Remodeling," *Journal of Laboratory and Clinical Medicine 92(6):964-970, 1978;* D.N. Kalu, C.-C. Liu, R.R. Hardin, et al., "The Aged Rat Model of Ovarian Hormone Deficiency Bone Loss," *Endocrinology 124(1):7-16, 1989;* P.D. Saville, "Changes in Skeletal Mass and Fragility With Castration in the Rat: A Model of Osteoporosis,' *Journal of the American Geriatric Society 17(2):155-166, 1969.*

serum lipids adversely, the effect of combination therapy on the risk of cardiovascular disease may not be favorable (17).

Finally, better understanding of the role that estrogen plays in protecting premenopausal women against cardiovascular disease may lead to better diagnosis and treatment of cardiovascular disease in postmenopausal women. For example, some researchers have suggested that the perception that women tolerate cardiovascular disease better than men and hence have a better prognosis may be due in part to the inclusion of women without cardiovascular disease (who are misdiagnosed as having angina) in female patient populations with cardiovascular disease (64). This misunderstanding of the clinical presentation and prognosis of the disease in women may in turn lead to less aggressive preventive interventions (e.g., prescribing therapies, risk factor modification) and the postponement of referral for further noninvasive testing. Because women may be referred for procedures such as coronary bypass surgery later in the course of their disease than are men, they may be older and their condition more serious; not surprisingly, they experience increased operative mortality (29). **As this one example demonstrates, deficiencies in the ability to diagnose cardiovascular disease in women and ultimately deliver better medical care can be corrected only by increased understanding of the etiology and course of cardiovascular disease in this population group.**

Skeletal System

Given the bone status of those women already diagnosed as osteoporotic, it is estimated that half of all Caucasian women will develop vertebral fractures and one-third will suffer hip fractures by the age of 90 (43). Yet at least 50 percent will not have osteoporotic fractures even in extreme old age. Although estrogen deficiency undoubtedly plays a major role in the development of this disease by increasing the rate of bone loss throughout the skeleton, not all perimenopausal women lose bone at the same rate. Furthermore, although enhanced perimenopausal bone loss occurs at all sites, the effect of reduced endogenous estrogen levels on rates of loss varies from site to site; that is, the spine shows the greatest rate of estrogen-sensitive loss compared with the hip and radius, which reflect a greater component attributable to age.

Because estimates of bone loss in women may be based on study populations that commingled oophorectomized women with those who had experienced a natural menopause (not to mention smokers, women who never exercised, and women with a variety of other contributing risk factors), perceptions of what constitutes a "normal" rate of menopausal bone loss may be distorted, leading to overestimates of the number of women who are at risk for osteoporosis. The effects of a natural menopause (and of reduced ovarian hormone levels) need to be evaluated separately and compared with the effects arising from oophorectomy (and from ovarian hormone deficiency) on site-specific rates of bone loss. These studies should also include an assessment of the effect of age at menopause (and years from menopause) on rates of bone loss. Answers to these questions may help distinguish women who lose bone quickly from those who lose bone slowly.

Sensitive, specific metabolic markers are needed to indicate when skeletal depletion is occurring and to help monitor both early and later responses to treatment. Such markers should be capable of quantifying bone resorption and formation and the degree of imbalance between the two (59).

Research is also needed at the cellular level to determine the role of in vivo estrogen deficiency and the effects of estrogen therapy on the factors that regulate the coupling of processes of bone formation with those of bone resorption. Many physicians advocate estrogen therapy as the most effective available treatment for prevention of osteoporosis, but it is not clear how long estrogen (or combined therapy) should be prescribed to prevent fractures in later life. Also unknown is the length of time during which hormone therapy is effective in preventing or reducing rates of bone loss.

Research is needed to answer the following questions:

- Is estrogen therapy as effective in the femur as in the vertebrae?
- What is the effect of long-term progestin use on skeletal mass?
- What is the cumulative effect of periods of starting and stopping estrogen, a practice believed to be common among users of hormone therapy (26,37)?
- Are the effects of estrogen cumulative, or is there a threshold in terms of duration of use? Is

there an acceleration of bone loss when therapy is discontinued?
- Do the benefits to be realized (in bone density maintained or fractures reduced) depend on the age of the patient or the number of years postmenopause?
- Is the initiation of estrogen therapy in postmenopausal older women (over age 65) effective in preventing further bone loss and fractures?

Many observational studies suggest that both the use of unopposed estrogen and of combined therapy reduce the incidence of osteoporosis (or fractures) (17). Bias resulting from selection factors is likely to be less of a problem in these studies than in studies of cardiovascular disease. Thinness is related to an increased risk of osteoporosis and physical activity to a decreased risk. The presence of bias as a result of thin women 'selecting' themselves for hormone therapy will be in the direction of underestimation of a protective effect of therapy, whereas bias owing to the self-selection of physically active women will be in the direction of overestimation. In contrast, bias from selection factors in studies of cardiovascular disease is more consistently in the direction of producing an apparent protective effect of hormone therapy. If the only issue, then, was the effect of hormone therapy on the risk of osteoporosis, randomized trials might not be deemed necessary. However, in the context of trials to assess the effects of hormone therapy on cardiovascular disease, it is worthwhile to assess osteoporosis as well.

Nutrition, Energy Balance, and Body Composition

With the exception of considerable clinical data on calcium consumption, few studies of middle-aged women have examined the effects of the menopause or of hormone therapy on the requirements for vitamins, minerals, and other nutrients. Alterations in the efficiency of absorption, excretion, and metabolism of various nutrients are known to occur during periods of altered ovarian hormone levels such as those that occur during pregnancy or oral contraceptive use. It was also demonstrated recently that oophorectomy reduces calcium absorption (18). Because it is likely that the efficiency of processes related to nutrient assimilation, utilization, and retention may be compromised or altered by the ovarian hormone deficiency characteristic of the menopausal period, actual nutrient requirements may be different in peri- and postmenopausal women compared with premenopausal women. Considering the potential impact of nutrition on the prevention or modification of disease processes, an assessment of nutrient requirements in menopausal women should be an area of high priority.

Data on the relationships among weight gain and changes in dietary patterns and caloric intake in middle-aged women are also severely limited, particularly with regard to changes in ovarian hormone status. Increases in weight are common in middle-aged women and are strongly associated with enhanced risks of diabetes and cardiovascular disease (66). In fact, an increased risk of cardiovascular morbidity and mortality-which persisted even after controlling for the influence of weight on blood pressure and cholesterol—has recently been demonstrated in overweight, middle-aged women (35).

Although the effects of hormone therapy on body weight in humans have not been systematically explored, it has been reported that estrogen users appear to be significantly slimmer and taller than nonusers at all ages (4). Studies in rodents (63) and nonhuman primates (28) have shown that the gonadal hormones exert profound effects on food intake, weight gain, and body composition. For example, ovariectomy in rodents is associated with overeating, rapid and profound increases in body weight, and obesity. These changes can be prevented or reversed with estrogen treatment. The addition of a progestin, however, counteracts the effect of estrogen and leads, again, to increases in weight and obesity (63). Knowledge of the effects of estrogen, especially in combination with progestins, on the regulation of energy balance and adiposity in middle-aged women is critical to appropriate prescribing of hormone therapy. (See box 5-A for a discussion of animal models.)

Renal Function

Few studies of renal physiology have focused on women in general, let alone on transmenopausal changes or changes as a result of hormone therapy. The kidney plays a major role in mineral homeostasis. Ovarian hormone deficiency and hormone therapy are known to produce marked changes in serum levels and urinary excretion of calcium and phosphorus. An assessment of age- and menopause-related alterations in renal function (particularly in renal tubular function) will foster a better understanding of mineral homeostasis in women of all

ages and provide an additional perspective on peri- and postmenopausal bone loss (47).

A study of water and electrolyte metabolism, with which the kidney is integrally involved in both pre- and postmenopausal women, could lead to better understanding and hence more effective treatment of problems related to water retention and bloating. Such problems, which commonly occur both premenstrually and as an unwanted side effect of hormone therapy (often resulting in reduced compliance with many hormone regimens), can have marked adverse effects on the quality of life of young and old women.

Pharmacology

It is presently assumed that any given pharmacologic agent administered to women will have similar action, metabolism, and disposition, regardless of where a woman maybe in her menstrual cycle or of whether she is having regular cycles. Such an assumption is also made regardless of whether a woman is taking oral contraceptives or is postmenopausal and receiving hormone therapy. This assumption is surprising, given the possibility of profound metabolic alterations (e.g., those reflected in severe vasomotor instability or in changes in bone mineral metabolism) that may result from the menopause, oophorectomy, or hormone therapy. Scant attention has been focused on the issue of whether ovarian hormone status itself or alterations of metabolism secondary to changes in ovarian hormone status may affect pharmacodynamic responses.

