

Chapter 2

Understanding the Menopause

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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 child-bearing years. In some Eastern cultures, for example, 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 following: “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 still 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 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.

1966—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 replacement 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. Brambila “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 recognition 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 Yonamamo 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*, 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 from J.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 2-1). 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 cultural 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 adequate 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 director of 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."

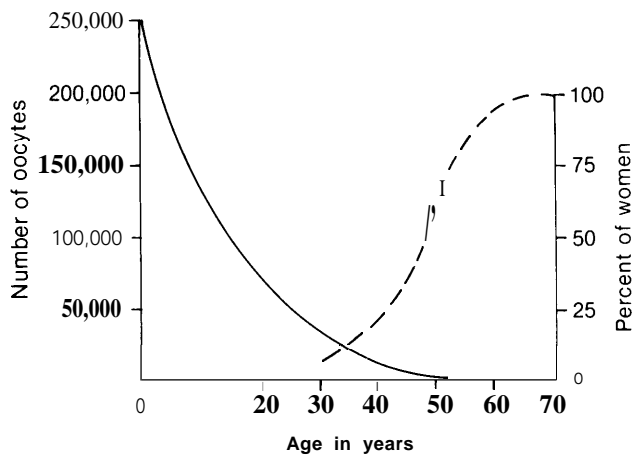
SOURCE: Adapted from Associated PressWise stories, May 24 and May 26, 1991.

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-I—Relation of Age, Oocyte Number, and the Menopause



SOURCE: Adapted from D.R. Mattison, M.S. Nightingale, and K. Shimizu, "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), metrorrhagia (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 after 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,

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 Flashes,” *Obstetrics and Gynecology* 75(4, Suppl.), 1990, pp. 3S-8S.

erroneous characterizations of the progression of the perimenopause; it may also be responsible for overstatements about common symptomatology.

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 2-1—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	8.3	8.3	7.6
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 common (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 hysterectomy as a preventive procedure to guard against cervical or endometrial cancer. A woman undergoing an elective hysterectomy 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.

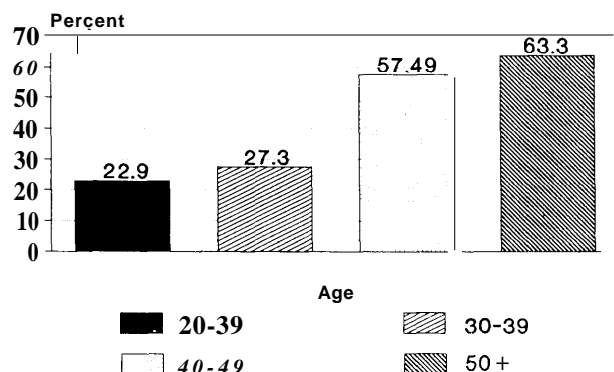
Other factors that affect the rate of hysterectomies are race and income. The only racially relevant data available focus on black versus white women: The rate of hysterectomies performed on black women is higher than for white women, although the absolute number performed on white women is greater. 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 capitation 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, D.A. 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," *Health 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 involuntional melancholia) was a syndrome characterized by agitated psychotic depression and somatic (bodily) preoccupation. Despite the fact that 25 percent of all cases of involuntional 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

Age	Diagnosis						
	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 years and older	176	60	14	15	z	65	20

NOTE: Estimates under 10,000 are not considered reliable and should be used with caution.

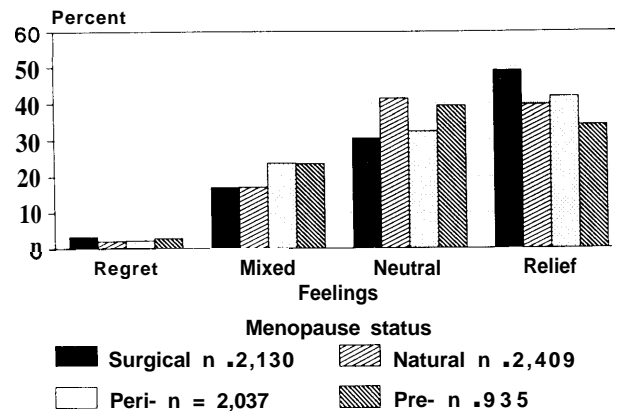
Z—Too few records sampled to produce an estimate.

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.

