Tools for making correct decisions regarding hormone therapy. Part II. Organ response and clinical applications

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Objective: To review existing scientific knowledge of the complicated and variable behavior and response to hormone therapy (HT) of different organs during aging, and to summarize long-term consequences on human health.

Design: A MEDLINE computer search was performed to identify relevant articles.

Result(s): Five body organs were evaluated. [1] Physiologic aging of the bone has deleterious consequences on women’s health and quality of life. Bone fractures could be attributed to the combination of estrogen depletion and osteoporosis, mechanisms of applied forces, and disturbed brain function, partially reversible by timely estrogen administration. [2] Estrogen seems to have a profound neuroprotective effect. As physiologic aging of the brain is an unhealthy phenomenon, possible intervention is justified. The therapeutic time window seems crucial. [3] The differentiation between response of a healthy or already damaged organ to sex hormones is the key factor to understanding the possible cardioprotective effects. [4] Based on doubling time of tumor cells, intracrinology, epidemiological data on breast cancer, and behavior of breast cancer survivors in response to estrogen treatment, estrogen seems to be mainly a promoter and even a protector of breast cancer survivors. [5] Colon cancer appears to be an estrogen-dependent tumor with a wide therapeutic window, as every report regardless of age and dose demonstrates protective effects.

Conclusion(s): Knowledge of each organ’s response to aging and sex hormone substitutions demonstrates that the organs could benefit from properly designed intervention. In the wake of the publication of the Women’s Health Initiative Study, which shocked the medical community, we suggest that the results be reevaluated according to the aforementioned principles, and that menopausal medicine could play an important role. (Fertil Steril® 2004;81:1458–77. ©2004 by American Society for Reproductive Medicine.)

Key Words: Menopause, hormone replacement therapy, aging process, estrogen, progesterone, breast cancer, osteoporosis, cardiovascular disease, brain, colon

MENOPAUSAL SYMPTOMS

In 1870, 135 conditions were ascribed to the “change of life” in women, ranging from aortic pulsation, hysterical flatulence, blind lips, and boils in the seat, to pseudonarcotism and hot flushes (2). Today, the climacteric symptoms can be divided into four major groups: [1] somatic symptoms, including headache, joint pain, and urogenital atrophy; [2] psychological effects, which range from minor irritability, emotional liability, changes in mood, anxiety, irritability, nervousness, to severe depression and withdrawal from usual activities; [3] vaso-motor symptoms, such as atypical hot flushes and migraine; and [4] changes in sexuality.

It is most important to note the wide variability in the clinical appearance of climacteric...
Hot Flashes

Hot flushes and night sweats are the most characteristic symptoms of the menopausal period. These symptoms are described as recurrent, transient periods of flushing and a sensation of heat, often accompanied by palpitation, feelings of anxiety, and sometimes subsequent chills. The flushes physically present as a sudden reddening of the skin on the head, neck, and chest lasting 3 to 4 minutes, followed by profound sweating (3).

The approach to this phenomenon varies between various cultures and countries. It is thought to be influenced by socioeconomic and physiologic factors, which provides some form of explanation for the wide range of reported incidence between 0 in Mayan women to 80% to 85% in Dutch women. It has been reported that flushes occur in 4 out of 10 women over the age of 40 who still have regular cycles; at the time of menopause, 85% experience hot flushes, and 30% describe it as a severe phenomenon. The hot flushes decline slowly; 57% of women report still experiencing this phenomena for 10 or more years after menopause begins (4).

In an effort to discover an explanation for the hot flushes, several theories have been postulated. The basis for all hypotheses is that a sudden downward trend or an alteration in the set point of the hypothalamic thermoregulatory center occurs, because the core temperature before and during the event remains normal (5). The hot flush, with its characteristic sweating and vasodilation, represents an attempt to decrease the body’s core temperature and restore equilibrium (6).

It has also been hypothesized that hot flushes may be a part of a broader neurologic phenomenon that may lead to other neurologic problems. A decrease in cerebral blood flow during a hot flush may lead to cerebral ischemia and free radical formation. The greatest change occurs in the hippocampus, a center for memory and cognition, leaving the brain with lessened ability to tolerate aging and susceptibility to the development of Alzheimer disease and memory impairment. The ability of HT to resolve hot flushes and restore normal patterns of cerebral blood flow can explain its positive effects on brain function and disease (7).

Genital Atrophy

The tissues of the lower vagina, labia, urethra, and bladder trigone are estrogen dependent. As estrogen levels decrease during menopause, the female reproductive organs undergo striking changes. Pubic hair becomes sparse and lank, the labia majora lose their fullness, and the skin and mucous membranes of the genitalia become thin, dry, and pale due to diminished vascularity.

The vaginal pH becomes more alkaline, because the epithelial cells contain less glycogen, previously metabolized by lactobacilli to produce an acidic pH that protected the vagina from bacterial overgrowth. The vaginal pH can serve as an indicator of the vaginal response to HT. Alkaline pH may indicate the necessity of local estrogen administration. The term “atrophic vaginitis” relates to the condition of a vagina without its rugae, eventually becoming shorter and inelastic. This change and the mucosal atrophy may result in a chronic vaginitis with itching, discharge, and local tenderness. Patients with atrophic vaginitis may report symptoms such as dyspareunia, vaginismus secondary to vaginal dryness, or vaginal discharge with burning, itching, and bleeding secondary to vaginal ulceration and infection. Many women report decreased lubrication at intercourse and complain of dyspareunia (8, 9).

Similar atrophic changes can occur in the urethral epithelium, which may lead to the development of dysuria, urgency, frequency, and stress incontinence. Loss of estrogens may also affect the muscles that help maintain continence (10, 11).

The cervix, uterus, and fallopian tubes also shrink. Estrogen deprivation is implicated in the relaxation of pelvic ligaments and muscles, which may result in uterine or bladder prolapse and contribute to stress and urge incontinence.

Estrogen treatment can reverse most of these nonphysiologic phenomena, because estrogen-induced glycogenization of the vaginal epithelium results in an acidification of the vaginal epithelium and maintains a low pH (pH <4.5) and normal bacterial environment. The vaginal epithelium is the organ most sensitive to a hypoestrogenic state; therefore, approximately 40% of women on systemic HT, who are otherwise asymptomatic, have been found to show signs of atrophic vaginitis that may require the addition of local estrogen therapy (12).

BONE METABOLISM AND OSTEOPOROSIS

Loss of stature, dowager’s hump, and kyphosis are some of the more visible signs of osteoporosis in older women. The most important reason for these involutorial changes is a progressive loss of bone mass that affects the axial (primarily trabecular) as well as the appendicular (primarily cortical) skeleton. Loss of bone mass in conjunction with microarchitectural deterioration of the skeleton generates
enhanced bone fragility, that is, the disease coined osteoporosis. In 1941, Albright et al. (13) postulated that estrogen deficiency plays a primary role in the development of osteoporosis. Since their publication, numerous researchers have studied this condition. Since their publication, numerous researchers have studied this condition. Since their publication, numerous researchers have studied this condition. Since their publication, numerous researchers have studied this condition.

Several definitions of osteoporosis have been proposed, and for the purpose of this discussion we have chosen that of the Consensus Development Conference, which defined osteoporosis as “a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fracture” (14). Other definitions are more practical, such as “femoral BMD >2.5 SD below the mean for young, healthy, Caucasian women.” A decline in bone mass density (BMD), loss of trabecular connectivity, and a decrease in bone mineralization can be found (15).

The onset of age-related bone loss occurs around age 40, with 35% to 40% and 55% to 60% loss of cortical and trabecular bones, respectively. The rate of cortical bone loss is approximately 2% to 3% per year for the first 5 years, with a subsequent loss of 1% to 2% in later years (16). Bone loss affects 4% of women aged 50 to 60 years, reaching a rate of 52% for women 80 years and older (17). This brings us to the detrimental effects of the disease: the risk of developing an osteoporotic fracture. Women >50 years of age have a 40% risk of suffering fractures in later life, with two-thirds of the fractures occurring after 75 years of age (18). The incidence of hip fracture in women is 574 per 100,000 woman-years (19), and a second fracture in the contralateral hip may occur in as many as 10.6% of patients (20). Hip fractures can cause a mortality increase of up to 33% within a year of the incident (21). After hip fracture, approximately 25% of women require long-term care, and more than 50% sustain a certain degree of long-term loss of mobility (22). This obviously has a tremendous impact on patients, their families, and society as a whole.

Prevention of osteoporosis would be ideal; however, when a diagnosis has been made, the treatment regimen should stimulate bone formation, increase bone mass, and restore trabecular connectivity. Physiologically, the quality of bone is determined in adolescence, and is based on estrogen and nonestrogen factors. A model of the estrogen-dependent status is demonstrated in women who experience amenorrhea because of low serum estrogen, as seen in Turner syndrome, hypogonadotropic hypogonadism, anorexia nervosa, and young athletic women. These pathologic conditions are associated with the real risk of osteoporosis. The BMD in these women has been found to be 15% lower than in age-matched controls, and 28.5% showed signs of sustained osteoporotic fractures (23). Thus, such conditions must be diagnosed and treated as early as possible. It is important to emphasize that although BMD will probably improve after normalization of hormone status, it is improbably that improvement would be beyond an additional 5% to 10%, and probably will not return to normal values. This emphasizes the important role of estrogen in the early stages of both bone growth and bone loss.