Oophorectomized women who are not taking estrogen show a marked reduction in vertebral bone density and a substantial decline in intestinal calcium absorption compared with presurgery baseline values. Oophorectomized women receiving estrogen therapy show no decline in bone mass or calcium absorption (18). This suggests that comparable or presumably adequate blood levels of a given drug or minerals do not ensure comparable pharmacodynarnics in physiological states that are dissimilar because of ovarian hormone status (whether as a result of oral contraceptive use, menopause, or hormone therapy). The question of impaired or altered action of other pharmacologic agents on other tissues as a result of changes in the levels of ovarian hormones calls for critical examination. The efficacy and side effects of drugs should be assessed in populations of women whose ovarian hormone status reflects that of future users of the drugs.

Exercise

Experts increasingly advocate physical activity and exercise as being of benefit to the cardiovascular and skeletal systems and contributing to a sense of overall well-being by their positive effects on mood. Sedentary behaviors and physical inactivity, on the other hand, are associated with a higher incidence of coronary heart disease and with underlying risk factors for atherosclerosis-- e.g., obesity, hypertension, and diabetes (40).

Although physical fitness and cardiovascular disease are not well studied among women, researchers have shown that in comparison with sedentary women, women who regularly engage in endurance activities have higher HDL cholesterol levels (40). Furthermore, women who participate in aerobic conditioning show improvements in glucose tolerance and response to insulin (61). Studies have also found that women who exercise have reduced mortality from cardiovascular disease and cancer, leading to a fourfold reduction in mortality from all causes (5).

To achieve maximal benefits for the skeleton, it is believed that exercise that has a significant weight-bearing component is necessary (41). Although moderate exercise may be effective in increasing or preserving bone mass in the lumbar spine in postmenopausal women, it is unclear whether the beneficial effects of exercise extend to the period of accelerated bone loss during the perimenopause. A number of important questions arise regarding specific recommendations for exercise prescription in women. The effects of exercise on site-specific changes in bone mass, on risk factors for cardiovascular disease, and on long-term endpoints such as fractures and cardiovascular morbidity and mortality all need to be evaluated. In particular, research is needed to establish guidelines on the type, intensity, frequency, and duration of exercise necessary to derive maximal benefits to both the musculoskeletal and cardiovascular systems and to avoid ineffective training and possible injury. In older women, the interaction of exercise with lifestyle or environmental factors such as nutrition or hormone therapy deserves study, because it has been demonstrated among younger women that calcium consumption plays an important role in optimizing the potential benefits of physical exercise on the skeleton (24).

Effects of Ovarian Hormone Levels: Modalities of Study

Given the present dearth of data, both short- and long-term multidisciplinary observational studies could make substantial contributions to an understanding of the natural history of the menopause. Cohorts (of a sufficiently broad age range) of premenopausal and postmenopausal women should be included in initial subject populations to generate immediate cross-sectional comparative data, as well as to establish premenopausal values for the assessment of transmenopausal changes and long-term outcomes. These studies should be multidisciplinary, cutting across the major biological and psychosociocultural systems. They should assess the role of reproductive history vis-à-vis pregnancy and lactation, as well as the effects of *cumulative* exposure to exogenous hormones such as diethylstilbestrol (DES) and oral contraceptives.

There are almost no data on the menopausal experience or on the use of hormone therapy among women of color or women of various ethnic backgrounds. The study of individuals from different genetic backgrounds is valuable not only in understanding unique pathophysiologies but also in understanding differential susceptibilities to disease. For example, compared with Caucasians, African Americans have a substantially lower risk of osteoporosis but a much higher incidence of hypertension, diabetes, and cardiovascular and renal disease. To date, however, research has largely ignored the role played by the menopause and by reduced ovarian hormone levels in these diseases among African Americans and other ethnic subgroups.

With the exception of the PEPI study, there is a decided lack of randomized placebo-controlled or comparable-treatment clinical intervention trials, as well as a lack of trials of clinical endpoints, that address the effects of hormone therapy. Experimental randomized clinical trials of hormone therapy as it affects morbidity and mortality are needed to obtain an unbiased assessment of the effects of such therapy, to develop algorithms regarding prescribing practice, and to assess the effectiveness of nonhormonal interventions.

FEDERAL INVESTMENT IN MENOPAUSAL AND RELATED RESEARCH

In the summer of 1991, OTA requested that NIH and ADAMHA provide budget data on research related to the menopause. The responses of each agency are reported below.

National Institutes of Health

The PHS has no standard definition of hormone therapy that is used throughout the agency. Therefore, NIH chose the following definition, which was provided by the National Institute of Child Health and Human Development, to use in collecting budget data:

> Hormone therapy is the use of exogenous sex hormones for the relief of menopausal symptomatology. The hormones may be synthetic or natural and are derived from humans and animals. The concept of hormone therapy pertains to the use of estrogen and progesterone or synthetic progestin. Estrogen therapy pertains to the use of only estrogen for the same purposes. Hormone regimens pertain to any of the above variations in terms of hormone dosage and duration.

Data were derived from the NIH Computer Retrieval of Information on Scientific Projects (CRISP) database as well as directly from the appropriate institute and center directors (ICDs). CRISP is a major scientific information system containing data on all research programs supported by units within the PHS. Two searches of the CRISP databases were conducted: one based on the single term ***menopause,*** which included postmenopause, and a second based on the terms ***menopause*** and *hormone replacement therapy. The* first search revealed $145.5 million in funding (see table 5-l); nearly $72 million of that research is related to breast cancer and is funded through the National Cancer Institute.

The second search revealed no studies specifically associated with hormone therapy; consequently, the search was expanded to include the following related terms: estrogen, estradiol, estriol, estetrol, estrone, estrogen analog, diethylstilbestrol, ethynylestradiol, mestranol, mestranol norethindrone, and mestranol norethynodrel. Including these terms revealed obligated total funding of $15.5 million for fiscal year 1991 (see table 5-2). The figures in the

Table 5-l—Estimated Volume of General Research Related tot he Menopause and the Postmenopausal Period, National Institutes of Health, Fiscal Year 1991

Institute, center, or division	Total dollars (in millions)	Total number of projects
National Institute on Aging	$ 5.6	24
National Institute of Arthritis and Musculoskeletal and Skin Diseases	7.8	43
National Cancer Institute	119.7	NA
National Institute of Diabetes and Digestive and Kidney Diseases	3.9	22
National Institute of Child Health and Human Development	1.3	7
National Heart, Lung, and Blood Institute	5.2	21
National Center for Nursing Research	0.4	2
National Center for Research Resources	1.2	52
National Institute of Dental Research	0.4	2
Total	$145.5	173

NOTE: NA = Data not available.

SOURCE: National Institutes of Health, 1991.

Table 5-2—Estimated Volume of Research Related to the Menopause and Hormone Therapy, National Institutes of Health, Fiscal Year 1991

Institute, center, or division	Total dollars (in millions)	Total number of projects
National Institute on Aging	$ 4.2	15
National Institute of Arthritis and Musculoskeletal and Skin Diseases	1.8	10
National Cancer Institute	1.6	NA
National Institute of Diabetes and Digestive and Kidney Diseases	2.3	14
National Institute of Child Health and Human Development	0.5	4
National Heart, Lung, and Blood Institute	4.4	17
National Center for Nursing Research	0.2	1
National Center for Research Resources	0.2	23
National Institute of Dental Research	0.3	1
Total	$15.5	85

NOTE: NA = Data not available.

SOURCE: National Institutes of Health, 1991.

table reflect the total funds awarded, including direct and indirect costs.

The data have certain limitations that require consideration. The CRISP database does not distinguish new projects from continuing ones; thus, the dollar amounts do not reflect the total funds spent for research related to the searched term. In addition, a particular project may be counted more than once if it is associated with more than one of the searched index terms.

In total, NIH support for research related to the menopause and its consequences includes studies of basic reproductive, cellular, and molecular biology and more clinically related investigations of, for example, osteoporosis, coronary artery disease, stroke, and cancers of the breast and uterus. In addition, NIH supports research related to changes in various organs and tissues that occur as a result of the physiological changes associated with the cessation of ovarian functions. It also funds efforts that address the resultant symptoms and signs of the menopausal period that concern women and affect their well-being. (See box 5-B for descriptions of the types of research supported by various institutes of NIH.)

Alcohol, Drug Abuse, and Mental Health Administration

ADAMHA, an agency of the PHS, also funds research related to women's health and the menopause. The three ADAMHA institutes-the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH)-+onduct and fund research that is both directly and indirectly related to the menopause. Most of the work is done extramurally, but ADAMHA also supports three full-time intramural menopause researchers.

