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Estrogen and Cognitive Functioning in Women

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Research in basic neuroscience has provided biological plausibility for the hypothesis that estrogen replacement therapy (ERT) would protect against cognitive aging in healthy women. The weight of the evidence from randomized controlled trials of estrogen and cognition in women shows that this hormone preferentially protects verbal memory in postmenopausal women, whereas findings from observational studies are less consistent and show a more diffuse effect of estrogen on a range of cognitive functions. There is fairly consistent evidence from epidemiological studies that ERT significantly reduces the risk of Alzheimer's disease (AD) in women. On the other hand, findings from controlled treatment trials of women diagnosed with probable AD failed to show that physiological doses of ERT ameliorate existing deficits in cognitive functioning and/or prevent further deterioration in memory that inevitably occurs in these women over time.

Finally, an accumulating body of evidence is beginning to suggest that the immediate postmenopausal period may constitute a critical window for treatment with ERT that maximizes its potential to protect against cognitive decline with aging and/or to reduce the risk of AD. (*Endocrine Reviews* 24: 133–151, 2003)

I. Introduction

DURING THE PAST two decades, the availability of new medical technologies and a focused research effort have combined to provide considerable new knowledge of the mechanisms of action of estrogen on the central nervous system (CNS) that may underlie its possible influence on cognitive functioning. The intensity of this research effort has been spurred by the potential clinical applications of these findings, which are related to the dramatic increase in female life expectancy during the past century. Whereas in 1900 female life expectancy was 54 yr, women now live to an average age of 83 yr in industrialized countries (1). On the other hand, the age of spontaneous menopause has remained stable at approximately 50 yr since recorded history (2, 3). The fact that women now live more than one third of their lives after the menopause has encouraged research efforts to discover new ways to prevent degenerative diseases that jeopardize the quality of life for elderly women. To the extent that estrogen protects aspects of cognitive functioning, it might help to preserve those functions and to delay the onset of dementia during the latter one third of women's lives.

This article will review the human clinical literature on the effects of estrogen on cognitive functioning in women. An attempt will then be made to provide an explanation for the inconsistencies in the human literature. However, before these areas are reviewed, the most relevant neurobiological and behavioral effects of estrogen will be briefly described.

Abbreviations: AD, Alzheimer's disease; BSO, bilateral salpingo-oophorectomy; BVRT, Benton Visual Retention Test; CAH, congenital adrenal hyperplasia; CASI, Cognitive Abilities Screening Instrument; CBF, cerebral blood flow; CEE, conjugated equine estrogens; CI, confidence interval; CNS, central nervous system; E_2, estradiol; E+P, estrogen plus progestin; ER, estrogen receptor; ERT, estrogen replacement therapy; IQ, intelligence quotient; LAD, leuprolide acetate depot; LTM, long-term memory; mMMSE, modified Mini Mental State Exam; MPA, medroxyprogesterone acetate; MRI, magnetic resonance imaging; OR, odds ratio; P, progesterone; PET, positron emission tomography; RCT, randomized controlled trial; SERM, selective ER modulator; SES, socioeconomic status; SPECT, single photon emission tomography; STM, short-term memory; TAH, total abdominal hysterectomy; TS, Turner syndrome; WHI, Women's Health Initiative.

II. Mechanisms of Estrogen Action on the CNS

A comprehensive account of the mechanisms of action of estrogen on the CNS is beyond the scope of this article, and several recent reviews of the area are available (4, 5). However, in the attempt to describe the biological plausibility for the hypotheses that estrogen affects aspects of cognitive function, the mechanisms that are likely the most relevant will be briefly described here.