To understand the role of the various treatment modes, more exploration of the processes of bone remodeling, bone resorption, and bone formation should be carried out. The physiologic purpose of the remodeling process is to remove microdamaged areas and allow physiologic bone growth. The first stage in this process is the activation of resorption: cells that normally cover the bone surface retreat, and osteoclasts then resorb the exposed mineralized tissue over a period of 2 weeks. Once the resorption phase is completed, osteoblasts migrate to the resorption pit and refill it with new osteoid matrix, which becomes well mineralized within 1 to 2 weeks of deposition. A further increase in the density of mineralization occurs within the next 4 to 6 months (24). Loss of bone quality occurs when resorption exceeds formation, representing focal areas of weakness and resulting in too little bone, or osteoporosis (24).

Despite the established role of estrogen in bone formation, and although both osteoclasts and osteoblasts express estrogen receptors and are direct targets for estrogens, the mechanism of action is still uncertain (25, 26). One of the several mechanisms suggested is that estrogen preserves positive calcium balance by suppressing the bone remodeling rate (i.e., decreases activation of new remodeling units, thereby suppressing parathyroid hormone-mediated bone resorption). Several cell lineages and multiple cytokines (including interleukins 1 and 7) have been implicated in the mechanism whereby estrogen deficiency up-regulates osteoclasts (27).

Estrogen acts to conserve bone mass at the tissue level by suppressing bone turnover, and at the cellular level by affecting the generation lifespan and functional activity of both osteoclasts and osteoblasts. Both types of cells contain the key enzymes involved in local production of estrogen (intracrinology): the seven isoforms of 17β-hydroxysteroidhydrogenase (17β-HSD), aromatase, steroid sulfatase, 3β-hydroxysteroidhydrogenase, and 5α-reductase (28). Estrogen treatment increases bone formation and bone mass; a rise in serum osteocalcin has been found 2 weeks after initiating estrogen treatment, suggesting that estrogen may stimulate bone formation (29).

Lack of estrogen induces high bone turnover, which causes remodeling imbalance by prolonging the resorption phase and shortening the formation phase by increasing the osteoblast apoptosis. Consequently, the volume of resorption cavities increases beyond the capacity of the osteoblast to refill it. This can only be demonstrated by bone biopsies, as bone markers and BMD are only indirect measurements of this process. The process of osteoporosis in cancellous and cortical bones varies because of their basic structure. Osteoporosis causes multiple trabecular plate perforations in can-
cellular bone (vertebra and mandibular bone) and suben-
docortical cavitation in cortical bone (30).

In 1981, Christiansen et al. (31) published one of the first
studies that demonstrated the benefits of estrogen for bone in
preventing osteoporosis. This study compared the effect of
estrogen/progesterone with placebo. It was found that bone
mineral content increased in the drug-treated group, but
continued to decline in the placebo-treated group. Subse-
sequently, numerous studies have been published, supporting
the observation that administration of estrogen increases
bone density and significantly decreases fracture rate in
postmenopausal women.

Several investigators have addressed the question of
whether the increase in BMD during treatment with antiab-
sorptive drugs is due to new bone formation, thus resulting in
greater bone mass, or due to increased mineralization of the
preexisting osteoporotic bone. This is a crucial question,
because the answer will resolve the issue of whether antire-
sorption treatment only stops remodeling or also physiolog-
ically increases new bone formation. It is logical to assume
that physiologic bone remodeling will generate long-term,
healthy, strong bone. The common denominators available
today for bone quality do not provide a good solution to this
problem. As yet, it is not known whether any of the drugs
used today for treatment of osteoporosis are anabolic in the
bone, and, if they are, to what degree and what resulting
physiologic quality.

Bone markers and BMD, the common estimations of
bone quality, do not provide a satisfactory description of the
processes occurring in the bone during antiresorption treat-
ment. The only real answer can come from direct histologic
examination of a bone biopsy specimen. In studies by Khast-
gir et al. (32) and Vedi et al. (33) estrogen serum levels
between physiologic and supraphysiologic concentrations
(range: 180–2,568 pmol/L) were achieved by SC estrogen
implants in doses of either 50 or 75 mg, then architectural
changes in cancellous bone (cortical iliac bone) biopsies,
including the structural, static, and dynamic parameters of
the bone, were measured. The results revealed a statistically
significant increase in trabecular thickness and number, and
a decrease in trabecular separation, denoting that estrogen is
capable of exerting an anabolic effect in women with osteo-
porosis.

A direct correlation between the anabolic effect and se-
rum E2 levels was observed in several parameters. The most
pronounced anabolic effect was noted when supraphys-
ologic serum levels were achieved. These findings were not
detected in a similar study with a set-up of alendronate and
conjugated equine estrogen (CEE) in conventional doses, as
histomorphometric analysis showed normal bone histology
with the expected decrease in bone turnover. Anabolic ef-
fects were not demonstrated (34). The aforementioned res-
ults have demonstrated that natural hormone exerts a natu-
ral effect, and this can be achieved by recognizing the
therapeutic window of estrogen level in the bone.

This information has encouraged further research into
basic questions on bone, osteoporosis, and fractures. Osteo-
porosis has other consequences than fractures, including
possible detrimental effects on oral bone.

**Fractures**

What is the role of the skeleton in the aging woman? It is
known that the skeleton serves three major functions: [1]
protection to the internal organs, [2] a rigid joint structure
against which the musculature can pull to induce move-
ments, [3] a reserve of minerals such as calcium. Under-
standably, osteoporosis does not have a direct effect on the
well-being of the aging woman unless a traumatic fracture
occurs. So, if the main purpose of the skeleton is not affected
by osteoporosis, what then is its importance? As mentioned
previously, fractures are a primary, complex detrimental
issue in relation to mechanisms, location, and consequences.

Hallmark osteoporotic fractures include vertebral, femo-
ral neck, and distal radial fractures. The mechanism of spine
fractures differs significantly from femoral neck fractures.
Gravitation and body weight, not behavior, play a major role
in the mechanism of spine fractures. These fractures are
clinically relatively innocent, but can negatively contribute
to general health. Two-thirds of cases are not symptomatic
and are diagnosed by radiologic examinations. It is therefore
important to understand that research aimed at estimating
bone quality by bone fracture rate should focus only on spine
fractures. However, assessment of cortical bone quality
based on fracture rate only is not absolutely accurate, as
fractures of the cortical bones depend on several unrelated
factors such as trauma, age, body weight, frailty, and visual
acuity. Femoral neck fractures are mainly the consequence
of trauma from falling, which raises a different question:
why do menopausal women fall in such a way that hip
fractures occur?

**Why Do Menopausal Women Fall?**

There are many reasons for increased probability of age-
related falls in women. Several arise from direct pathologic
causes such as medication, neurologic disease, stroke, or
hearing impairment. In this review we would like to concen-
trate on sources other than those related to natural aging, as
some may be associated with estrogen deficiency, such as
impaired vision, frequent episodes of imbalance, ability to
regain balance, joint movement, and cognition.

Simple energy consideration suggests that any fall from a
standing height may cause hip fracture (35); however, only
2% of falls in elderly women result in this trauma. Several
other factors may result in hip fractures, as neither age-
related osteoporosis nor the increasing incidence of age-
related falls can sufficiently explain the exponential in-
creased incidence of hip fractures associated with aging.
Several conditions have been suggested: [1] a woman may
be oriented to impact near the hip, so instead of falling forward or backward, she falls on her side; [2] she may experience a failure of protective responses; [3] she may have a loss of muscle strength and decreased padding or local soft tissues that absorb the energy to prevent the fracture; or [4] the residual energy of the fall may exceed the bone strength. Several of these factors can be attributed to aging, but estrogen therapy can prevent some of them (35, 36).

One of the main purposes in preventing the fall is to restore postural instability, which in postmenopausal women may be related to abnormal sensory input (visual, vestibular, and somatosensory), poor central processing, and suboptimal musculoskeletal biomechanics. Younger individuals avoid impact to the lateral aspects of the hip by performing a substantial trunk rotation during the descent phase of the lateral fall. This movement cannot be performed during an anterior or posterior fall. Impairment of this mechanism in elderly women may explain the increased incidence of hip fractures in postmenopausal women (37).

Administration of estrogen to postmenopausal women improves their postural balance function, and may explain the rapid dynamics between estrogen exposure and hip-fracture protection (38, 39), an observation also noted in the WHI study.

**Oral Bone**

Oral bone quality is affected by age, a manifestation of osteoporosis in the mandible engendering not fractures but tooth loss. The latter contributes to deterioration in quality of life and to high financial expenditures. The possible association between osteoporosis, estrogen status, and oral bone loss was first suggested in 1960 and became a controversial issue. A substantial number of studies have attempted to address this important topic. This subject is of particular importance as there may be a correlation between mandible bone mass, tooth loss, and the observation that women on HT have improved tooth retention and a reduced likelihood of edentulism (40, 41).

Osteoporotic changes in the jaw directly affect tooth stability and retention. In the United States, nearly 32% of women aged 65 to 69 are toothless. Tooth loss may reflect systemic osteoporosis, and postmenopausal hormone therapy protects against osteoporosis. Indeed, a review of studies published between 1989 and 1998 (42) clearly shows that postmenopausal women who used estrogen had improved teeth retention (after menopause) compared with nonusers of estrogen.