Grant abstracts for the three institutes were analyzed for menopause-related topics. From 1989 to 1991, ADAMHA provided close to $5 million for 32 research grants that were directly related to the menopause (see table 5-3). Many of these projects are oriented toward basic research; only 7 of the 32 grants are for research on human subjects. Those 7 grants fired 3 projects that focus on alcohol effects in postmenopausal women; biobehavioral studies of narcotics abuse, including alcohol-induced changes in endocrine function in postmenopausal women; and research on the psychobiology and treatment of perimenopausal mood disorders.

Box 5-B—Menopause-Related Research at the National Institutes Health

Many **of the institutes, centers, and divisions (ICDs) of the National Institutes of Health contribute resources and support to research on** women's health. Because of the various missions and objectives of the ICIDs, they may **place different emphases on the many areas of womens' health. The following are the primary institutes that provide resources to support research on the menopause and on hormone therapy.**

The National Institute of Child Health and Human Development historically **has been associated with** issues **related to human development and the reproductive health of women. The Center for Population Research leads the** Federal Government's effort in this regard. Through grants and contracts, the center sponsors work ranging from basic biomedical research in the reproductive sciences to epidemiologic studies on the menopause and on the postmenopausal period.

The National Heart, Lung, and Blood Institute (NHLBI) is supporting research that will contribute to an **understanding of how interventions to improve lipid and cholesterol profiles in postmenopausal women may be useful in preventing the progression of coronary artery atherosclerosis. Other research supported by** NHLBI **includes studies on postmenopausal use of estrogen and progestin in relation to the risk of coronary disease.**

The National Cancer Institute **supports studies of postmenopausal women that focus on the prevention, treatment, screening, and detection of cancer and on the relationship of obesity, smoking prevention and cessation, and hormone therapy to the development of malignancy.**

The National Institute on Aging **has begun a major new initiative related to hormonal therapies for osteoporosis, which is reflected in the large increase in funds for the institute in fiscal year 1991. Studies range from longitudinal studies of the menopause, bone loss, and aging to behavioral treatment of menopausal hot flashes.**

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) hasanendocrinology program that includes a significant effort in support of research on the menopause and on hormone therapy. In addition, NIDDK is involved in clinical and basic research on the action of estrogen on various tissues. The institute has a strong research interest in this field, as well as in the closely related field of osteoporosis.

The National Center for *Nursing Research* supports basic and clinical interdisciplinary research related to women's health across the lifespan.

The National Institute for Dental Research supports research that examines the status of various oral tissues during physiologic aging and, more specific to women's health issues, the observable effects of the menopause and hormone therapy on salivary gland functions.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases provides funds for research efforts on osteoporosis, bone density, and pathological bone reabsorption along with research on the effects of estrogen or combined hormone therapy.

Some studies ***supported by the National Center for Research Resources include,*** but are not limited to, exercise intervention in relation to bone mineral content in postmenopausal women, ovarian steroids in menopausal women with endometrial cancer, and thermoregulation during menopausal hot flashes.

SOURCE: National Institutes of Health, 1991.

In response to the health promotion and disease prevention goals of the PHS's Healthy People 2000 program, NIMH is seeking to expand its research base on issues related to women's health through basic, clinical, and epidemiologic research. Currently, the agency is designing a program that will encourage extramural research on changes in women's mental health during the lifecycle; one of the research goals of the program is related to changes in mood and behavior that are associated with the menopause.

SUMMARY

As the proportion of older women in the U.S. population continues to grow, the need for prevention or, alternatively, early diagnosis and treatment of morbidity and disability in this group similarly increases. The development of appropriate intervention strategies depends on substantially improved knowledge in two areas: the natural history and sequelae of the menopause and the role of estrogen and progesterone deficiency and replacement in the prevention or modification of disease.

Thus far, hormone therapy is the most efficacious treatment modality for the amelioration of menopausal symptoms and prevention of osteoporosis. Epidemiological and animal studies strongly suggest that estrogen therapy has the potential to reduce morbidity and mortality from cardiovascular disease. But in the absence of randomized clinical trials, a definitive, unbiased assessment of the beneficial effects of estrogen with and without progestin in preventing or ameliorating cardiovascular disease is not possible. Objective evaluation of the risks is likewise precluded. Moreover, there are virtually no studies on the effects of long-term use of estrogen with progestin (i.e., combined hormone therapy)—a recommended treatment regimen for nonhysterectomized women.

Because estrogen and progesterone affect a host of tissues throughout the body, future research should foster an integrated, multidisciplinary approach, such as that used in the new PEPI trial in its multiorgan system evaluation of risk factors and intermediate points of disease. Furthermore, randomized clinical trials of this kind, with their long-term followup studies and assessments of multiple morbidity and mortality endpoints, are crucial to an objective evaluation of risks and benefits. Without such an evaluation, some of the historical disasters that have accompanied the use of exogenous ovarian hormones may be repeated: for example, the increased risk of reproductive cancers in mother and offspring from the use of (or in utero exposure to) DES; the marked number of hypertensive and thromboembolic episodes attributed to use of early formulations of the pill (which took 10 years to uncover, even though the pill was being used by millions of women) (25); and the excess of endometrial cancer in users of unopposed estrogens before the recommendation that progestin should be added.

An increase in the quality of life of older women depends on early improvements in diagnosis, which in turn require the identification of risk factors (that may be different from those for men) and the development of practice plans with regard to preventive and therapeutic strategies. It also requires objective findings from well-controlled studies to determine who will benefit and how, for how long a particular intervention (either hormonal or nonhormonal) will be effective, and in which body systems. It requires increased understanding of women's physiology in general. And it requires the dissemination of badly needed information regarding the menopause to physicians and their patients.

Table 5-3-Extramural Research Related to the Menopause, Alcohol, Drug Abuse, and Mental Health Administration, 1989-91

Fiscal year	Institute	Institute funding($)	Total ADAMHA funding ($)
1989	National Institute of Alcohol Abuse and Alcoholism	$560,413	
	National Institute on Drug Abuse	480,505	
	National Institute of Mental Health	468,727	$1,509,645
1990	National Institute of Alcohol Abuse and Alcoholism	591,111	
	National Institute on Drug Abuse	432,109	
	National Institute of Mental Health	711,298	1,734,518
1991	National Institute of Alcohol Abuse and Alcoholism	580,374	
	National Institute on Drug Abuse	613,288	
	National Institute of Mental Health	411,865	1,605,527
	3-year total		$4,849,690

SOURCE: Alcohol, Drug Abuse, and Mental Health Administration, 1991.

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Chapter 6

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Chapter 6
Conclusions

The menopause is defined as the final menstrual period that a woman experiences. It is a single event, retrospectively diagnosed after a year with no menstrual periods. The period of time preceding a woman's last period and the frost year after the menopause constitute the ***perimenopause.*** After a woman experiences the menopause, she is considered ***postmenopausal.*** Throughout the perirmenopause, ovarian hormone production slows and finally ceases; at the end of this time, the female hormone estrogen is no longer secreted by the ovaries. This loss of ovarian estrogen can produce symptoms such as hot flashes and night sweats and is implicated in the development of osteoporosis and cardiovascular disease. For these reasons, some women and their physicians elect hormone therapy for the treatment of symptoms or the prevention of osteoporosis or cardiovascular disease. If a woman is taking only estrogen (unopposed by a progestin), the therapy is referred to as ***estrogen therapy,*** or ET. If the woman's ovaries have not been surgically removed, common practice increasingly is to prescribe a progestin in addition to the estrogen. (Estrogen alone increases the risk of endometrial cancer; the addition of a progestin reduces that risk.) Women who take both an estrogen and a progestin are receiving combination therapy, which is commonly referred to as ***combined hormone therapy,*** or CHT. In CHT, the estrogen is opposed by a progestin. The term ***hormone therapy*** refers either to ET or CHT.

Many American women now face the question of whether to undergo hormone therapy during the menopause and how long to continue it once it has been elected. Few life events, other than aging, affect as many people as the menopause. In the frost decade of the 21st century, more than 21 million women from the baby boom generation will reach the age of 50 and become menopausal. Although universal among women, the menopause is a highly individualized experience: some women may hardly notice it while others maybe disabled by it. Often, physicians treat menopause monolithically, as a threat to health, without any recognition that many women traverse the menopause and enter old age with few medical problems. This clinical variability has contributed to the debate about the appropriate management of the menopause, as part of the natural process of aging in women. Complicating any decision about using hormones for treatment of the symptoms of menopause (e.g., hot flashes, night sweats) is the issue of hormone therapy and the risks it carries, both increased and decreased, for osteoporosis, heart disease, and cancer.