In 1980, the identification and mapping of estrogen receptors (ERs) in the brain led to the discovery that these proteins were concentrated in the hypothalamus and the pituitary (6), and, later on, in the hippocampus, the cerebral cortex, midbrain, and brainstem. Two types of intracellular ERs have

now been identified, ERα and ERβ (see Ref. 4 for a review). Although the distribution of ERα in brain has been fairly well established by steroid autoradiography, immunocytochemistry, and *in situ* hybridization (6, 7), there is less certainty concerning the localization of ERβ. Recently, the colocalization of ERβ mRNA with cell nuclear ERβ immunoreactivity was demonstrated in the rat cerebral cortex, in the paraventricular nuclei, and in the preoptic area of the hypothalamus (8). Importantly, the use of [^{125}I]estrogen, which labels ER with a higher specific radioactivity than [^{3}H]estradiol (E_2), led to detection of label in pyramidal cells of CA1 and CA3 in the ventral hippocampus (9), areas shown to be important for memory. In addition to its ability to effect both direct genomic actions, estrogen can also act in the CNS via nonnuclear receptors that involve interactions of ERs with second messenger systems (10). Third, there is *in vitro* evidence that E_2 can modulate the functions of neural and vascular cells via nongenomic actions (11). Documented forms of nongenomic estrogen effects include rapid actions on excitability of neuronal and pituitary cells, the activation by estrogens of cAMP and MAPK pathways that affect activity of targets such as kainate and IGF-1 receptors, modulation of G protein coupling and effects on calcium channels and calcium ion entry, and the protection of neurons from damage from free radicals and excitotoxins (5).

Because of the widespread presence of the ERs in their various forms throughout the brain, estrogen actions are also widespread and affect many neurotransmitter systems including the catecholaminergic, serotonergic, cholinergic, and γ-aminobutyric acidergic systems (5). Several well described effects of estrogen on brain structure and function offer possible explanations for the mechanisms of action by which this steroid hormone may influence cognitive functioning in women. For example, one of the actions of estrogen is to increase dendritic spine density on CA1 pyramidal neurons in the hippocampus within 24–72 h after acute administration (12, 13). When progesterone (P) is administered after E_2 priming, spine density increases during the first 6–8 h, followed by a rapid return to low baseline levels. Interestingly, changes in memory function in rats show a strong temporal relationship with these hormonal alterations in neuronal structure. When ovariectomized rats were primed with 10-μg injections of E_2 72 and 48 h before testing, memory retention was improved compared with retention in rats primed with oil (14). An injection of P maintained the retention enhancement if testing occurred within 8 h of the P injection but not when testing occurred more than 24 h after the P injection (14).

Second, estrogen increases the concentration of choline acetyltransferase, the synthetic enzyme for acetylcholine (15), a neurotransmitter critically implicated in memory functions and the levels of which are markedly reduced in Alzheimer's disease (AD) (16). Finally, estrogen's numerous neurotrophic effects might explain how this hormone could protect against declines in cognition with aging. Widespread colocalizations of ER and nerve growth factor are found mainly in neurons of the cerebral cortex, hypothalamus, hippocampus, and sensory ganglia, implying that estrogen facilitates neurotrophin responses (17). Estrogen may also exert neuroprotective effects via modulation of molecules involved in apoptosis (18) and via its action as an antioxidant (19). Both 17β- and 17α-E_2 provide neuroprotection against oxidative stress via an antioxidant effect (19). Moreover, E_2, *in vitro*, promotes the breakdown of the β-amyloid precursor protein to fragments less likely to accumulate as β-amyloid (20). Estrogenic effects on neural systems that affect mood, fine motor control, and pain have also been described (10). The potential for these myriad mechanisms of action of estrogen to influence the structure and function of brain areas that subserve a variety of cognitive functions, described only briefly here, provides biological plausibility for the clinical hypothesis that estrogen helps to maintain aspects of cognition in women.