Grodstein et al. (43) examined the risk of tooth loss in relation to HT in a prospective study of 42,171 postmenopausal women. In general, the risk of tooth loss was 24% lower in women on HT at the time of the study, although there was little effect for women who had stopped taking hormones.

An association between postmenopausal HT and tooth retention was also found in a cohort of 488 women aged 72 to 95 years. These patients participated in the Framingham Heart Study during the period 1948 to 1995. An association was found between duration of HT and tooth retention for the total number of remaining teeth, and for the various types of teeth (incisors, canines, and premolars, but not molars) retained. The risk of being edentulous was reduced by 6% for each 1-year increase in duration of HT use (44).

Similar and even better results were demonstrated in the Leisure World Cohort Study, in which 3,921 women (median age 82 years) who had been on estrogen therapy retained more teeth than nonusers (21.2 vs. 19.2). The age-adjusted risk of having fewer than 25 teeth decreased with increasing duration of estrogen replacement therapy: 0.87 for <4 years of estrogen replacement therapy, 0.74 for 4 to 14 years, and 0.70 for 15+ years, compared with nonusers. In long-term users (15+ years), the risk of becoming toothless was 50% less than in nonusers (45).

The data from these studies suggest that prevention of osteoporosis via the administration of estrogen in postmenopausal women contributes to sustained oral health, improved tooth retention, and reduced risk of edentulism. This important issue should be broached when discussing HT with female patients.

Because osteoporosis is such a complex issue, with biologic variability dependent on many variables, a physiologic drug such as estrogen is probably the most suitable solution. However, to achieve optimal benefits, the complex pathophysiology should be further investigated and treatment should be adapted accordingly.

**THE BRAIN**

Extensive data are available on both basic science and clinical results examining the relationship between estrogen and brain function, but these do not always concur. Although laboratory data regarding the beneficial effect of estrogen on brain function appear promising, controversy exists when this is applied to clinical experience. The rationale behind the assumption that estrogen plays a major role in brain function is based on its numerous effects throughout the life-span, beginning during gestation and continuing through puberty and reproductive age until the manifestation of detrimental effects during menopause.

In the aging process, the most important organ is the brain. It determines quality of life, health, and social behavior. As estrogen levels decline during menopause, brain functions, including cognitive mood and certain types of memory, are affected. Most of the typical climacteric symptoms originate in the central nervous system (CNS); phenomena such as depression, loss of libido, memory loss, cognitive dysfunction, sleep disturbances, depression, hot flushes, migraines, fatigue, night sweats, vertigo, and bal-
ance disorders increase in frequency. These are only a few examples of the major role played by the brain in the aging process. Studies of estrogen action on the extra- and intrahypothalamic area of the brain have emphasized our relative lack of information regarding basic cellular and molecular mechanisms.

In the mid-1980s a study performed by Sherwin (46) initiated systematic analyses of the impact of estrogen loss and estrogen replacement on memory function. The study demonstrated that verbal memory declined with estrogen loss after natural, chemical, and surgical menopause, but the memory loss was restored to almost premenopausal levels with estrogen administration if the replacement therapy was instituted at the manifestation of menopause (7). A critical factor in determining therapy efficacy appeared to be the length of the intervening period between estrogen loss and initiation of replacement therapy. Furthermore, the time window for complete reversal of memory loss due to estrogen-deficit appeared to be limited (47).

Rather than one estrogen-regulated process, several types of estrogen actions on various neurochemical and neuroanatomic substrates, and a number of molecular mechanisms, are likely to underlie the actions of estrogens on cognition and other aspects of behavior, such as mood, pain perception, and nociception. The affected areas of memory were those influenced by the hippocampus conjointly with the basal forebrain cholinergic system, and other neurochemical systems. The hippocampus is the region in the brain involved in episodic, declarative, contextual, and spatial learning and memory, and it serves as a component in the control of autonomic and vegetative functions such as adrenocorticotropin hormone (ACTH) secretion (48). The hippocampus is vulnerable to damage during aging or repeated stress (49).

The discovery of the various types of estrogen receptors (ER-α, ER-β, and membrane ER) (50, 51) have inspired the scientific world to reevaluate the potential role of estrogen in the brain, as well as possibilities of new targets and diverse mechanisms that have not been previously considered. The mapping of ER, which modulate genomic action, has revealed the presence of estrogen and/or progestin receptors in regions such as the olfactory lobe, hippocampus, cortex, locus ceruleus, dorsal raphe, midbrain central gray, and cerebellum (49), implying that several brain functions depend on estrogen.

The findings of high levels of aromatase and other enzymes involved in estrogen biosynthesis adjacent to androgen receptors have demonstrated the importance of intracri-nology in the brain for local production of estrogen from androgen precursors. This mechanism facilitates high local estrogen concentration at the target areas of the brain.

The reverse is true of menopausal symptoms. An accumulating body of laboratory evidence clearly establishes that E₂ is a potent neuroprotective and neurotrophic factor in adults. Evidence from animal experiments and cross-sectional, case-controlled, prospective human studies supports the hypothesis that HT is a promising treatment for the delay of dementia symptoms, and may even slow the progression of deterioration. In brain tissue of the rat, estrogen induces synaptic and dendritic remodeling, and causes glial activation (52, 53).

Estrogen modulates growth factors specifically associated with axonal elongation, enhances the outgrowth of nerve processes in cultured neurons, and promotes the formation of dendritic spines and synapses (54). It was also demonstrated that E₂ affords protection against cell death in numerous in vitro models of brain injury (55). Morphologic analyses demonstrated that estrogen significantly increased neuronal outgrowth in hippocampal, basal forebrain, and occipital, parietal, and frontal cortex neurons. Estrogen induces highly significant neuroprotection against beta-amyloid, hydrogen-peroxide, and glutamate-induced toxicity (56).

Clinical studies have established that E₂ influences aspects of memory, cognition, and mood in healthy young and postmenopausal women. In addition, E₂ appears to delay the onset and slow the decline in cognitive function associated with neurodegenerative diseases such as Alzheimer disease (AD) or Parkinson disease, and may attenuate the extent of acute injury associated with stroke and brain trauma (55, 57).

The neuroprotective effects of estrogen are multifaceted and encompass mechanisms ranging from chemical to genomic. One such mechanism is the antioxidant effect of estrogen against a wide variety of free radical generators, described in multiple organ system and cell types (58). Thus, 17β-estradiol can attenuate the lipid peroxidation induced by beta-amyloid exposure, glutamate toxicity, or FeSO₄ exposure and reduces intracellular peroxides affected by beta-amyloid, haloperidol, and H₂O₂ (59). Green et al. (60) in the United States and Behl et al. (61) in Germany identified the C3 position on the phenolic androstenedione (A) ring of estrogens as the critical chemical requirement for estrogenic antioxidant function in the CNS. The phenolic androstenedione ring estrogens are inhibitors of lipid peroxidation with an efficacy equivalent to α-tocopherol (59). Behl et al. (58) have shown that the phenolic ring structure is both necessary and sufficient for the antioxidant properties of estrogens. Thus, the phenolic ring structure should make it possible for phytoestrogens, isoflavones, and flavones to exert an estrogenic-like antioxidant property. Unfortunately, such effects remain undetermined.

The translation of these studies into clinical applications is demonstrated in the involvement of estrogen during the development of brain dementia. It has been suggested that the loss of ovarian hormones may increase the vulnerability of brain cells to damage and degeneration that can lead to Alzheimer disease (62). Multiple epidemiologic studies have indicated that estrogen HT can significantly reduce the risk of Alzheimer disease (62). Furthermore, a cross-sectional
study showed that women who were current users of HT performed significantly better on a visual memory test that has been shown to predict the onset of Alzheimer disease than did those who had never received HT (47).

The biologic credibility of the estrogen hypothesis is strengthened by the actions of estrogen that are potentially relevant to Alzheimer pathogenesis. Estradiol in vitro promotes the breakdown of the amyloid precursor protein into fragments that are less likely to accumulate as beta-amyloid peptides. Together with the antioxidant property, this may be important in blunting neurotoxic effects of beta-amyloids, which are believed to be partially mediated through free radical damage to susceptible neurons (54).

However, recent data have shown that administration of estrogen to women with Alzheimer disease did not ameliorate their condition (63). Therefore, it is important to emphasize that the critical factor in determining the efficacy of HT appears to be the intervening period between the loss of estrogen and the initiation of HT. Data indicate that the time window for complete reversal of memory loss induced by estrogen deficit appears to be limited (64–66). This could explain the results of the Women’s Health Initiative Memory Study (WHIMS) (67), which demonstrated that women aged 65 years and older who actually have been estrogen deficient for more than 10 years do not gain any benefit from such treatment.

The National Institute on Aging (NIA) supports the Baltimore Longitudinal Study of Aging (BLSA), the longest-running scientific study of human aging in the United States, begun in 1958. The BLSA scientists are studying changes that occur with progressive aging, and how to differentiate these changes from those due to disease or other causes. The study comprises more than 1,200 men and women volunteers, who range in age from 20 to 90 years. A vast amount of data is available from this long-standing study. One of the recent publications deals with the effect of HT on cognitive and brain function in postmenopausal women without dementia. In this study, women who received and did not receive HT were comparable with respect to educational attainment, general medical health, and performance on a test of verbal knowledge. Despite these similarities, women on HT performed better on tests of verbal and visual memory than those who had never been treated. Both groups also differed in the patterns of regional brain activation evoked during performance of delayed verbal and figural memory tasks. Furthermore, longitudinal comparisons revealed women receiving HT had greater relative blood-flow increases over 2 years for the hippocampus and other mesial temporal lobe structures that subserve memory (68).