As long as certain issues remain unaddressed and unanswered, a woman's decision regarding the management of her menopause and the possible reduction of future disease risk must be made under conditions of confusion and uncertainty. Research and time will answer some of the questions raised by current menopause management practices; women today, however, have no choice but to face this conundrum with what is known. This background paper reports on what is known about the menopause, hormone therapy, drug prescribing and review, and research needs. Much research has already been conducted, and more is proposed. Interest in the menopause and in the effects of reduced ovarian hormone levels has accelerated in recent years, producing new data that have yet to be fully analyzed or comprehended. Despite increasing efforts to fully understand the mechanisms of the menopause and its relationship to subsequent disease, many issues remain unresolved or in need of attention. They are summarized here.

DETERMINING THE RELATIONSHIP BETWEEN THE MENOPAUSE AND DISEASES OF AGING

One of the most pressing issues related to the menopause is the lack of knowledge about characteristics of women that place them at higher or lower risk for health problems during the menopause and later in life. A better understanding of the natural history of the menopause is critical. Despite its universality in human female aging, the biology of the menopause is incompletely understood. Substantive progress in understanding the etiology and symptomatology of age-related disease among women requires increased knowledge of their inherent biological and psychosociocultural differences. Such

progress is fundamental to accurate diagnosis and effective treatment to reduce morbidity and mortality and to maintain the independence of the rapidly growing postmenopausal population.

The significance of menopausal symptoms (i.e., hot flashes) to subsequent pathophysiology has never been studied. Undoubtedly, incomplete understanding of ovarian hormone action and of the effects of ovarian hormone levels in nonreproductive target tissues has severely constrained the generation of hypotheses about this relationship. A further complication is the marked interindividual differences among women with respect to the manifestation of menopausal symptoms, as well as to susceptibility to chronic diseases. A major challenge to the prevention of disease in older women lies in exploring the effects of both short- and long-term reductions in ovarian hormones on the development of symptoms and disease. Of particular interest are the effects of reduced levels on the development of diseases that may have along latency period or that are temporally removed from the menopause.

As the proportion of older women in the population continues to grow, the need to focus on the prevention of morbidity and disability increases as well. Such prevention will require an understanding of the potential consequences of modifying lifestyle variables (e.g., nutrition, exercise, smoking cessation) and the identification and use of appropriate intervention strategies (both hormonal and nonhormonal). Identifying appropriate strategies requires substantially improved knowledge of the natural history and sequelae of the menopause, and of the role of exogenous and endogenous estrogens and progesterones in the etiology and prevention of disease.

A more complete understanding of the physiological consequences of reduced ovarian hormone levels requires research protocols and subject selection procedures that can assess the effects of age and type of menopause (natural or surgically induced by bilateral oophorectomy) on intermediate biological variables and, ultimately, on the risk of disease. Sensitivity to the potential role of age and cause of menopause is also important in assessing the effects of hormone therapy: there may be marked differences between younger and older women in tissue-specific responses to hormonal therapy and in the benefits to be realized from such treatment in oophorectomized women compared with those who experience a natural menopause. Other significant covariates include the time elapsed since the menopause before commencement of hormonal therapy and a woman's prior history of hormone use, especially oral contraceptives.

RANDOMIZED CLINICAL TRIALS ARE NEEDED

Thus far, estrogen therapy is the most efficacious treatment modality for the amelioration of menopausal symptoms and the prevention of osteoporosis. Epidemiologic and animal studies strongly suggest ET has the potential to reduce morbidity and mortality from cardiovascular disease. But in the absence of randomized clinical trials, a definitive, unbiased assessment of the beneficial and adverse effects of estrogen with and without progestin in preventing or ameliorating cardiovascular disease is not possible. Objective evaluation of the risks is likewise precluded. Moreover, there are virtually no studies on the effects of long-term ET with progestin—a treatment regimen sometimes recommended for nonhysterectomized women.

Randomized trials to assess the health effects of hormone therapy must be large enough to detect protective effects against cardiovascular disease and osteoporosis (or fractures); in addition, they must be of long enough duration to detect effects that may occur only after relatively long periods (10 years or more) of use. Both the use of unopposed estrogen and of combination therapy should be assessed to identify any differential protective or risky effect. In addition to cardiovascular disease and osteoporosis, the risk of which may be reduced by hormone use, other outcomes that reportedly increase with hormonal therapy-breast cancer, endometrial and other gynecologic cancers, and cerebrovascular disease are in need of evaluation. Also worth studying (on the risk side of the benefit-risk ratio) is hysterectomy and the morbidity associated with that procedure.

Disease incidence and mortality should be assessed. Comparisons of total morbidity and total mortality among the treatment groups are important to determine overall risks and benefits. Yet an "overall' comparison is insufficient. Rather, comparisons should be made among various age groups, because the benefit-risk ratio may be quite different at various ages. For example, the major benefits of

hormone therapy may be more substantial for older women, while the major risks may increase for those who are younger; such an outcome would influence one's interpretation of the benefit-risk ratio for hormone therapy. As these results are obtained, it will become possible to calculate the costs of treatment for each group and to compare them with the benefits and risks.

For both cardiovascular disease and osteoporosis, a protective effect of estrogen therapy appears to be related to the duration of use: women may have to take the drugs for relatively long periods (10 to 15 years) to prevent disease. In addition, because the adverse effects of hormone therapy on the risk of breast cancer also may not become apparent until decades later, trials must be of sufficient duration to detect any effects that may occur. A large study of nurses showed that those nurses who had ''ever used" hormones were no more likely to develop breast cancer than women who had never used them; "current users, " on the other hand, had a higher incidence. These findings are interpreted to mean that hormone therapy accelerates the development of breast cancers in some women and that those cancers are detectable soon after therapy begins. Furthermore, the findings indicated such cancers appear to be less malignant than most breast cancers. The nurses' study, however, was a general investigation into women's health; other studies are needed to examine each of these hypotheses in a more focused way.

Besides the issue of sufficient duration of the research, experimental design must be carefully considered and treatment regimens carefully constructed. Hormone therapy, particularly combination therapy, can have unpleasant side effects. To encourage adherence to combination therapy in study groups will require substantial attention; otherwise poor adherence could diminish the ability of a trial to detect any effects from long durations of use. For these reasons, randomized trials of hormone therapy will be neither easy nor inexpensive to conduct.

Because estrogen and progesterone affect a host of tissues throughout the body, future research should foster an integrated, multidisciplinary approach such as that used in the National Institutes of Health (NIH) current Postmenopausal Estrogen/Progestin Intervention (PEPI) Trial with its multiorgan system evaluation of risk factors and intermediate points of disease. Randomized clinical trials of this kind, with their long-term followup studies and assessments of multiple morbidity and mortality endpoints, are crucial to an objective evaluation of risks and benefits. Through the PEPI trial, NIH is investigating the effects on intermediate endpoints of different regimens of combined therapy used for 3 years each.

REFINING ESTIMATES OF INDIVIDUAL RISKS AND BENEFITS FROM HORMONE THERAPY

If women and their physicians had a better understanding of predictors of risk, they could make more informed decisions about interventions related to menopausal symptoms, cardiovascular disease, osteoporosis, and gynecologic and breast cancer. Few other recently introduced medical interventions have as great a potential for affecting morbidity and mortality as does hormone therapy. Some risks are reduced, some are increased, and some remain uncertain, and these data continue to be interpreted differently by various scientific, medical, and consumer groups.

Women who seek treatment for menopausal symptoms and the doctors who treat them are more likely to advocate a treatment approach, whereas those who report few symptoms are more sympathetic to the avoidance of medical interventions. The most common diagnosis mentioned in relation to prescription of estrogen is menopausal symptoms. Researchers are becoming increasingly convinced that loss of ovarian hormones plays a significant role in the etiology of age-related pathology in women, yet the relationships are not clear. Although cessation of the menses is not a disease, many researchers and clinicians believe that the resulting decrease in ovarian hormone production can lead to disease in some women, thereby justifying preventive intervention through hormone therapy, either as estrogen alone or in combination with a progestin.

The debate over hormone therapy focuses on whether it should be used to treat menopausal symptoms for a short period of time, thereby reducing any risks associated with long-term treatment, or whether it should also be used to prevent future disease, thereby requiring longer treatment that could increase the risk of cancer.

For most women, the short-term use of hormones has known benefits (e.g., relief of hot flashes) and some known risks (e.g., endometrial cancer); long-term use has known risks (again, endometrial cancer) and benefits (e.g., prevention of osteoporosis and cardiovascular disease), as well as unknown outcomes (e.g., risk of breast cancer). To prevent osteoporosis and cardiovascular disease, estrogen must be taken for long periods of time, possibly until death. The impact of such long-term use is not clear. The effects of adding a progestin to the treatment are even less clear, and in this case, the dilemma is sharper.