III. Components of Cognition

Whereas a comprehensive review of the components of cognition will not be attempted here, several basic concepts are important for an understanding of the results of the clinical studies on estrogen and cognition, the focus of this review. Cognition is an umbrella term for the totality of human information processing. It is multidimensional and includes such functions as attention, pattern recognition, memory, learning, language processing, problem solving, abstract reasoning, or higher-order intellectual functioning and psychomotor skills. Memory, a critical aspect of cognition, is composed of numerous component processes that localize to different anatomical sites (21). Human memory may be regarded as a system that stores and retrieves information acquired through the senses. Visual and auditory systems have been the most thoroughly explored. Short-term visual memory implies that the visual memory trace decays after a fraction of a second to several seconds (22), and long-term visual memory describes the ability to identify a visual stimulus for days, months, or years after exposure. The same is true for verbal memory; *i.e.*, short-term verbal memory describes the situation in which a verbal stimulus (for example, a word) is held in memory for seconds, whereas long-term verbal memory describes the ability to recognize or remember a verbal stimulus or association over an extended period of time.

The most compelling evidence that short-term memory (STM) and long-term memory (LTM) are mediated by two separate systems came from studies of patients with hippocampal lesions resulting in STM deficits, which drastically reduced their ability to acquire new information. On the other hand, these adult patients could easily and accurately recall incidents from early life, indicating that LTM was intact (23, 24). Whereas learning is concerned with encoding and storing information, forgetting often occurs because material that has been learned can no longer be accessed or retrieved. The inability to retrieve previously learned material may be due to the fact that it had never been encoded (25) or because the recall or recognition cues are not effective. Either or both of these possibilities could impair LTM.

Working memory refers to the ability to "hold in mind" and flexibly manipulate information over a short period of time to make a response (26). During the past decade, considerable progress has been made toward specifying the

neural mechanisms underlying working memory in humans (27, 28). Functional neuroimaging studies show prefrontal cortical activation during the performance of working memory tasks (29, 30). Moreover, there is evidence that working memory efficiency decreases with increasing age (31, 32).

As discussed above, patients with hippocampal lesions have anterograde amnesia; that is, they are unable to remember new facts for more than 30 sec (23, 25). Indeed, there is convincing evidence from studies of nonhuman primates that the consolidation of a memory occurs in the hippocampus (21), although the mechanisms that facilitate consolidation are not clear. Findings from studies on rats, monkeys, and humans have consistently provided evidence of the importance of medial temporal-lobe structures in the acquisition of new information as well as in the retrieval of previously learned information (33). Recently, these findings have been confirmed by neuroimaging studies using magnetic resonance imaging (MRI)-based volumetric measurements of the hippocampus that demonstrated a structural-functional relationship between memory loss and hippocampal atrophy in individuals with AD (34). Based on the information that estrogen induces cyclic changes in synapse formation and spine density of the hippocampus (12, 13), and in embryonic hippocampal neurons in cell culture (35), and also increases the synthesis of acetylcholine in basal forebrain and the cholinergic neurons that project to the hippocampus and cortex (36, 37), it might be predicted that estrogen would have its most profound effect on hippocampally dependent cognitive functions such as memory and learning, which involve the acquisition, encoding, and consolidation of new information. Estrogen may also be important for working memory, which is mediated by the frontal lobes, because this hormone enhances STM, an important component of working memory.

In summary, there are numerous cognitive functions in humans that are differentially mediated by specialized, anatomically distinct brain areas. Therefore, a lesion in a discrete area of the brain, such as might occur after a stroke, will result in a deficit in the specific cognitive function subserved by the area in which the brain injury occurred, whereas other cognitive functions mediated by brain areas remote from the locus of the brain injury will be unaffected. Certain neurotransmitters and brain structures, along with neural pathways and projections, are also critical for cognitive function. The extreme complexity of this system makes it unlikely that any one neuroactive chemical could influence the totality of cognitive functions. Rather, it is probable that any given neuroactive compound would exert a specific action on certain domains but not on the totality of cognitive functions. Estrogen is a neuroactive hormone; the largest concentrations of ERβ receptors are in the hypothalamus, the amygdala, and in the hippocampus (38); and the neurotransmitter that estrogen up-regulates most profoundly is acetylcholine (36), although it affects the serotonergic, noradrenergic, and dopaminergic systems as well (5). Moreover, the hippocampus itself has been shown to be critical for explicit or declarative memory. One possible interpretation of these findings, taken together, is that estrogen would have its most profound effects on memory, although it does not exclude the possibility that it might influence other cognitive functions as well. The description of sex differences in cognitive function that appears below provides some support for this prediction.