Thus, of utmost importance is the question, What is actually being treated when HT is administered to women during menopause? Is it the reduction of a standard deviation in BMD, or minimal increase in the incidence of breast cancer? Can these affect the global quality of a woman’s life? It is well known that 30% to 50% of women over 50 years of age suffer from depression, more than 60% experience lack of libido, and up to 80% endure fatigue, with daily functional disturbance mainly due to sleeping disorders and gradual decrease of memory function. From the aforementioned data it is clear that the brain is the major contributor to a woman’s health during the aging process and is highly dependent on estrogen for its functions. It was clearly demonstrated that normal, physiologic aging is an unhealthy phenomenon, and possible intervention in this phenomenon is justified. Hormonal intervention may prove promising in alleviating these conditions.

THE CARDIOVASCULAR SYSTEM

Only a decade has passed since a consensus emerged that administration of estrogen to postmenopausal women markedly reduced the burden and mortality associated with coronary heart disease (CHD). Following the Heart and Estrogen/Progestin Replacement Study (HERS) (69) and WHI study (1), what was thought to be a consensus has become a heated controversial topic, as these studies failed to verify the expected benefits of estrogen and progestrone treatment on the cardiovascular disease (CVD) in postmenopausal women. After reviewing the clinical, experimental, and basic science data, the unanswered question is not whether estrogen is a cardioprotective agent, but rather what drug to use, in what doses and formulation, and when to initiate treatment and for how long to attain cardioprotective effects.

Estrogen-Modulating Cardiovascular Disease: What Evidence Is There?

Observations of gender-based differences in the physiologic and pathologic behavior of the cardiovascular system have indicated the possible role of estrogen in this important organ. For example, well-known physiologic phenomena are the tremendous hemodynamic and cardiac function changes that take place during advanced singleton and multiple pregnancies. The cardiovascular system can accommodate these changes with the aid of high levels of sex hormones. Also, CHD is extremely rare in premenopausal women, even in high-risk populations, and the overall incidence of cardiovascular complications is considerably lower than that in men of similar age (70). After menopause, the incidence, or risk for CHD gradually increases (71), which suggests a delay in disease onset of 5 to 10 years after menopause, lagging the incidence in men (72).

It has also been documented that women experiencing natural menopause between ages 45 and 49 years, or surgical menopause between ages 40 and 44 years, are more prone to develop CHD than premenopausal women of the same age (73). In contrast to natural menopause, bilateral oophorectomy increases the risk of CHD. This increase appears to be prevented by estrogen replacement therapy (74). These physiologic and pathologic observations suggest the role of protective effects of endogenous estrogen.
The cardiovascular system is another example of how estrogen can function as an antiaging compound. The normal aging process can be harmful to the heart and can be reversed by estrogen therapy. A few examples demonstrate this effect: the metabolic syndrome which includes weight gain, change in lipids, insulin resistance, and endothelial dysfunction, as well as increased level of homocysteine, lipoprotein(a), and several coagulation factors is, in part, attributed to estrogen deficiency, and may partially be reversed by HT (75).

Another example are the changes that occur during aging in endothelial function. The balance between vasodilatation and vasoconstriction is hampered during aging, with the end result of more vasoconstriction and less vasodilatation. Vasoconstriction is largely mediated by endothelin, while vasodilatation is mediated by nitric oxide (NO) and acetylcholine (76). This can be reversed by estrogen administration, which not only modulates NO synthesis and production, but also acts as an angiotensin-enzyme inhibitor that contributes to the decrease in vascular resistance and increase in blood flow and tissue perfusion. It was also shown that myometrial contractility, hypertrophy of the heart wall and septum, occurs during estrogen deprivation and can be reversed by HT (77).

It was noted that estrogen can dramatically reverse coronary spasm in women with syndrome X (78) and reduce coronary artery stenosis during angiographic examination (79). However, when the vessels are damaged by plaque, as was demonstrated in the study conducted by Herrington et al. (80), progression of coronary atherosclerosis was the same for hormone users and nonusers. Therefore, it appears that if a woman develops arterial disease, estrogen has no effect on its progression. This adds to the hypothesis that was also demonstrated in other organs, such as the brain and the bone, that healthy tissue and damaged tissue respond to estrogen differently, or even conversely. The window for favorable hormonal intervention may be a short time. The main obstacle for adapting this hypothesis to human epidemiologic studies is the difficulty in defining healthy tissue. Because histology, biopsy, or other invasive techniques would be necessary for such studies, it may be impossible to recruit women with so-called healthy organs.

Among the first observational studies that sought possible cardioprotective effects of estrogen was that performed by the late T. L. Bush. This study, published in 1987 (74a), comprised a cohort of 2,270 menopausal women (593 estrogen users and 1,677 nonusers) who were followed up for an average of 8.5 years as part of the Lipid Research Clinics Program Follow-up Study. There were 44 deaths due to CVD among the 1,677 nonusers of estrogens, and 6 deaths among the 593 estrogen users. The investigators attributed these significant differences to the favorable lipid changes in the group of estrogen users, but this marked propitious effect could not be explained by favorable lipid change only. Therefore, extensive scientific research was performed in an attempt to understand this tremendous cardioprotective effect of estrogen. These experiments revealed an attenuation in metabolic changes of the typical metabolic syndrome of menopause. Many parameters of vascular changes, such as vascular activity, free radical activity, endothelium-dependent and nondependent vascular activity, inflammatory parameters such as cytokine-dependent cascade, and hemostatic parameters, were found to respond favorably to estrogen. An extensive review on these topics can be found in a review by Mikkola and Clarkson (81).

The cardioprotective effects that were so convincingly demonstrated in laboratories and animal experiments were confirmed by several observational studies. The Nurses’ Health Study (NHS), first published in 1985 (82), was the most notable comprehensive investigation, and was updated in 1991 (83), 1996 (84), 2000 (85), and 2001 (86). This study, initiated in 1976, comprised 121,700 female nurses, 30 to 55 years of age; the latest report included 70,533 postmenopausal women followed up for 20 years. During the study period, 953 women had nonfatal myocardial infarctions, 305 died from coronary disease, and 767 suffered strokes, 119 of which proved fatal (85). In general, current use of HT is associated with a relative risk for major coronary events of 0.61 (confidence interval [CI], 0.52–0.71).

In summary, several major conclusions could be drawn from the long-term follow-up NHS study. The significant reduction of CVD in HT users indicated that HT was primary prevention, but the addition of P to the drug formulation had detrimental effects on the results. Decreasing the estrogen dose (0.3 mg of CEE) did not attenuate the CVD risk reduction observed with conventional dosages (0.625 of CEE; RR 0.54; 95% CI, 0.44–0.67) but still resulted in a statistically significant reduced relative risk (RR 0.58; CI, 0.37–0.92). Secondary prevention of cardiac disease demonstrated an increased risk for short-term HT users (RR 1.25; CI, 0.78–2.00); however, after more than 2 years of HT use, the RR significantly dropped to 0.38 (CI, 0.22–0.66), and the reduction in risk was persistent for up to 20 years.

**Primary and Secondary Prevention**

The definition of “primary prevention” and “secondary prevention,” as presented in the HERS (69) and WHI (1) studies, was not explicit. To the vascular surgeons and vascular biologists, primary prevention of atherosclerosis denotes prevention of the progression of artery-wall fatty streaks into atherosclerotic plaques. To cardiologyists who use this term, primary prevention means interference with progression of complicated atherosclerotic plaques into clinical CHD events. Therefore, clinical trials with coronary event end points can include clinically healthy volunteers who have markedly varied vascular wall conditions.

To solve this issue, and before presenting a randomized, controlled trial in women, a few studies should be discussed, such as examination of isolated arteries from animals and...
humans, and histologic evaluation of endothelial conditions. In the cynomolgus macaque monkey model (87), monkeys and humans share a >90% DNA homology, their hormonal profile is similar to those of women, they have a 28-day menstrual cycle, and menarche and menopause are comparable. Surgical menopause, combined with a moderately atherogenic diet, produces progressive atherosclerosis that is responsive to HT.

In a study performed by Adams et al. (88), ovariectomized monkeys who were treated for 30 months with parenterally administered 17β-estradiol showed an approximately 50% reduction in coronary artery atherosclerosis, compared with the control animals. This observation was confirmed in a subsequent study in which oral CEE treatment resulted in a 72% reduction in coronary artery plaque size relative to untreated, estrogen-deficient controls (89). The investigators showed clearly that estrogen therapy, with or without P, inhibits atherosclerosis progression in ovariectomized monkeys. It was also noted in this animal model that administering estrogen to monkeys who had already developed subclinical atherosclerosis (proven histologically) resulted in breakdown of the atherosclerotic plaque, with grave consequences and appearance of clinical disease.

As we do not have a routine method to define the accurate conditions of vascular endothelium in women, it would be almost impossible to recruit women for true primary prevention trials. As a direct correlation between the vascular wall condition and age was observed, we may assume that an accurate primary prevention trial should include women in the early stage of menopause. This issue was demonstrated in the WHI study, in which the age of the recruited women was far too advanced to be suitable for primary prevention trials.