Should women be treated with a drug to prevent a disease they might never get? Across-the-board prescriptions for hormone therapy may, in the aggregate, reduce morbidity and mortality. It is a practice that must be questioned, however, when some individuals will be placed at higher risk, even though others benefit. Risks and benefits must be considered individually.

Although the menopause can be expected to occur naturally around age 50, many women, as many as 37 percent, will experience the symptoms of menopause at an earlier age owing to removal of their ovaries through hysterectomy. Oophorectomized women are also at higher risk for diseases of aging such as osteoporosis and cardiovascular disease. In this group of women, appropriate treatment for the severe, sudden symptoms of the menopause following hysterectomy is a critical issue, and not as simple as short-term relief. For many women, the use of estrogen will be an essential postoperative therapy that may have to be continued for 20 to 30 years.

Approximately 15 percent of women who are eligible for hormone therapy are now receiving it. This means 85 percent of eligible women either do not want or need the therapy, or do not know about it. There is little argument about the benefits of estrogen for the alleviation of the most uncomfortable symptoms of the menopause, specifically, hot flashes. Approximately 15 percent of women report symptoms so disruptive that they consider them disabling and consequently seek treatment. Although most women experience hot flashes, most do not seek treatment. There have been no studies to document the number of women who suffer severe symptoms and either do not choose or do not know how to seek treatment.

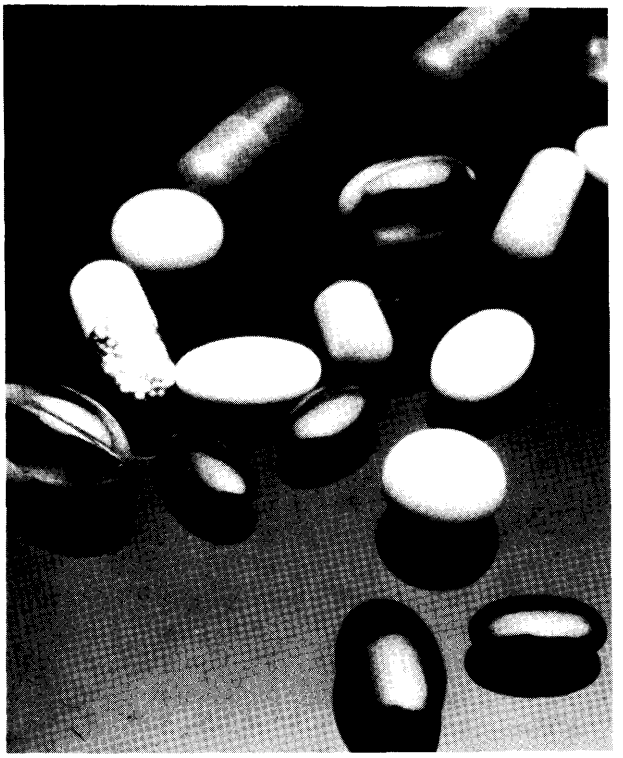


Photo credit: National Cancer Institute

Deciding which therapy to undergo, estrogen or combined, is a sometimes oonfusing proposition.

There are a number of reasons women may not elect to use hormone therapy. First, it is an optional drug treatment; a woman's life is not immediately threatened if she 'does without it.' Second, women who discontinue hormone therapy after a few years may experience a "rebound effect,' or return of symptoms, and bone loss again accelerates. Some women may want to put the experience of hot flashes behind them more quickly by avoiding treatment. Third, side effects such as cramping, water retention, and withdrawal bleeding may be a disincentive to continue or even to seek treatment. Fourth, and perhaps the most critical, in considering long-term use of hormones, women may fear cancer more than heart disease. Discerning how the epidemiologic data refine and define relative versus absolute risk is complex, and interpretation of risks depends on how women define ***quality of life (see*** box **6-A).**

Quality-of-life issues must be decided by each woman. What is a disability to some women maybe merely a nuisance to others. Research has demon-

Box 6-A-Comparing Risks and Benefits

In late 1991, convincing data from the Nurses' Health Study described the apparently protective effect of postmenopausal estrogen replacement therapy in relation to cardiovascular disease. In discussing the findings of the study as they relate to the competing risks and benefits posed by hormone therapy, Lee Goldman and Anna N.A. Tosteson concisely articulated the quandaries of competing risks and benefits:

> A fundamental and not widely appreciated principle of epidemiology is that relative risks should not be confused with absolute risks. A twofold increase in the risk of a rare event may not be nearly as important as a 10 percent decrease in the risk of a common event. Consider the following: from the age of 65 through the age of 74, a woman has about a 6 percent risk of dying from ischemic heart disease, a 1 percent risk of dying from breast cancer, a 0.6 percent riskof dying from complications related to a hip fracture, and if her uterus has not been removed, a 0.4 percent risk of dying from endometrial cancer. If the sum of epidemiologic evidence is approximately accurate, what will estrogens do to those 10-year risks? A 60 percent reduction in the risk of hip fracture will lead to an absolute benefit (a 0.36 percent absolute reduction) that is roughly equivalent to the absolute increase (0.30 percent) in the risk of breast cancer attained with a relative increase in that risk by 30 percent. After these two competing factors have canceled each other out what other issues are we left with? First, hip fracture is only one of the many complications of osteoporosis, so there is substantial additional benefit from estrogen in this regard. Second estrogens relieve perimenopausal symptoms, although it is uncertain how women will value this benefit as compared with the inconvenience of estrogen-related bleeding.
>
> Perhaps the most intense debates relate to heart disease and endometrial cancer. A 40 percent reduction in a 6 percent risk of death from ischemic heart disease would result in a substantial benefit (a 2.4 percent absolute reduction in mortality), A sixfold increase in a 0.4 percent risk of death from endometrial carcinoma would result in a nearly equivalent 2.4 percent increase in the absolute risk; however, epidemiologic data suggest that mortality is only about 10 percent as high for endometrial cancer associated with the use of exogenous estrogen as for "naturally occurring" disease, presumably because of earlier detection brought on by symptoms and closer observation. If this much lower risk is the true one, a major reduction in the incidence of ischemic heart disease with postmenopausal estrogen-replacement therapy would greatly outweigh all other effects on life expectancy.

What individual women would do with this type of analysis is not clear. Numerical risks, although quantitatively equal, may be perceived as qualitatively different. In addition, women will make decisions based on their family history (or genetic risk) of disease and their own life experiences (e.g., a friend who dies of breast cancer, an elderly neighbor hospitalized for repeated fractures). Risk assessment, even if sharpened over time, must be considered in the light of risk perception when evaluating the current and future use of hormone therapy by postmenopausal women.

SOURCE: L.Goldman and A.NA. Tosteson, "Uncertainty About Postmenopausal Estrogen: Time for Action Not Debate," ***New England Journal of Medicine 325(11):800-802, 1991.***

strated that women give high priority to the short-term impact of hormone therapy on their lives and do not make their decisions based on the risks of morbidity and mortality. In effect, they afford greater weight to considerations of quality of life over quantity of life.

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 ET or CHT, projections of risks and benefits are bound to be erroneous. The discrepancy between the stated prescribing philosophies of physicians and the actual use of hormone therapy suggests the menopausal woman may be assuming the role of informed consumer rather than accepting without question the treatments prescribed by her doctor.

CLARITY IN PRESCRIBING PRACTICES AND LABELING

There is no official standard or protocol for administering or prescribing combination therapy. Moreover, no conclusive studies have been performed to indicate which regimen (opposed or unopposed estrogen) is most beneficial. Finally, no studies have been done that meet adequate design, duration, and sample size requirements to determine conclusively the risks and benefits of long-term use of combined therapy.

At present, the Food and Drug Administration (FDA) has approved no combination estrogen and progestin product for sale in the United States, although some are undergoing clinical testing. In contrast, several combination products are available

in Europe. Regimens that prescribe separate estrogen and progestin products are common both here and in Europe. Anecdotal information indicates that as many as 19 different regimens are prescribed in the United States and more than 100 are prescribed in Europe. This variety means that women face a confusing range of options and often conflicting recommendations.

In 1990, total sales of estrogen products were close to $460 million. Premarin, the top-selling estrogen, is the fourth most prescribed drug in the United States. Estrogen products approved for treatment of the menopause have labeled indications for the treatment of vasomotor symptoms or hot flashes, and Premarin and Estraderm have been approved for the prevention of osteoporosis. None of the progestins used in CHT have been approved by the FDA for treatment of menopausal symptoms, but their use for this purpose is common medical practice. The FDA is considering changes in labeling of the hormones that would reflect the cardioprotective effect of unopposed estrogen use and whether to recommend the use of combined estrogen and progestin therapy for women with intact uteri.