IV. Sex Differences in Cognitive Functioning: Organizational and Activational Effects of Sex Hormones

Although there are no qualitative differences in cognitive skills between the sexes, quantitative differences have been consistently found. Whereas women tend to excel on tasks of verbal skills and memory, on perceptual speed and accuracy, and on fine motor skills (female-typical skills), men tend to outperform women on tests of visual memory and on mathematical and spatial ability (male-typical skills) (39). Although the effect sizes of these sexual dimorphisms in cognitive function are modest (0.5–1.0 SD), they have been found consistently in studies that have attempted to document them. These sex differences in cognitive functioning are thought to occur as a result of the exposure of the fetal brain to differential levels of the sex hormones during prenatal life. These so-called organizational effects of sex hormones are thought to permanently alter the structure and/or function of specific brain areas during fetal life, perhaps by directing the development of certain neural pathways. Postpubertally, circulating levels of a given sex hormone serve to amplify the neural "hard-wiring" laid down prenatally under its influence, usually referred to as the activational effect of that hormone. Therefore, this psychoendocrine theory proposes that, during prenatal life, the presence of significant quantities of a sex hormone organizes neural substrates for a certain behavior or function that becomes manifest after puberty under the influence of high circulating levels of that same hormone.

An impressive amount of evidence is available to suggest that this psychoendocrine theory of the genesis of sex differences in cognition may be true. Perhaps the most compelling support comes from studies of individuals who have a genetic disorder that resulted in their having been exposed to abnormal levels of sex hormones during prenatal life. For example, girls with congenital adrenal hyperplasia (CAH) have a 21-hydroxylase deficiency that prevents them from synthesizing cortisol (40). This results in high ACTH levels and, consequently, in an overproduction of adrenal androgens. CAH girls may be born with different gradations of genital virilization that are surgically corrected after birth when necessary. If the prenatal sex hormone environment contributes to cognitive sex differences as the psychoendocrine theory proposes, it would be predicted that, compared with normal controls, girls with CAH would have better performance on tests of male-typical cognitive functions such as enhanced spatial ability because of the prenatal exposure of their brains to large amounts of androgens. Indeed, CAH girls performed better on tests of spatial ability and worse on tests of verbal ability compared with their unaffected sisters (41). The superior spatial skills of CAH girls were later confirmed using spatial tasks that normally show sex differences (42). Finally, in two methodologically rigorous investigations, girls with CAH performed significantly

better on three separate tests of spatial ability compared with their unaffected female relatives (43). When CYP21 genotyping was used to determine the degree of fetal androgen exposure in girls with CAH, a dose-response relationship was evident between disease severity and degree of masculinization of behavior of the affected girls (44). Therefore, the combined evidence of these studies on girls with CAH suggests that prenatal exposure of genetic females to excessive amounts of androgens masculinizes their cognitive profile.

Additional evidence of the influence of prenatal sex hormone exposure on subsequent sex differences in cognition comes from studies of girls with Turner syndrome (TS). The ovaries in TS girls apparently form normally but involute prematurely at 4 to 5 months' gestation (45). TS children lack ovarian estrogen production, do not undergo spontaneous pubertal maturation, and are infertile (46). They display a marked deficit in visuospatial abilities consistent with the notion that early exposure to androgen (from the fetal ovaries) promotes subsequent visuospatial abilities (47). In a recent multicenter trial, 7-yr-old TS girls were randomized to treatment with either estrogen or placebo for 2 yr, and their performance on a comprehensive battery of neuropsychological tests was compared with a control group of normal girls matched for age and socioeconomic status (SES) (48). Two years of estrogen treatment were associated with improvement in verbal and nonverbal memory in the TS girls. Interestingly, scores on tests of short- and long-term verbal memory were significantly impaired in the placebo-treated TS group compared with those of the normal, age-matched control group.