Two large randomized, controlled trials, HERS (69) and WHI (1), demonstrated that the combination of estrogen and P in the formulation of CEE and medroxyprogesterone acetate (MPA) did not improve (HERS study) or deteriorate (WHI study, during the first year only) the situation of patients with CVD. Based on these two studies, world opinion on the cardioprotective effects of HT changed, despite the favorable results seen in both the HERS and the “healthy” WHI population. As a result, HT is no longer recommended for primary or secondary CVD prevention.

At this time we should question whether greater caution is required in interpreting the results, or whether we should discard all information in the literature accumulated over the last 60 years based on one or two studies.

The field of research in CVD in human and HT or estrogen therapy is saturated with contradictory data, in which scientific proof can be found for the physician’s attitude toward the patient, and other data may be ignored, such as an almost neglected 2001 study on the effect of HT on the fatal incidence of myocardial infarction (90). This study comprised 114,724 women aged ≥55 years with confirmed myocardial infarctions, from 1,674 hospitals participating in the National Registry of Myocardial Infarction. Postmenopausal HT appears to be associated with significantly reduced mortality after myocardial infarction (90). In this extremely large-scale study, authentic cardioprotection from HT was demonstrated.

As CVD and CHD are multifactorial in origin, it would be almost impossible to design a large clinical study that would supply accurate answers to all the questions. Thus, we are obliged to rely on experimental data supplied by laboratories and large observational studies. Obviously, research should be undertaken to evaluate the effects of different types of treatment with different drug compositions, formulations, and doses, among different patient populations. The cardiovascular system is so central to human health that any possibility of variable interference must be thoroughly investigated, not discouraged due to nonoptimal results or treatment.

THE BREAST

The association between estrogen and tumors was first reported in the early 19th century by Beatson (91), who demonstrated that bilateral ovariectomy resulted in remission of inoperable premenopausal breast carcinomas. Subsequently, in the late 1930s this association was described in guinea pigs, and then in the early 1940s by Gardner in mice (92). The biologic mechanisms underlying the effects of exogenous hormones on the breast are still undetermined; however, estrogen stimulates growth and differentiation of the ductal epithelium, induces meiotic activity of ductal cylindrical cells, and stimulates the growth of connective tissues (93).

It appears that gonadal hormones also play an important role in the development of breast cancer, as there is a correlation between breast cancer, early age at menarche, late menopause (94, 95), number and timing of deliveries, and obesity (96). To appreciate the role of the gonadal hormone in the development of breast cancer, we should consider three major systems. The first mechanism to consider is the endogenous serum concentration of bioavailable estrogen. Several large studies have shown that postmenopausal women in whom breast cancer subsequently developed had higher serum concentrations of free E₂ than did those in whom breast cancer did not develop (97, 98). In addition, it was shown that low levels of serum sex hormone binding globulin (SHBG), as found in obese women, are considered a risk factor because of the relative high level of bioavailable estrogen (99, 100). The second mechanism is the intracellular production of estrogen, based on the existence of an enzyme system (e.g., sulfatase and aromatase) that can create a high local level of E₂ (101, 102). The third mechanism is exogenous estrogen.
From the laboratory perspective, it has been shown that progestins, when added to estrogen, may enhance the proliferation of epithelial cells in the breast (103). It was found that P does not down-regulate estrogen receptors in the breast, and thus may contribute to the adverse effects (104, 105). Moreover, the isozyme of 17β-hydroxysteroid dehydrogenase induced by P in the breast predominantly catalyzes the conversion of the less potent estrone to the more potent E₂ (106).

The possible association between exogenous estrogen therapy and breast cancer in healthy, postmenopausal women has been a controversial issue over the last two decades. One of the first studies to investigate this issue was undertaken by Ross et al. (107), who observed a statistically significant increased risk of breast cancer (RR = 2.5) in a subgroup of women (<75 years of age) with intact ovaries, who had been on estrogen therapy for more than 8 years. Conversely, Gambrell et al. (108), in a prospective study at the Wilford Hall USAF Medical Center, followed up 5,563 postmenopausal women (observation of a total of 37,236 woman-years from 1975 to 1981), and found that estrogen therapy in postmenopausal women did not increase the risk of breast cancer—and perhaps even provided some protection.

Colditz et al. (109) made an important contribution to this field with their observation that HT—whether estrogen, or estrogen combined with P—increased the risk of breast cancer development in low-risk women. This prospective study followed up women aged 30 to 55 years, for a period of 12 years (480,665 woman-years). Generally, in comparison with nonusers, in women who were currently using unopposed estrogen (RR 1.42, CI, 1.19–1.70), estrogen and P (RR 1.54, CI, 0.99–2.39), or P alone (RR 2.52, CI, 0.66–9.63), the risk of developing breast cancer was increased. In a subsequent publication that added 50% more prospective data to what had already been published (110), the investigators confirmed the previous results.

As a consequence of the WHI publication (1) and another recent publication of the same study (111) that specifically investigated breast cancer, it was noted that women who started estrogen (CEE) and P (MPA) treatment at a mean age of 63 years or more were diagnosed as having a significantly more advanced stage of breast cancer compared with the placebo group. However, the investigators stressed that [1] 82 women with suspected findings in prestudy mammography were enrolled in the study, and three subsequently developed invasive breast cancer; [2] treatment with estrogen plus progestin (MPA) increased mammographic breast density versus estrogen alone or placebo; and [3] the appearance of breast cancer after a short treatment period suggests an effect on the growth of established breast cancer. The most important observation to be stressed for this study is that it showed no increase in breast cancer in the group of women who were treated with estrogen only.

These two studies have drawn enormous public attention, with resulting pressure imposed on physicians worldwide, but it is wise to clarify the known available data relating to breast cancer and sex hormones. Based on the extensive, cumulative data from these studies and the conclusion that treatment with estrogen alone had no apparent role in the increased incidence of breast cancer, the role of MPA and other progestins should be further investigated. In the interim, we should not prevent estrogen treatment in postmenopausal women, especially younger women.

In 1997, a study in the Lancet (112) reanalyzed and summarized approximately 90% of the worldwide epidemiologic evidence from 51 studies in 21 countries on the relationship between risk of breast cancer and use of HT. This collaborative reanalysis included data on 108,411 postmenopausal women of known age at menopause who did not have breast cancer, and 53,865 postmenopausal women with known age at menopause who had breast cancer, of whom 17,830 (33%) had used HT at some period. The investigators concluded that “In North America and Europe the cumulative incidence of breast cancer between the ages of 50 and 70 in never-users of HT is about 45 per 1000 women. The cumulative excess numbers of breast cancers diagnosed between these ages per 1000 women who began HT at age 50 and used it for 5, 10, and 15 years, respectively, are estimated to be 2 (95% CI, 1–3), 6 (3–9), and 12 (5–20).” One of the reasons for early termination of the combined sections of the WHI study was the increase of 0.7 new cases of breast cancer per 1,000 treated patients per year, yet this increased risk was very similar to that reported in the 1997 study (112). The number clearly indicates that the use of combined HT will alter the risk of cancer in women, but most of the risks involved are related to the women belonging to an at-risk age group.

To correctly estimate the real magnitude of the absolute risk of breast cancer due to HT, it may be wise to compare the relative risk of developing breast cancer due to other reproductive indicators. The relative risk with menarche <12 years is 1.2–1.5, with age at birth of first child >30 years is 1.9–3.5, with lack of breastfeeding is 1.37, with age at menopause >55 is 2.0, and with family history of breast cancer is 2.6 (113). It is important to mention at this point that none of these studies have demonstrated an increase in mortality from breast cancer. On the contrary, some of these studies showed a “protective” effect against mortality.

**Combination of Estrogen and Progesterone Compared With Estrogen Alone**

The third section of the WHI study includes treatment with estrogen alone, and that study is still in progress. If this message is correctly interpreted, it signifies that treatment of postmenopausal women with estrogen alone has not increased the risk for development of breast cancer, and thus did not cross the threshold to warrant termination of that section of the study.
This suggests that the risk with estrogen treatment is lower than that with combined estrogen and P. The afore-mentioned review of the physiologic mechanism for the development of breast cancer and other clinical studies support this conclusion. The recent study by Schairer et al. (113) indicated that, with each year of therapy on estrogen-only or estrogen-progestin alone among recent users, increases in relative risk were 0.03 (95% CI, 0.01–0.06) and 0.12 (95% CI, 0.02–0.25), respectively. Persson et al. (114) found similar results in a cohort of 11,231 Swedish women prescribed different replacement hormone regimens. One potential conclusion might be that the use of P is related to the detrimental effect of HT on the incidence of breast cancer. A search of the literature reveals no data on the effect of different progestins on the breast or on the development of breast cancer; obviously, this area warrants immediate research.

Prognosis of Breast Cancer Detected During Estrogen Treatment
It would be logical to assume that women on HT have dense breast tissue, thus making mammographic evaluation more difficult—that is, that detection of their tumors would be delayed and have more devastating prognosis compared with women who are not on HT. Contrary to this belief, studies have demonstrated that patients with breast cancer who have received HT have a better prognosis than those who have never received HT. No difference was found in time interval of detection by mammography between users and nonusers of HT. However, those who used HT had a 100% survival rate of 6 years as opposed to 87% among nonusers (112, 115, 116).