The approval of generic forms of estrogens also remains a topic of debate within the industry and at the FDA. Until the spring of 1991, generic conjugated estrogens were on the market. In that year, however, the FDA withdrew approval for these compounds on the basis of demonstrated bioinequivalence.

Although Premarin is relatively inexpensive (approximately $14 for a month's supply), monitoring programs to screen for cancers of the breast and uterus are not. If hormone therapy is to be widely administered, consideration of costs must include all relevant expenditures.

INVESTIGATING ALTERNATIVES TO HORMONE THERAPY

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; consequently, they and others seek nonhormonal, nondrug treatments for these symptoms. As with any drug, hormones are not without side effects, a circumstance that may dissuade some women from either starting or maintainingg treatment. There is limited research on alternatives to hormone therapy-i.e., other hormones, nonhormonal drugs, and nondrug products—and large-scale clinical investigation of 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 is as effective as estrogen). Anecdotal evidence indicates that many women try "home remedies" for the alleviation of menopausal complaints. It is not clear how effective these remedies are and if so, for what severity of complaint.

Convincing research into alternatives to hormone therapy is limited. In addition, the true contributions to cardiovascular disease and osteoporosis of such factors as lifestyle-e. g., diet, exercise, smoking—socioeconomic status, race, and genetic predisposition deserve further investigation. Better understanding of these areas could identify more effective alternatives to hormone therapy.

PROFESSIONAL AND PUBLIC EDUCATION

Many studies have shown that women feel disenfranchised from the health care system and contend that providers do not listen to them. They also report having inadequate information on which to base a decision concerning hormone therapy. Patients and health care professionals alike tend to know relatively little about the menopause and about the risks of conditions that may be associated with it. There is no consensus within the medical community about even the definition of the menopause, let alone the risks and benefits associated with hormone therapy, and there is little information about a woman's 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.

Physicians and women need more and better resources to learn about the menopause and hormone therapy. Even the limited information now available is not well distributed to women and their physicians. For example, better informed decisions would flow from more information about the menopause and potential symptoms; about changes in the risks of cancer, heart disease, and osteoporosis that occur after menopause and with increasing age; about the pros and cons of hormone therapy; and about the role

of diet, nutrition, and exercise programs in health promotion and disease prevention.

PROSPECTUS

An enhanced quality of life for older women depends on improvements in early diagnosis, which in turn require the identification of risk factors (some of which are entirely different from those for men) and the development of strategies for prevention and therapy. It also requires objective findings from well-controlled studies to determine who will benefit and how, for how long a particular intervention (either hormonal or nonhormonal) will be effective, and how such interventions affect different body systems and organs. Better quality of life for women after the menopause also requires increased understanding of women's physiology in general. And it requires the dissemination of badly needed information relating to the menopause to physicians and their patients.

Appendixes

Appendix A
The Menopause in Japan

Examination of the experiences of menopausal women in a non-Western culture offers alternative perspectives to North American attitudes toward the menopause. However, this is not necessarily inappropriate. Research on the menopause in Japan reinforces the assumption that there is universal menopausal experience.

Japanese women, with a current life expectancy of more than 82 years, live longer than anyone else in the world (2). But such longevity is a recent trend: in 1940, the average age at death for Japanese women was 49.6 years (5). Thus, the population of postmenopausal women in Japan historically has been small, and the limited attention it has received within the Japanese medical community is not surprising. *Konenki", the* Japanese term that describes the menopause, was created at the turn of the century under the influence of German medicine ***(5).*** ***Care*** and treatment for Japanese menopausal women has begun to receive more attention recently; at the urging of the Japanese gynecological association, the Japanese Government approved the group of symptoms labeled "climacteric syndrome" for inclusion in the list of diseases covered under the Japanese socialized medicine system (5).

The Japanese health care heritage reflects a long-standing interest in preventive medicine as well as the more recent influences of, first, German and, subsequently, American medical thinking and practices (4). The current Japanese medical system arose from a historical arrangement in which physician payments were contingent on the continuing good health, not the illness, of the patient (4). Concern with a growing elderly population, cultural commitment to prevention of disease, and familiarity with Western medical research findings might lead one to expect that hormone therapy would be widely and increasingly used by menopausal Japanese women. Yet, interestingly, hormone therapy is only marginally prescribed by the Japanese medical profession (2). One study conducted in 1974 concluded that only 2.6 percent of Japanese women aged 45 to 55 were currently using replacement hormones, and followup studies have revealed no significant increase in use (l).

This low level of utilization has been attributed to the interaction of a complex set of factors: patterns of morbidity and mortality among elderly Japanese, culturally constructed expectations and subjective experiences associated with the end of menstruation, ideology about who is susceptible to distress during menopause, and patient and physician attitudes toward the use of physicians and medication (3,6).

The causes of death and disability among Japan's elderly are strikingly different from those of the West. Currently, as it has been for more than 30 years, the primary cause of death for both sexes in Japan is cerebrovascular disease (3). Although breast cancer, cardiovascular disease, and osteoporosis are predominant concerns for aging North American women, incidence of these conditions among Japanese women is relatively low, although rates for breast cancer and heart disease have been increasing slightly (3). The World Health Organization estimates that the mortality rate for coronary heart disease in Japanese women is about one-quarter the rate for American women, and the mortality rate from breast cancer is between one-quarter and one-third that in North America (3). Reliable data on rates of osteoporosis are lacking, but estimates are that, despite the lower average bone mass and greater longevity of Japanese women in comparison to Caucasian women, only about half as many Japanese women are affected by osteoporosis (3).

Such variations in morbidity and mortality are poorly understood at this time, but it is thought that they arise from a complex combination of contributing factors including dietary, genetic, and, possibly, cultural differences (3). Particular attention to lifestyle, rather than genetic, protective factors against cardiovascular disease may be justified in light of the fact that the death rates from cardiovascular disease for Asian Americans over 45 years of age-while at least 60 percent lower than the rate for Caucasian Americans of the same age group--are higher than those observed in Japan (8). These differences in the incidence of various chronic diseases in later life may account in part for the lower rates of use of hormone therapy for prevention in Japan, but questions remain about its lack of use by the Japanese to combat menopausal symptoms.

The hot flash, which is discussed in detail elsewhere in this report, is a common experience of Western menopausal women, affecting at least 50 percent of American women at some time during the menopause (7). But a menopausal woman's experience of a hot flash has been found to be highly individualized; studies monitoring the measurable skin temperature elevation and luteinizing hormone secretion occurring during hot flashes report that women do not always report corresponding subjective experiences (9).

Relatively few menopausal Japanese women report having hot flashes (6). In a survey of 1,141 nonhysterectomized Japanese women aged 45 to 55, researchers recorded menopausal symptoms in the preceding 2 weeks based on self-reporting (6). Only 9.5 percent of the

women surveyed reported a hot flash in the preceding 2 weeks, and only 3.6 percent reported night sweats during the same period (6).

A study of 1,310 women, 45 to 55 years of age, in Manitoba, Canada, reported that 30.9 percent had experienced a hot flush in the preceding 2 weeks and 19.8 percent had experienced night sweats (4). Nearly 20 percent of Japanese women acknowledge having a hot flash at some point in the past; by contrast, 64.6 percent of Canadian women who were surveyed have experienced the symptom (4). Moreover, Japanese women encountered fewer difficulties with hot flashes than did Canadian women (4). These differences may be related to, or possibly account for, the fact that the Japanese language has no direct translation for the term itself-despite the Japanese sensitivity to bodily states (3).

Differences in symptomatology between Japanese and North American women are not limited to the reported incidence of hot flashes; Japanese women also report the following with greater frequency than their American counterparts: graying hair, changes in eyesight, short-term memory loss, headaches, shoulder stiffness, dizziness, unspecified aches and pains, and lassitude (2). To fully appreciate the implications of these variations, it is helpful to examine cultural differences. *Konenki", the* Japanese equivalent of the menopause, is commonly understood to be associated with aging; it is believed to be a gradual transition beginning at age 40 or 45 and entails an entrance into the latter stage of the life cycle(2). Distressing symptoms of the menopause are not usually linked in the Japanese mind to the cessation of the menses (3). Indeed, the biological transition has been shown to be inconsequential to Japanese women: 24 percent of self-reported postmenopausal Japanese women said that they had no sign of *konenki,* indicating that, for them, the end of menstruation is not a significant marker in comparison to the external signs of aging (3).

Such cultural differences extend to expectations about who is susceptible to distress at the menopause. One view of menopause symptoms in Japan is that such a' 'disease' is a result of modernity, "a luxury disease affecting women with too much time on their hands who run to doctors with their insignificant complaints" *(2).* Cultural dispositions of this kind toward menopausal distress may contribute to the low incidence of medical intervention during this phase of a Japanese woman's life. As revealed by the symptomatological differences, however, the reason for nontreatment is not clear-cut.