One possible explanation for the impaired neurocognitive performance of girls with TS on verbal memory tests may be related to the fact that they do not experience the surge in estrogen production that occurs in normal girls during the first year of life (49), which likely influences brain development. If that is true, then it could be concluded that underexposure of the female brain to estrogen during critical developmental windows results in deficits in female-typical cognitive functions in girls, whereas the exposure of female brains to excessive amounts of androgens during fetal life causes an enhancement of male-typical cognitive functions in childhood, as occurs in girls with CAH.

Of course, the evidence from these so-called "experiments in nature," which are provided by psychoendocrine studies of children with genetic abnormalities affecting the production of sex hormones, constitutes the only information we are ever likely to obtain from humans with regard to the organizational effects of these hormones on cognition because of the obvious ethical constraints on experimentally testing this theory in humans. However, the voluminous animal literature on reproductive and social behaviors in rats and monkeys demonstrates clearly that sex differences in both brain organization and in behavior can be reversed by early hormonal manipulation. For example, prepubertal male rhesus monkeys normally engage in more rough-and-tumble play than females. When pregnant rhesus monkeys were injected with androgens, the female offspring engaged in rates of rough-and-tumble play that were intermediate between those of normal males and normal females (50). The conclusion that their increased rates of masculine-like behavior was due to an organizational effect of androgen on their brains was confirmed by the failure of postnatal castration to alter the atypical behavior of the affected females.

A hypothesis that derives from this literature on the organizational and activational effects of sex hormones on behavior relevant to this review is that, in adulthood, estrogen would have its most profound effect on cognitive tasks, such as verbal skills and memory, perceptual speed and accuracy, and fine motor skills, in which females are known to excel. If this is true, then the administration of estrogen to postmenopausal women should preferentially enhance female-typical cognitive skills.

V. Estrogen and Cognition

A. Human menstrual cycle studies

Perhaps the most obvious strategy to investigate whether changes in cognition may be associated with fluctuations in circulating levels of sex hormones is to observe whether scores on cognitive tests change in association with serum hormone levels during different phases of the menstrual cycle. Unfortunately, the early studies suffer from numerous methodological problems including samples that are too small to detect a significant difference in the variables of interest, failure to confirm menstrual cycle phase by measuring hormone levels, and use of inappropriate cognitive tests or cycle phases to properly test the hypotheses. Indeed, early investigations failed to find any meaningful associations between cognitive abilities and cyclic fluctuation in estrogen levels in women (51–54). In 1981, Broverman *et al.* (55) suggested that the relationship between cyclic hormonal changes and specific cognitive abilities was highly dependent upon a precise identification of cycle phases, exclusion of women who were anovulatory, and use of gender-sensitive cognitive tests (55). More recent studies that have incorporated these factors into their experimental designs and procedures have had somewhat greater success in observing changes in certain cognitive abilities across the menstrual cycle. Most (56–61), but not all, of these studies have found that women perform better on sexually dimorphic tests in which females typically excel during the midluteal phase compared with the menstrual phase, suggesting that estrogen facilitates verbal and fine motor abilities. However, it is important to consider that P levels also peak during the midluteal phase, a fact frequently ignored in these studies, which, with several exceptions (61–62), failed to measure hormone levels to confirm cycle phases. When we performed RIAs on serum to determine cycle phase, we failed to confirm any effect of estrogen on verbal memory or on attention (63). Although performance on a test of visual memory was enhanced during the midluteal compared with the menstrual phase, these higher scores were positively and significantly correlated with serum levels of P but not with levels of E_2 (63). In a recent, well controlled study, however, poorer performance on a test of spatial ability (which favors males) and better performance on tests of motor skills and verbal fluency (which favor females) occurred during the midluteal phase of the cycle in healthy young women compared with their performance during the early follicular phase. More-