A recent overview of the literature by Bush et al. (117), examined 65 studies (between 1975 to 2000) on breast cancer and estrogen therapy or HT; five had assessed the risks of HT and death from breast cancer, and six assessed the risks of HT and surviving breast cancer. The data from all five studies showed that the estimated risk for death from breast cancer in HT users compared with nonusers was <1.0, and was statistically significant in some of the studies. Bush et al. concluded that “the body of literature does not support an association between estrogen therapy and HT use and breast cancer.” It was assumed that, in light of this data, additional observational studies would not alter this conclusion.

We are of the opinion that the most important finding in the meticulous overview by Bush et al. (117) of such extensive data is the persistent findings of all studies that estrogen users are less likely to die from breast cancer compared with nonusers. The rarity of metastatic disease at the time of initial diagnosis can contribute to this observation. This finding was consistent in all the studies. The observation is supported by the work of Schneider (118), who summarized breast cancer mortality in current HT users from nine studies (1976 to 1997) that demonstrated a relative risk of 0.6–0.8 (CI, 0.3–0.9). Based on the analysis of the data, it may even be hypothesized that use of HT provides protection and decreased mortality from breast cancer.

A study in Sweden of 984 breast cancer patients diagnosed and treated between 1978 and 1997 showed that HT treatment prior to diagnosis was significantly associated with a longer overall survival rate (RR of mortality 0.73; 95% CI, 0.62–0.87; P=.0005) (119). Currently, there is an increasing body of data showing that breast tumors that develop during HT are more likely to be estrogen receptor–positive, less aggressive, lower grade, well-differentiated with low S-phase, and more node-negative than those in nonusers, suggesting that these tumors may be intrinsically more benign (115, 120–122).

Several theories have been postulated in an attempt to understand the biologic processes responsible for better prognosis in women with breast cancer who have received HT. A major dilemma is whether the sex hormones are carcinogenic initiators or promoters. As epidemiologic studies have demonstrated an increased incidence of breast cancer as early as the third and fourth years of HT, the current general recommendation is to stop HT use after 4 to 5 years. This 5-year recommendation runs counter to the known physiologic phenomenon of tumor growth. In development of breast cancer, 20 doublings will be needed for a single cell to reach a 1- to 2-mm diameter (i.e., the threshold size for cancer detection by mammography), and 10 more doublings will be needed for the cell to grow from 1 mm to 1 cm in diameter (i.e., the threshold size for cancer detection by palpation) (123). In a study of 23 patients by Heuser et al. (124), measurements of doubling times of tumor volume demonstrated a wide variation (range: 109 to 944 days; mean doubling time, 325 days). Using an estimate of a high doubling time of 125 days and volume calculations, the time interval from inception to mammography detection was approximately 2,500 days (6.8 years), and from mammography detection to clinical detection by palpation would be an additional 1,250 days (3.4 years).

A similar estimation was presented by Gullino (123) in 1977, who demonstrated a 10-year interval of tumor growth, from transformation initiation of a single cell into a tumor cell until the size of a clinically detectable tumor (1-cm diameter). Thus, it is evident that 4 to 5 years are not sufficient to prove initiation. If a positive relationship between breast cancer and HT exists, the HT is probably a promoter and not an initiator. It has been speculated that the use of HT may promote preexisting clinically occult cancers, accelerating their natural biologic history. The acceleration of tumor growth creates a different tumor, probably with altered biologic behavior.

In 1994, Squitieri et al. (125) suggested that good prognosis is due to the slower growth of tumors at an earlier stage. They compared breast carcinomas in 35 postmenopausal women who had taken hormones, with carcinomas from age and histologically matched postmenopausal...
women who had never taken hormones. Despite the higher risk factors in hormone users, such as an average 1.1 fewer pregnancies ($P<.005$) and 1.4 fewer live births ($P<.0005$), the carcinomas had significantly lower S-phase fractions (5.36 vs. 6.77; $P>.01$) and less nodal involvement (1.2 vs. 1.9; $P<.0005$). In addition, it may appear that, the longer the period of HT use, the higher the rate of tumors at an earlier stage, with better tumor differentiation (126).

Similarly, endometrial tumors detected during HT have demonstrated different biologic properties, appeared to be more highly differentiated, with fewer numbers of metastases, with rare deep invasion into the myometrium (127). As a result, estrogen-induced endometrial cancer has to 95% complete remission (128). In addition, endometrial hyperplasia induced by unopposed estrogen therapy can be easily reversed by P, whereas the spontaneous hyperplasia cannot (129).

The main question to be addressed is whether high estrogen levels have a detrimental influence on the development of existing breast cancer. Physicians can acquire knowledge from these two clinical models: [1] a patient who had been pregnant 1 to 3 years before the diagnosis of breast cancer, and [2] a patient who had been diagnosed with breast cancer after the use of oral contraception for a period of 1 to 3 years. As it takes several years for a breast cancer lesion to become clinically detectable, these models suggest that both types of patients had a microlesion that was exposed to high endogenous or exogenous estrogen plus P.

A comparison of breast cancer in pregnant and nonpregnant patients who were matched for age and stage of disease revealed that prognosis was not exacerbated in the pregnant patients (130–133). In addition, several studies showed, during the 3 to 5 years after delivery, a gradual increase in the incidence of breast cancer, which subsequently declined to normal rate or even below at 10 years after delivery (130, 134). This observation demonstrates that pregnancy or hormonal changes during pregnancy, such as high levels of serum estrogen and P, may serve as a promoter to an existing lesion, but it may also serve as a protector from the development of a new carcinogenic lesion (135). This conclusion was supported by Dupont et al. (136) in their reevaluation of benign breast biopsy samples from 3,303 women (mean: 17 years follow-up). The relative risk of developing breast cancer was 0.98 for women who took exogenous estrogens compared with 1.8 for nonusers. Exogenous estrogens lowered the observed breast cancer risk in women with atypical hyperplasia (RR 3.0 vs. 4.5), with proliferative disease without atypia (RR 0.92 vs. 1.9), and without proliferative disease (RR 0.69 vs. 0.91).

These results suggest that exogenous estrogen reduces the risk of breast cancer associated with benign breast disease. Estrogen had little effect on cancer risk in women without proliferative disease, but it significantly reduced the risk in women who had proliferative disease without atypia.

**Breast Cancer Survivors and Hormone Therapy**

In a retrospective study of 77 breast cancer survivors who were on HT, DiSaia et al. (137) showed that no significant adverse outcome was detected in this group compared with a control group. In a very recent publication, a meta-analysis was performed on studies that included 717 women who had used HT some time after diagnosis of breast cancer, and 2,545 women who had not. Breast cancer survivors using estrogen therapy experienced no increase in the risk of recurrence, compared with controls (RR 0.72; 95% CI, 0.47–1.10), and had significantly lower mortality rates (3.0%) than the nonusers (11.4%) over the combined study periods (RR 0.18; 95% CI, 0.10–0.31) (138). In 2001, O’Meara et al. (139) studied 2,755 women aged 35 to 74 years, who were diagnosed with invasive breast cancer, of whom 174 used HT. Each HT user was matched (similar age, disease stage, and year of diagnosis) to four randomly selected nonusers of HT. Women in the meta-analysis were recurrence free at HT initiation. The rate of breast cancer recurrence was 17 per 1,000 woman-years in those who used HT after diagnosis, and 30 per 1,000 woman-years in nonusers (adjusted RR for users compared with nonusers = 0.50; 95% CI, 0.30–0.85). Breast cancer mortality rates were 5 per 1,000 woman-years in HT users and 15 per 1,000 woman-years in nonusers (adjusted RR 0.34; 95% CI, 0.13–0.91). Total mortality rates were 16 per 1,000 woman-years in HT users and 30 per 1,000 woman-years in nonusers (adjusted RR 0.48; 95% CI, 0.29–0.78).

Based on these studies as well as current information, we can conclude that high endogenous (i.e., in pregnancy) or exogenous estrogen (i.e., oral contraception or HT) does not exacerbate the existing state of breast cancer, and may even serve as a protector.

In an attempt to summarize the previous information regarding the issue of sex hormones and breast cancer, we would like to emphasize the following points. The controversy regarding the influence of estrogen on the development of breast tumors is based partially on the confusion of the role played by endogenous and exogenous estrogen. It is noteworthy that estrogen is synthesized within breast cancer cells as in other cells, and it acts predominantly at the local tissue level. Thus, the total amount of estrogen synthesized by this extragonadal site may be small, but the high local tissue concentrations achieved probably exert biologic influence. It has been determined that the intracellular estrogen concentration present in breast tumors of postmenopausal women is at least 20-fold higher than found in plasma (101, 102). Consequently, this extragonadal estrogen biosynthesis plays a major physiologic and pathophysiologic role that has been largely unrecognized in the development of breast cancer. Breast tumor cells are independent in their estrogenic milieu on the serum levels of estrogen, as estrogen is produced by local aromatase and other locally existing enzymes.
It is important to mention that this production of estrogen (in intracrinologic fashion) depends on an external source of C19 androgenic precursors, because these extragonadal tissues are incapable of converting cholesterol to the C19 steroids (140, 141). As a result, circulating levels of T and androstenedione, as well as dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS), become extremely important in providing adequate substrate for estrogen biosynthesis. Therefore, we can question the actual role of external estrogen as administered by HT.