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Appendix B
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Appendix C
Acronyms and Glossary

Acronyms

ACOG —American College of Obstetricians and Gynecologists
ADAMHA-Alcohol, Drug Abuse, and Mental Health Administration
ARC —Arteriosclerosis Research Center
CHT -combined hormone therapy
BLSA —Baltimore Longitudinal Study of Aging
CRISP -Computer Retrieval of Information on Scientific Projects
CVD -cardiovascular disease
DES -diethylstilbestrol
DESI —Drug Efficacy Study Implementation (program)
ERT -estrogen replacement therapy
ET -estrogen therapy
FDA —Food and Drug Administration
FSH —follicle-stimulating hormone
GAO -General Accounting Office
GnRH —gonadotropin-releasing hormone
HDL —high-density lipoprotein (cholesterol)
HRT —hormone replacement therapy
ICD —Institute and Center Director
LDL —low-density lipoprotein (cholesterol)
LH —luteinizing hormone
LRC —Lipid Research Clinic
MPA —medroxyprogesterone acetate
MRH —menstrual and reproductive health
NCI —National Cancer Institute
NCNR —National Center for Nursing Research
NCRR —National Center for Research Resources
NDTI —National Disease and Therapeutic Index
NHLBI —National Heart, Lung, and Blood Institute
NIA —National Institute on Aging
NIAAA —National Institute on Alcohol Abuse and Alcoholism
NIAMS —National Institute of Arthritis, Musculoskeletal and Skin Diseases
NICHD —National Institute of Child Health and Human Development
NIDA —National Institute on Drug Abuse
NIDDK —National Institute of Diabetes and Digestive and Kidney Diseases
NIDR —National Institute for Dental Research
NIH —National Institutes of Health
NIMH —National Institute of Mental Health
NPA —National Prescription Audit
OTA —Office of Technology Assessment
PDR —Physician's Desk Reference
PEPI —Postmenopausal Estrogen/Progestin Interventions Trial
PHS —Public Health Service
PMS —premenstrual syndrome
Rx —prescription
USP —United States Pharmacopoeia
VLDL —very low density lipoprotein (cholesterol)
WHR —waist-to-hip ratio

Glossary

Amenorrhea: Absence or abnormal stoppage of the menses.

Androgen/androgenic: Any substance, e.g., androsterone and testosterone, that stimulates male characteristics.

Angiogram: A picture of a blood vessel filled with contrast medium.

Anovulular: Not associated with ovulation.

Atherosclerosis: A disease characterized by the thickening and loss of elasticity of the arterial walls in which atheromas (a mass of plaque of degenerated thickened arterial intima) containing cholesterol, lipoid material, and lipophages are formed within the intima and inner media of large and medium-sized arteries.

Atrophy: A wasting away; a diminution in the size of a cell, tissue, organ, or part.

Beta-blockers: A class of drugs that block cardiac beta receptors.

Bilateral oophorectomy: Surgical removal of both ovaries.

Bioavailability: The degree to which a drug or other substance becomes available to the target tissue after administration.

Bioequivalence: The requirement that a generic product include the same therapeutic ingredient, and that its rate and extent of absorption be the same as the innovative product.

Biofeedback: The provision to a person of visual or auditory evidence of the status of an autonomic body function, e.g., the sounding of a tone when blood pressure is at a desirable level so that the person may exert control over the function.

Cardiovascular disease: Diseases pertaining to the heart and blood vessels.

Case-control studies: An epidemiologic study design that involves two groups, those that have the disease or condition being studied (the cases) and those that do not (the controls), which are compared to a past or existing characteristic relevant to the etiology of the disease or condition.

Central nervous system: The part of the nervous system that in vertebrates consists of the brain and spinal cord, to which sensory impulses are transmitted and from which motor impulses pass out, and that supervises and coordinates the activity of the entire nervous system.

Cholesterol: A sterol (fatty substance) produced by all vertebrate cells, particularly the liver, skin, and intestine, and found most abundantly in nerve tissue. See also *high-density lipoprotein cholesterol* **and low-***density lipoprotein cholesterol.*

Climacteric: The syndrome of endocrine, somatic, and psychic changes occurring at the end of the female reproductive period (menopause).

Combined hormone therapy (CHT): The use of estrogen combined with progestin for the treatment of menopausal symptoms, e.g., hot flashes, and/or the prevention and treatment of osteoporosis; progestin opposes the carcinogenic effects of estrogen on the endometrium. Also known as hormone replacement therapy (HRT).

Conjugated estrogens: The sodium salts of the estrogenic compounds, primarily estrone and equilin, that are present as sulfate ester conjugates in pregnant mare urine.

Contraindication: Any condition that renders a particular line of treatment improper or undesirable.

Coronary perfusion: The pumping of a fluid through the heart by way of an artery.

Corpus luteum: A yellow glandular mass in the ovary formed by an ovarian follicle that has matured and discharged its ovum.

Cyclic regimen: Interrupted episodes with ongoing medication.

Depomedroxyprogesterone acetate (depo-MPA): A form of progestin.

Diethylstilbestrol (DES): A synthetic estrogenic compound used to treat menopausal symptoms, vaginitis, and suppressed lactation.

Dyspareunia: Difficult or painful coitus/intercourse in women.

Dysuria: Painful or difficult urination.

Endogenous: Produced within or caused by factors within the organism.

Endometriosis: The presence of endometrial tissue (the normal uterine lining) in abnormal locations such as the fallopian tubes, ovaries, or the peritoneal cavity.

Endometrium: The mucous membrane lining the uterus.

Endothelium: The layer of epithelial cells that lines the cavities of the heart and of the blood and lymph vessels, and the serous cavities of the body.

Epidemiology: The study of the relationships of various factors determining the frequency and distribution of diseases in the human community.

Equine estrogen: Estrogen pertaining to, characteristic of, or derived from the horse.

Erythema: Redness of skin due to congestion of the capillaries.

Estradiol: The most potent naturally occurring estrogen in humans.

Estrogen: A generic term for estrus-producing compounds; the female sex hormones including estradiol, estriol, and estrone. In humans, the estrogens are formed in the ovary, adrenal cortex, testis, and fetoplacental unit and are responsible for female secondary sex characteristic development; during the menstrual cycle, they act on the female genitalia to produce an environment suitable for fertilization, implantation, and nutrition of the early embryo. Estrogen is used as a palliative in postmenopausal cancer of the breast and in prostatic cancer, as oral contraceptives, and for relief of menopausal discomforts.

Estrogen deficiency: The notion that menopause causes an estrogen deficiency that requires replacement.

Estrogen replacement therapy (ERT): See *estrogen therapy.*

Estrogen therapy (ET): The use **of estrogen for the relief of menopausal symptoms, e.g., hot flashes, and/or the prevention and treatment of osteoporosis. Also known as estrogen replacement therapy (ERT).**

Estrone: An estrogen isolated from pregnancy urine, the human placenta, and palm kernel oil, and also prepared synthetically.

Etiology: The science dealing with causes of disease.

Exogenous estrogen: Estrogen that is not produced within the body but is provided by other means, e.g., tablets, injection, cream.

First-pass hepatic effect: See *hepatic effect.*

Follicle: The structure on the ovary surface that nurtures a ripening oocyte. At ovulation the follicle ruptures and the oocyte is released. The follicle produces estrogen until the oocyte is released, after which it becomes a yellowish protrusion on the ovary called the corpus luteum.

Follicle-stimulating hormone (FSH): A pituitary hormone, also known as a gonadotropin, that helps to stimulate hormone and gamete production by the ovaries and testes.

Follicular depletion: The gradual depletion of follicles in the ovary.

Food and Drug Administration (FDA): The government agency responsible for drug approval.

Germ cell: Any cell of an organism whose function is reproduction, e.g., gametes (ova and spermatozoa).

Gonadotropin: A substance that has a stimulating effect upon the gonads, especially the hormone secreted from the anterior pituitary.

Gonadotropin-releasing hormone (GnRH): The hormone released from the hypothalamus that causes secretion of gonadotropins from the pituitary gland.

Healthy user effect: A phenomenon observed in epidemiologic studies in which subject participants exhibit lower incidence of morbidity or mortality than the general population because they are generally in good health while the less healthy either choose not to participate in the study or are excluded.

Hemostasis: The arrest of bleeding, whether by the physiological properties of vasoconstriction and coagulation or by surgical means.

Hepatic effect: Pertaining to the liver; the metabolism of estrogen by the liver.

Hepatobiliary: Related to the gallbladder.

High-density lipoprotein cholesterol (HDL): A class of cholesterol; low levels of HDL are associated with a decreased risk of heart attack.

Hormone: A chemical substance produced in the body that has a specific regulatory effect on the activity of certain cells or a certain organ or organs.