over, the fact that scores on verbal fluency were positively associated with E_2 levels and spatial ability scores were negatively associated with E_2 levels provided indirect evidence that E_2, and not P, was responsible for these cycle-related changes in aspects of cognition in young women (62). Therefore, the results of this recent study support the idea that estrogen positively influences performance on sexually dimorphic tasks that favor females and negatively influences performance on tasks that favor males (64).

Perhaps the most consistent finding of the menstrual cycle studies is that performance on visual and on spatial tasks (in which men typically excel) is better in women during the phase of the menstrual cycle that is characterized by relatively low levels of estrogen. The implication that higher levels of estrogen impair visual and spatial abilities in women is consistent with the finding that performance on spatial tasks is significantly better in untreated ovariectomized female rats (67, 68) and cynomolgus monkeys (69).

Despite the methodological problems in the menstrual cycle literature cited earlier, there does seem to be some consistent evidence that variations in performance on cognitive tasks known to be sexually dimorphic occur during phases of the cycle characterized by high or by low levels of estrogen. This is in line with the proposition that estrogen facilitates those cognitive skills in which females typically excel. A corollary of this proposition, that young, cycling women would perform better on tasks in which men typically excel when their estrogen levels are relatively low (*i.e.*, during the menstrual phase of the cycle), also occurs. However, the magnitude of the effect of these menstrual phase differences on test scores is quite small and, for most women, would go unnoticed in everyday life. It must also be considered that the so-called estrogen "deficit" that occurs during menses is relative to the ovulatory and luteal phases of the cycle when levels are much higher. The constant, albeit variable, background of estrogen secretion during all phases of the menstrual cycle makes it more difficult to document positive effects of the hormone on aspects of cognition if they indeed occur. One possible conclusion from the extant literature on the menstrual cycle is that although minor fluctuations in some cognitive abilities occur simultaneously with fluctuations in ovarian hormones during different menstrual cycle phases, levels of sex hormones are sufficient at all times to maintain cognitive functions in women of reproductive age.

The clinical relevance of cognitive fluctuations associated with the menstrual cycle is probably quite minor because these changes are rather modest in magnitude and highly limited in scope. However, documentation of such changes provides important support for the notion that fluctuations in estrogen levels within the physiological range can influence specific aspects of cognition in gonadally intact adult women.

B. Studies in postmenopausal women

1. Randomized controlled trials (RCTs). Another experimental strategy to investigate whether estrogen influences aspects of cognitive functioning has been to carry out prospective RCTs in naturally and in surgically postmenopausal women. Because of the drastic alterations in the hormonal milieu that occur at the time of menopause, this population provides a unique opportunity for investigating the possible effects of estrogen on cognitive functions in women using rigorously controlled experimental designs. A RCT reported in 1952 (70) provided the first evidence for an estrogenic influence on cognition in older women. In that study, 75-yr-old women living in a nursing home randomly received either E_2 benzoate, 2 mg, or placebo im once per week. After 12 months of treatment, verbal intelligence quotient (IQ) scores on the Wechsler Bellevue Intelligence Scale and scores on the Wechsler Memory Scale had increased significantly from pretreatment baseline in the estrogen-treated women, whereas verbal IQ scores decreased significantly in those given placebo during the same time span. Two additional findings from this early study are noteworthy. First, exogenous estrogen failed to influence scores on the IQ performance subscales that mainly measure visual/spatial abilities, and second, the estrogenic enhancement of memory did not endure after the discontinuation of treatment. The fact that the cognitive status of these elderly women was poorly assessed beforehand, that many had history of prior mental illness, and that some had dementia constrains the ability to conclude that estrogen improved verbal IQ and memory in these subjects. Nonetheless, given the positive outcome of this early study, it is puzzling that no further research was carried out in this area for the next 25 yr.