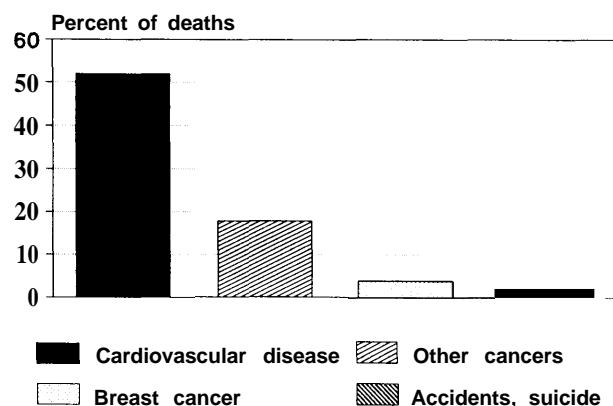
Some women report decreased sexual desire during the perimenopausal and postmenopausal periods. Most evidence, however, shows that sexual pleasure among older women is not compromised over time, although not much is known about their sexuality (8). Researchers thus attribute the decline in sexual satisfaction 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.

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 (1). Today, an im-

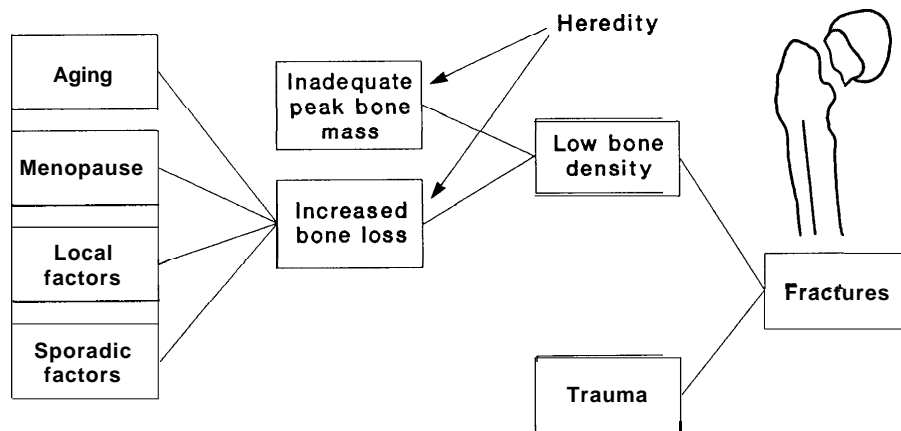
pressive body of literature has accumulated on this linkage, and the Office of Technology Assessment is conducting a major assessment of Policy *Issues in the Prevention and Treatment of Osteoporosis* (88).

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 risk of 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

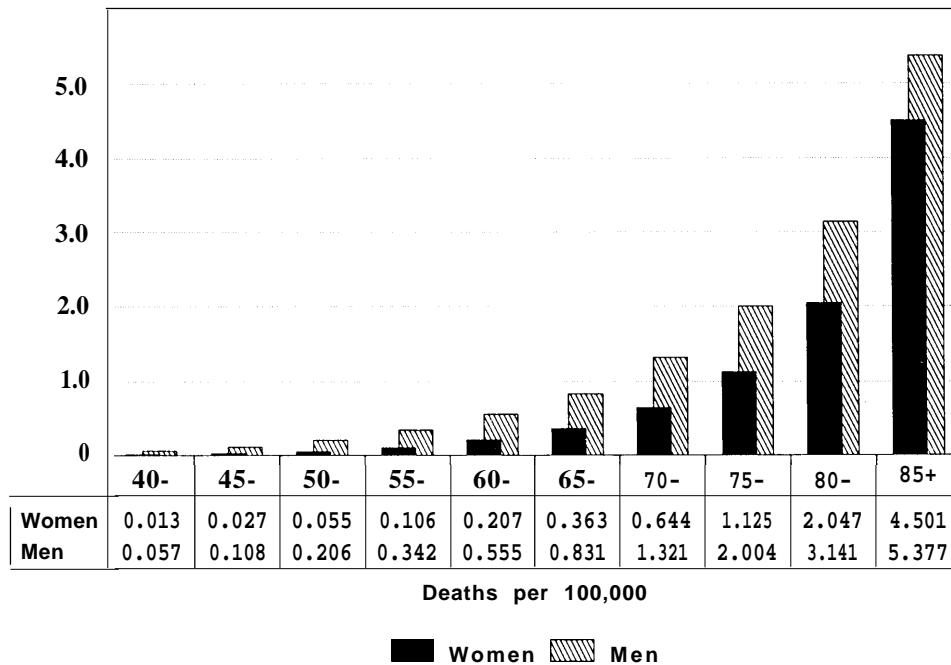
Cardiovascular diseases (CVD), which include both heart disease and stroke, are the leading cause of mortality in women, accounting for approximately 50 percent of all deaths in women over the age of 50 (figure 2-4) (13). Mortality rates are low among younger women: e.g., among women aged 30 to 34 years, 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



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.

decline in the levels of HDL cholesterol and a rise in the levels of LDL. These changes may be 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 random-

ized, 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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