Hormone replacement therapy (HRT): See *combined hormone therapy.*

Hormone therapy: Collectively and generally, this term describes either estrogen therapy or combined hormone therapy when a distinction is not necessary. See *estrogen therapy, combined hormone therapy.*

Hot flash: Sudden sensations of heat and flushing of the face and torso.

Hyperinsulinemia: Excessive secretion of insulin.

Hypermenorrhea: Excessive menstrual bleeding, but occurring at regular intervals and being of usual duration.

Hyperplasia: Abnormal increase in the number of normal cells in normal arrangement in an organ or tissue, which increases its volume.

Hypertension: High arterial blood pressure; it may have no known cause, or it may be associated with other diseases.

Hypertriglyceridemia: An excess of triglycerides in the blood.

Hypomenorrhea: Diminution of menstrual flow or duration.

Hypothalamus: The part of the diencephalon forming the floor and part of the lateral wall of the third ventricle; anatomically, it includes the optic chiasm, mammillary bodies, tuber cinereum, infundibulum, and pituitary gland, but for physiological purposes the pituitary gland is considered a distinct structure.

Hysterectomy: Excision of the uterus.

In vitro: Literally "in glass"; pertaining to a biological process or reaction taking place in an artificial environment, usually a laboratory.

In vivo: Literally "in the living"; pertaining to a biological process or reaction taking place in a living cell or organism.

Involutional melancholia: A prolonged psychotic reaction occurring in late middle life, characterized by depression and paranoid ideas, also known as involutional psychosis.

Lactation: The secretion of milk

Life expectancy: An expected number of years of life based on statistical probability.

Low-density lipoprotein (LDL) cholesterol: A class of cholesterol; high levels of LDL are associated with a greater risk of heart attack.

Luteinizing hormone (LH): A gonadotropin that, along with FSH, stimulates and directs hormone and gamete production of the ovaries and testes.

Medicalization: The practice of treating or defining people's experiences as medical problems.

Medroxyprogesterone acetate (MPA): A form of progestin.

Menopausal syndrome: Symptoms associated with menopause, e.g., hot flashes, vaginal dryness, osteoporosis.

Menopause: Cessation of menstruation; the immediate postreproductive phase of a woman's life, when menstrual function ceases due to failure to form ovarian follicles and ova.

Menorrhagia: Excessive menstruation.

Menses: The monthly flow of blood from the female genital tract.

Menstruation: The cyclic physiological discharge of blood from the nonpregnant uterus, occurring usually at approximately 4-week intervals during the reproductive period in female humans.

Metrorrhagia: Uterine bleeding, usually of normal amount, occurring at completely irregular intervals, the period of flow sometimes being prolonged.

Moieties: Any part or portion of a molecule.

Morbidity: The condition of being sick the sick rate; the ratio of sick to well persons in a community.

Morphology: The science of organic forms and structure.

Mortality: The ratio of actual deaths to expected deaths; the ratio of the total number of deaths to the population of a specified area in a given time period, generally figured in terms of number of deaths per 1,000,10,000, or 100,000 of population.

Natural estrogen: An estrogen that is derived from natural sources, e.g., conjugated equine estrogens.

Natural menopause: Menopause that occurs as a natural part of the aging process, not surgically induced.

Neuroendocrine stimulation: Stimulation related to the interactions between the nervous and endocrine systems.

19-nortestosterone: A form of progestin.

Norethidrone: A progestational agent similar in action to progesterone.

Norethidrone acetate: A form of progestin.

Nulliparity: The state of being a woman who never has borne a viable child.

Observational studies: An epidemiologic study in which there is no artificial manipulation of the study factor.

Oligomenorrhea: Abnormally infrequent menstruation.
Oophorectomy: Excision of one or both ovaries.
Opposed estrogen: Estrogen that is used in conjunction with progestin.
Osteoblast: A cell arising from a fibroblast, which, as it matures, is associated with bone production.
Osteopenia: Any condition involving reduced bone mass.
Osteoporosis: Abnormal rarefaction of bone; it maybe idiopathic or occur secondary to other diseases.
Ovaries: Either of the paired female sex glands in which ova are formed.
Pathophysiology: The physiology of discorded function.
Percutaneous: Performed through the skin.
Perimenopause: The time around the menopause.
Peripheral conversion: Conversion of estrogen outside of the liver, in peripheral tissues.
Peripheral nervous system: The autonomic nervous system, the cranial nerves, and the spinal nerves including associated receptors.
Pharmacodynamics: The study of the actions of drugs on living systems.
Pharmacokinetics: The rate of change in a physical or chemical system, specifically in relation to drugs.
Pituitary gland: A gland at the base of the brain that secretes a number of hormones related to reproduction.
Pituitary gonadotropins: Substances, released by the pituitary, that act to stimulate the gonads.
Platelets: Any of the disk-shaped structures in the blood of all mammals, chiefly known for their role in blood coagulation.
PMS: See *Premenstrual syndrome.*
Postmenopause: The period of time after the menopause.
Premature ovarian failure: Condition characterized by the failure to ovulate before the normal age of menopause.
Premenopause: The stage of life before menstruation stops.
Premenstrual syndrome: The pattern of symptoms related to the menstrual cycle.
Progesterone: The steroid hormone produced by the corpus luteum, adrenal cortex, and placenta which serves to prepare the uterus for reception and development of the fertilized ovum by inducing secretion in the proliferated glands. A synthetic preparation is used in the treatment of functional uterine bleeding, menstrual cycle abnormalities, and threatened abortion.
Progestin: Originally, the crude hormone of the corpus luteum; it has since been isolated in pure form and is now known as progesterone. Certain synthetic and natural progestational agents are called progestins.
Puerperal: Pertaining to a woman who has just given birth to a child.
Randomized trials: An epidemiologic experiment in which subjects are randomly allocated into groups, the "study" and "control" groups, to receive or not to receive an experimental preventive or therapeutic procedure, e.g., a drug.
Relative risk: In epidemiology, the ratio of the incidence of, or mortality from, a disease in a population exposed to the factor under consideration to the corresponding rate in a population not so exposed.
Releasing factors: Substances that act to release hormones.
Selection bias: A distortion in the estimate of effect resulting from the manner in which subjects are selected for a study population.
Serum lipid profiles: A quantitative representation of the level of serum lipids.
Serum triglycerides: Esters formed from glycerol and one to three fatty acids; fats and oils are triglycerides.
Steroid hormones: Hormonal compounds containing four carbon rings interlocked to forma hydrogenated cyclopentophenanthrene-ring system.
Subarachnoid hemorrhage: A form of stroke characterized by bleeding between the pia mater and arachnoid of the brain.
Surgical menopause: Menopause following the surgical removal of the ovaries.
Symptomatology: The combined symptoms of a disease.
Synthetic estrogen: A synthetically produced/manufactured estrogen product.
Systemic circulation: Channels through which nutrient fluids of the body flow; often restricted to the vessels conveying blood.
Testosterone: A hormone secreted by the interstitial cells of the testes, which functions in the induction and maintenance of male secondary sex characteristics; testosterone and its cypionate, enanthate, and propionate esters are used in palliative therapy in inoperable carcinoma of the female breast and certain gynecologic conditions.
Thromboembolitic disease: Disease related to the obstruction of blood vessels.
Thrombosis: The formulation or presence of a solid mass formed in the living heart or vessels from constituents of the blood.
Thyroid: An endocrine gland consisting of two lobes, one on each side of the trachea, joined by a narrow isthmus, producing hormones (thyroxine and triiodothyronine) that require iodine for their elaboration and that are concerned in regulating metabolic rate; it also secretes calcitonin.
Trabecular: Of or pertaining to a supporting or anchoring strand of connective tissue, e.g., a strand extending from a capsule into the substance of the enclosed organ.
Transdermal: Through the skin.

Transmenopausal: Occurring across the time period of the menopause.

Unopposed estrogen: Estrogen used alone.

Urethra: A passage through which urine is discharged from the bladder to the exterior of the body.

Urinary stress incontinence: Involuntary escape of urine due to strain on the orifice of the bladder, as in coughing or sneezing.

Urodynamics: A process that evaluates characteristics of the urine stream and the pelvic musculature, and the activity of the bladder.

Uterus: The hollow muscular organ in the female in which the fertilized ovum normally becomes embedded and in which the developing embryo and fetus are nourished. Its cavity opens into the vagina below and into a uterine tube on either side.

Vagina: The canal in the female, from the vulva to the cervix uteri, that receives the penis in copulation and is the birth canal.

Vaginal atrophy: The wasting or diminution in size of the vagina.

Vascular tree: The tree-like structure of the blood vessels.

Withdrawal bleeding: Bleeding associated with combined hormone therapy caused by the stimulation of the endometrium by progestin.

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