In 1977, Campbell and Whitehead (71) treated middle-aged postmenopausal women with conjugated equine estrogens (CEE), 1.25 mg, or placebo, each administered for 2 months in a double-blind, cross-over design (72). Estrogen treatment was superior to placebo with regard to reduction in insomnia, irritability, headache, anxiety, and the enhancement of memory, and the improvements were independent of hot flush frequency. Changes in memory were assessed only with a self-administered analog rating scale.

Other investigators employed objective, standardized tests of neuropsychological function in studies of estrogen and cognition in postmenopausal women. Nine postmenopausal women treated with piperazine estrone sulfate, 3 mg/d, showed greater improvement in the Guild Memory Scale than women who randomly received a placebo (73). This report of a beneficial effect of estrogen on memory was soon confirmed by others in short-term studies with small sample sizes. After 3 months of treatment with E_2 valerate, 2 mg, or placebo daily, 11 women in the estrogen group had higher scores than 10 women in the placebo group in choice reaction time and in a test that is assumed to involve STM (74).

In contradistinction to these positive findings, other RCTs also undertaken in the 1970s failed to find any effect of estrogen on cognitive functioning. No differences occurred between scores of women given E_2 valerate, 2 mg, or placebo daily on the Integration Memory Test, on a test of logical thinking, or on a reaction time task (75). Similarly, the administration of estriol, 4 mg/d, a very weak estrogen, had no effect on scores on the Groninger Intelligence Test, on digit span, on concentration, or on tempo of work and attention (Spot Pattern Test of Bourdon-Wiersma) (76).

The inconsistent findings that derive from these RCTs

published in the 1970s are difficult to interpret for several reasons. Each of the studies used a different oral estrogen preparation in different doses, and none measured serum levels of estrogens, so that it is impossible to know how cognitive performance was related to actual hormonal status. Some studies included both naturally and surgically menopausal women whose pretreatment serum estrogen levels may have differed. Finally, each study used different measuring instruments to assess cognitive functions and, in some cases, information regarding the reliability and validity of the psychometric measures is not readily available (74–76). Equally important is the fact that no study used a sufficiently comprehensive battery of neuropsychological tests to allow the assessment of all the domains of cognition. It is therefore possible that the negative findings of any study mean only that the psychometric instrument used did not tap an existing cognitive deficit.

As the evidence that estrogen replacement therapy (ERT) endowed benefits with regard to the preservation of bone density started to accrue, the use of ERT for the treatment of postmenopausal women became a more popular clinical practice in the 1980s and beyond. These documented clinical benefits on other organ systems, coupled with new knowledge of estrogenic influences on brain structure and function, stimulated renewed efforts to investigate the possible causal relationship between estrogen and cognition in women. In a controlled, double-blind, cross-over design, Sherwin (77) investigated premenopausal women who needed to undergo total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) for benign disease. They were tested before surgery, after 3 months of treatment with E_2 valerate, 10 mg im, or placebo im every 4 wk and, again, after a 3-month cross-over treatment with the other drug. Scores on tests of verbal memory and abstract reasoning were maintained relative to their preoperative levels of functioning in these surgically menopausal women when they were being treated with ERT, but they decreased significantly when the women were given a placebo. Moreover, the protective effect of estrogen on aspects of cognition did not occur secondary to the alleviation of hot flashes in that study. In a subsequent pilot study, women who randomly received E_2 valerate, 10 mg/month im, after their TAH and BSO maintained their preoperative scores on two tests of verbal memory, whereas scores on those same tests decreased significantly in those treated with placebo (78). Finally, in a replication of the 1988 study, a more comprehensive battery of neuropsychological tests was used (79). Women who randomly received treatment with E_2 valerate, 10 mg/month im, after TAH and BSO had significantly higher scores on tests of short- and long-term verbal memory compared with women who had been treated postoperatively with an im placebo. In the latter two studies, there was a noticeable specificity of the estrogenic effect on verbal memory functions because scores on other tests of cognition such as visual memory were unaffected by hormonal status. Moreover, the earlier demonstration that the protective effect of estrogen on verbal memory was independent of its influence on mood and on hot flashes was confirmed.