Due to the physiologic model of tumor cell growth previously mentioned, the estrogens can be described as having a promoting, rather than an initiating effect in tumor development. Once breast cancer initiation has taken place, estrogens may promote the growth of transformed cells, leading to early development of detectable breast cancer. In addition, a group of normal tumor suppression genes is activated by estrogens, which can protect the breast from increase in genetic damage and neoplastic changes. Examples of these are the BRCA1 and p53 (142).

Another important point is the actual effect of estrogen on breast cancer mortality. Based on the attitude toward prevention and treatment of malignant diseases in which prevention of mortality is a gold standard, HT was found to cause a significant decrease in this disease. Whether HT increases the incidence of breast cancer is less convincing compared with the decrease HT promotes in mortality rate.

Most important, as in all biologic effects, there may be a tissue-specific threshold and ceiling levels for adequate response, below which no response would occur, and above which detrimental effects may result. This hypothesis is based on the paradoxically observed phenomenon that high doses of estrogen do not stimulate but rather inhibit tumor growth, a discovery that has also given rise to therapeutic applications. The results of in vitro experiments have revealed that many, but not all, endogenous E2 metabolites elicit a biphasic pattern of proliferation in the receptor-positive breast cancer cell line; that is, at low concentrations they have a stimulatory effect on cell growth, and at the highest concentrations they have an inhibitory effect on cell growth (143).

The fact that high estrogen dosages can induce remission in breast cancer has been known for some time. Synthetic estrogens such as diethylstilbestrol and ethinylestradiol exhibit the same magnitude of effect as the antiestrogen tamoxifen, although fewer side effects have been encountered with tamoxifen (144, 145). It also has been noted that tumors that cease to respond to tamoxifen may undergo clinical regression with the administration of synthetic estrogens, suggesting different mechanisms of inhibition (146). Thus, it would be correct to assume that the biologic effect of estrogen is composed of the sum of the total effects of the metabolites produced in the specific tissue, which are the important factors in determining the resulting effect.

COLORECTAL CANCER

The relatively neglected relationship between estrogen and human malignancies has been exemplified in several comprehensive epidemiologic reports on colonic cancer and estrogen. The recent discovery that the second estrogen receptor-β is dominant in the alimentary tract has contributed to the knowledge of the role played by estrogen in the pathophysiology of the alimentary tract (147). As expected, this relationship can be either beneficial or hazardous.

Colorectal cancer is the third leading cause of cancer deaths in women. On the basis of gender difference, in the early 1980s McMichael and Potter (148) hypothesized that exposure to exogenous estrogen may protect women against colon cancer. Recent clinical and experimental epidemiologic studies have revealed that estrogen may be involved in malignant colorectal tumors. The sex differences in site-specific incidence—colon carcinomas that originate proximally (right) or distally (left) to the splenic flexure exhibit differences in incidence according to age and gender—the increased incidence of colon cancer in women with breast cancer, the protective effect of increasing parity, and the reduced risk in postmenopausal women on hormone therapy are all elements with an implication that sex hormones may play a role. The magnitude of the protective effect of HT ranged from relative risk of 0.54 to 0.76 (149–152), as confirmed by the latest WHI publication which observed a colorectal cancer relative risk of 0.63 (95% CI, 0.43–0.92). As colorectal cancer is the second most common neoplasm and is a cause of death among nonsmoking women in developed countries, this observation may have a major public health impact.

The Framingham (Massachusetts) Study (153), initiated in 1948, which followed 1,394 women aged 28 to 62 years at first examination, revealed that 44 women developed colon cancer. The median age at time of diagnosis of colon cancer was 74.2 years (range: 74.2 to 89.2 years). During the follow-up period, the study population underwent a hand radiography examination (median follow-up after hand radiography: 23 years; range: 0.1 to 27.5 years). The incidence of colon cancer decreased from 2.19 per 1,000 woman-years among the women in the lowest age-specific percentile of bone mass, to 1.59 and 1.08 among women in the middle and the highest percentile, respectively. These figures correlated to the rate of colon cancer from the lowest to the highest percentile (1.0, 0.7 [95% CI; 0.3, 1.3]), and 0.4 (95% CI, 0.2, 0.9) (P for trend = .033). These findings suggest that women with increased bone mass density, which probably reflects greater cumulative estrogen exposure, have a decreased risk of developing colon cancer.

The precise biological mechanisms employed by estrogen to stimulate protective factors, have not yet been identified. Several hypotheses have been proposed to elucidate this inverse association. The presence of two estrogen receptors.
could explain the selective actions of estrogens on different target tissues.

Recently, estrogen receptor-β was detected in human colon cancer cell lines, and differential localization of estrogen receptor-β immunoreactivity was detected in normal colon, in adenomas, and in colorectal carcinomas (154). It was suggested that estrogen, via estrogen receptor-β, at concentrations found during replacement therapy, may inhibit the development of colon cancer by inducing apoptosis of cancer cells (155). It was also implied that estrogen acts on a single major transformation step in the oncogenic process, or is involved in multiple events that avert the course of this transformation (156). Several investigators have hypothesized that exogenous estrogens may protect colonic mucosa from neoplastic transformation by suppressing methylation of the promoter region of the estrogen receptor gene (157). This methylation-associated loss of estrogen receptor gene expression may result in deregulated growth of colonic mucosa. The tumor cell doubling time of colon cancer appears to vary from 204 days (158) to 936 days (159), which strengthens the theory that estrogen, or its metabolites, may play an important role in influencing growth of the tumor by inhibiting proliferation of colorectal cancer cells.

The aforementioned data, although not extensive, appear to indicate that in colorectal cancer the recent mode and dose of exogenous administration of estrogen is within the favorable therapeutic window for the disease. We believe that each of the estrogen-dependent tumors has a favorable therapeutic window, and that finding the proper mode of delivery and its associated dosage are important avenues of research.

REFLECTING ON THE WOMEN’S HEALTH INITIATIVE (WHI) STUDY

Due to growing scientific interest in research on women’s health, in April 1991 the U.S. National Institutes of Health (NIH) launched the WHI study to focus on strategies to prevent major causes of death and disability, such as heart disease, breast and colorectal cancer, and osteoporosis in postmenopausal women (1, 160). The WHI study comprises three components: a randomized clinical trial, an observational study, and a community prevention study. The first component is the HT study, the objective of which was to evaluate the prevention of heart disease and osteoporosis, and assess any associated risk for breast and colorectal cancer.

Osteoporosis, breast and colorectal cancer, and CVD were selected because of their long-term implications in the mortality and morbidity of postmenopausal women. Osteoporosis engenders hip fractures in one-sixth of all women, thus contributing to increased mortality and disability, with major implications for quality of life. Heart disease is the foremost cause of death in postmenopausal women, as more than 240,000 women die of heart attacks each year. Breast cancer is the second leading cause of cancer deaths in the United States. More than 46,000 women die of breast cancer annually, with an annual diagnosis of approximately 183,000 new cases. Colon cancer is the third leading cause of U.S. cancer deaths, resulting in over 28,000 deaths annually. Approximately 51,000 and 16,500 new cases of colon and rectal cancer, respectively, are diagnosed yearly.

The WHI study has been the largest long-term, placebo-controlled, randomized trial of HT. It is of extreme importance to the reproductive medicine community, and there has been immense interest in the findings. This study has provided data that could previously only be estimated from observational studies. The investigators’ objective was to publish detailed analyses of the effects of estrogen plus P on the development of CVD, cancer, osteoporosis, cholelithiasis, degenerative arthritis, sexual function, cognition and dementia, and quality of life. However, the study was terminated prematurely, because the results had crossed the threshold for adverse outcome (breast cancer combined with global outcome statistics). However, the estrogen versus placebo aspect of the trial continues, as an adverse threshold has yet to be reached.

The WHI study enrolled participants between 1993 and 1998 at more than 40 centers, and the investigation was scheduled to end in 2005. For this study, women of 50 to 79 years of age, who had intact uteri, were randomly assigned to receive a daily combination of 0.625 mg of CEE plus 2.5 mg MPA (Prempro; Wyeth, Philadelphia, PA) or placebo. Women who had undergone a hysterectomy received estrogen only (CEE-alone) (Premarin; Wyeth), or placebo. The section that studied treatment with CEE + MPA was terminated after 5.2 years (range: 3.5–8.5 years), because the risks of CEE + MPA (increase in breast cancer, CHD, stroke, and pulmonary embolism) were considered to outweigh the benefits (reduction in hip fracture and colorectal cancer). The other section of the study in which estrogen alone was administered to women after hysterectomy continues, with close monitoring by the Data and Safety Monitoring Board (DSMB). Participants in the CEE-only trial were informed that risk for breast cancer had not increased after 5.2 years. Similar to participants in the CEE + MPA trial, participants receiving only CEE had been notified in the years 2000 and 2001 of increased risks for heart attack, stroke, and blood clots during the early years of the trial.

These data demonstrated significant benefits as well as hazards. On the positive side, the fracture data (clinical vertebral, hip, and other fractures) confirmed significant reduction in fractures, with hip fracture reductions being the most important new finding. Similarly, the previous epide-

miologic estimation of reduction in colon cancer was con-

firmed (161). On the negative side, the risk of breast cancer conforms to the estimates provided by the meta-analysis of observational studies (112). The expected venous thrombo-
embolism risk was confirmed, and the previously ambiguous observational data on stroke were reflected in an adverse risk of stroke in the HT group. It was, therefore, concluded that the combination of CEE + MPA should not be initiated or continued for primary prevention of CHD, and that there is a substantial risk of breast cancer.

The WHI publication has had an enormous impact on women’s lives during their senior period. Worldwide, the attitude toward HT has changed dramatically from cautious treatment with limitations to a warning against its use. This ignores that HT has been in use for the last 60 years, and extensive data already have accumulated. In fact, an NIH MEDLINE search for the term “estrogen” will reveal more than 116,800 publications that deal with the complex and variable activities and applications of the sex steroid on the human body.

Irrefutable data should be collected and presented before adopting a negative attitude toward the use of estrogen in treatment of aging women. The WHI does not provide such a study; since its publication, hundreds of critiques have been published. The methodology, population involved, statistics, drug used, and the results have all come under question (162–165). We would like to summarize the main criticisms and to emphasize new points.

An important issue is that the second section of the study, featuring women who have undergone a hysterectomy and who are being treated with estrogen alone, has not been terminated. This signifies that, between the two sections, the difference is the use of MPA and not estrogen. Although the specific P used in this study, MPA, is the most commonly used in North America, it has certain disadvantages. It has a relatively long half-life (approximately 26 hours) compared with the 7- to 9-hour half-life of norethisterone (166) (more commonly known by this name in Europe). This implies that the use of MPA for HT creates a relatively high progestogenic milieu that will dominate the effect of hormones and interfere with the investigation of the effects of estrogen.

Another important factor is the age issue. Younger climacteric women are often symptomatic, making them unlikely to agree to participate in a study that includes administration of placebo. Thus, the practical considerations of recruitment selected women for treatment at an advanced age (mean: 63 years at initiation of the study; 45% were in their 60s and 21% in their 70s), who had been hypoestrogenic for more than 10 years. This is definitely not typical of the women who attend postmenopausal clinics. The basic physical conditions, needs, and physiologic responses of these women vary.

We also could speculate that the appearance of typical symptoms of menopause differentiated the study participants from the nonsymptomatic women in respect to the biologic alteration of menopause. In terms of basic physiology, it appears that women in the older age group have some degree of atherosclerosis, although they are not clinically symptomatic. Experimental evidence in the monkey has indicated that the use of estrogen in unhealthy, atherosclerotic vessels may cause a certain amount of harm (81). In addition, in postmenopausal women, the known vasodilator effects of estrogen evanesce with increasing age (167). Thus, characterizing the study group as “healthy postmenopausal” women may not be adequate. In other words, the WHI was not a true primary but a secondary prevention trial in terms of cardiovascular study.

Furthermore, the knowledge that has been acquired over the last decade—after the initial design of the WHI trial—facilitates a greater understanding of the subgroup of this aging population. For example, we currently have much greater knowledge about inherited coagulation defects known as thrombophilia. Women with such defects who are receiving HT are prone to 40-fold greater thromboembolic phenomena than controls. In the WHI study group, almost 2% of the population had a history of deep-vein thrombosis/pulmonary embolism, which categorized them as a subgroup with increased incidence of inherited thrombophilia. Even without taking into consideration this specific inherited defect, the presence of a history of venous thromboembolism/pulmonary embolism alone indicates that, in women who have previously had venous thrombolic embolism, the risk of recurrence when on HT is increased (168). The combination of HT use and thrombophilias (especially if multiple) causes a fourfold relative risk of venous thromboembolic embolism (169), so this unique subgroup of patients perhaps should have received other treatment.

We are of the opinion that the main error in the study is the “fixed dose” that was administered to all participants in the study. It is totally unrealistic and unjustified not to consider individual physical needs and conditions while planning treatment. Specialists in HT are well aware of the difficulties in adjusting the right formulation, combination, dosage, and duration of the specific drug used for a menopausal woman. The variety of medical conditions in women participating in the WHI that needed specific consideration while planning the treatment included hypertension, smoking, obesity, diabetes, and CVD.

For instance, avoidance of oral administration of estrogen is highly recommended in smokers, because of liver metabolism, where nicotine is known to act as an antiestrogen, causing a reduction in estrogen activity by enhancing the “detoxification” of E₂. There are two main pathways of estrogen hydroxylation that occur in the liver. One pathway results in the formation of 2-OH-estrone and 2-OH-estradiol, and the other results in 16-OH-estrone and 16-OH-estradiol. The first two metabolites are very weak estrogens, whereas the latter two are known to be potent estrogens, even stronger than 17β-estradiol. The pathway leading to the formation of 2-hydroxylation of E₂ is increased in female cigarette smokers (170), which may partially explain why they have a
lower risk of uterine cancer and a higher risk of osteoporosis than nonsmokers (171). Smoking has a known reduction effect on oral estrogen, so the relatively large number of WHI participants who smoke (10.5%) induced quite a large error in planning the treatment and evaluating the results. Female smokers who received oral treatment were, in fact, exposed to lower doses and different metabolites of estrogen during the study period compared with the others in the study group. All these metabolic effects could have been altered by administering the drug in a different form (172).

It also is well known that administration of oral estrogen exposes the liver to high concentrations of the hormone in the portal vein, which causes an increase in hepatic production of many substances, among them rennin-angiotensin, coagulation factors, and bile acids. In hypertensive women, the increased rennin-angiotensin system may cause imbalance in the antihypertensive treatment (in the WHI-treated group, 35.7% were treated for hypertension). These factors may also help to account for the increased incidence of venous thrombosis and pulmonary embolism in the high-risk groups (in the WHI study, 79 women with a previous history of thromboembolic phenomena were included).

The use of estrogen in these groups of patients ought to have been considered before administering a fixed treatment regimen. The administration of a fixed dose is contrary to the recommendation of starting with low-dose therapy in postmenopausal women who have not received estrogen for a long period after the initiation of menopause and who wish to start treatment. Furthermore, in the treatment group 42% of the women discontinued the drug prematurely because of disturbing side effects, one of which was persistent vaginal bleeding. These phenomena demonstrated that the women received inadequate treatment. We find that these studies emphasize how crucial it is to adjust the treatment to the woman; as clinicians, we would not consider discontinuation by almost 50% of the participants for side effects to reflect good individual treatment or clinical judgment.

When dealing with the climacteric syndrome, among other considerations is the effect of HT on SHBG. This plasma protein is produced in the liver and is known to bound to estrogen and androgen. Any drug that increases the serum level of SHBG will reduce the free levels of estrogen and androgen. It is well known that a low level of free T results in decreased libido in postmenopausal women. It is also well known that in oral administration of estrogen (especially Premarin), rather than transdermal estrogen, there is an increase in SHBG of up to 40%. It is, therefore, unwise to administer oral estrogen to patients who are known to have a 30% to 60% reduction in libido, as this form of treatment will further augment the reduction.

Therefore, it is our opinion that in a complex health situation, such as the menopausal period which involves almost every organ and system in the human body, administration of hormones without considering these variables raises many questions about validity and clinical applicability of this study. Prescribing a fixed dosage of estrogen, which might be an overdose for some but inadequate for others, without adjusting the route of administration, P type, dosage, or duration, is imprudent.

It is not our intention to underplay the importance of the information gathered by the WHI study, but this research should not serve as a milestone for change in the entire attitude toward treatment with sex steroids in the postmenopausal period.

**CONCLUSIONS**

The main points we have made require more research, but in our opinion the concepts are rational. [1] It appears that there are time windows for initiation of treatment and for dosage for each drug and organ. It is crucial to identify these windows to achieve the best treatment results with minimum risks. It is possible that, in the fields of brain health, colon cancer, and osteoporosis, these windows are more imminent than in those of breast, heart, and coagulation. [2] Data gathered on several systems in the body indicate that HT affects healthy and damaged tissues in varying ways. Therefore, it is crucial to identify damage before the initiation of therapy. Professionals should also be encouraged to advocate early initiation of treatment before the onset of damage. [3] The key to successful menopausal treatment is the development of methods to accurately measure and reproduce changes in biologic parameters. The variability among women could render this task extremely complex. However, even small changes should be detectable, and could be of significance in the long term. It is necessary to find a parameter with minimum variability to achieve accuracy. The current lack of such methods emphasizes the problems in interpretation of the clinical data. [4] It is logical to assume that genuine hormones would provide a true response, although there are few viable opportunities to investigate histologic changes, such as through bone biopsy samples.

Brain function is the most important variable in determining the course of human aging, so unlimited efforts should be invested in improving brain function. It appears that sex hormones have the potential to affect this process favorably. Thus, this effect should not be ignored when contemplating HT. Currently, HT appears to be the best form of pharmacologic treatment to improve brain function, as well as to reduce the risk of colon cancer. It is probably the best preventive strategy for osteoporosis. With this in mind, limiting HT to the treatment of climacteric symptoms only is unjustified.

Estrogen endocrinology is complex, with complex feedback mechanisms, many metabolite pathways, sex hormone binding protein and free hormone issues, intracrinology specific to humans, and wide variability among women. A vast amount of clinical and laboratory data are available on this
subject. In our opinion, assuming that one group of drugs at an unknown relative dose can replace the entire complex of estrogen in the human body is too naive. Thus, we believe that there is an urgent need to apply the knowledge available in this field to clinical therapy. The data are obtainable, so only the desire to search for and obtain appropriate information are needed. The response of the medical community to the latest results of the WHI study emphasizes that menopause should be recognized as a specialized section in reproductive medicine. Professionals who treat menopausal women should be dedicated to investing their time and effort toward gaining more knowledge and providing adequate treatment.

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