Support for these findings was provided by a recent RCT of healthy postmenopausal women (80). Sixty-five-year-old women who had never previously taken ERT randomly received either a transdermal patch containing 7.8 mg E_2 per week, designed to deliver 0.1 mg 17β-E_2/24 h, or a placebo patch for 3 wk. A selective improvement in performance on tasks of learning and memory occurred after treatment only in the estrogen group. Interestingly, ERT also enhanced performance on a mental rotations task, a test of spatial ability, but failed to influence frontal lobe functions such as planning skills and executive functions. In another RCT of postmenopausal women whose average age was 69 yr, higher serum E_2 levels in women who randomly received treatment with a transdermal E_2 patch (0.1 mg E_2/d) for 2 wk correlated positively only with scores on tests of verbal memory (81).

Four RCTs failed to find effects of ERT on aspects of cognitive functioning in postmenopausal women. In one study, women who had undergone TAH and BSO several years earlier were treated with either placebo or with either 0.625 mg or 1.25 mg CEE daily (82). No differences occurred on the only two tests of cognitive function administered, which are both primarily measures of attention. In a cross-over study, women less than 56 yr old received 2.5 g/d of an E_2 gel, and those over 55 yr received 50 μg E_2 via transdermal patch or a placebo gel or patch for 3 months per treatment, separated by a 1-month washout phase (83). Cognitive testing failed to find any effects of the active treatment. When 69-yr-old women were treated with either 0.625 mg CEE or placebo/d, no effects of ERT were apparent on working memory, the only test administered (84). Also, no differences in scores on tests of verbal memory, verbal fluency, psychomotor speed, attention, or visual scanning occurred in 81-yr-old women treated for 9 months with CEE, 0.625 mg/d, plus trimonthly progestin compared with treatment with placebo (85).

Using a different endocrine manipulation, the possible causal relationship between estrogen and cognitive functioning was further investigated in another RCT. Thirty-two-year-old infertile women with a large uterine myoma but with normal ovarian function were tested at pretreatment baseline and again after 12 wk of treatment with 3.75 mg of a GnRH agonist, leuprolide acetate depot (LAD) (Lupron Depot) im every 4 wk for 3 months (86). Then, all women continued to receive LAD, 3.75 mg im, every 4 wk and, concurrently, half randomly received either add-back CEE, 0.625 mg, or a placebo daily for an additional 8 wk. Levels of all sex hormones decreased significantly after 12 wk of LAD treatment, and only E_2 levels increased significantly in the add-back phase of the study in the group that received LAD plus CEE. Scores on neuropsychological tests of verbal memory and learning, but not on visual memory, decreased from pretreatment to 12 wk posttreatment with LAD. Moreover, these memory deficits were reversed in the group that randomly received LAD plus add-back CEE for 8 wk in the second part of the study, coincident with an increase only in their serum E_2 levels, whereas scores on tests of verbal memory and learning remained depressed in the LAD plus add-back placebo group, once again, demonstrating the specificity of estrogenic action on verbal memory and learning documented earlier (78, 79).

In summary, results of the post-1980 RCTs that included tests of verbal memory and learning and also assayed plasma

hormone levels provide evidence that estrogen acts to maintain these specific aspects of cognition in postmenopausal women. Although the findings of the RCTs are clearly not entirely consistent, in no study did placebo-treated women perform better than those who received estrogen, and performance on 47% of memory measures was better in women who received ERT (87). Moreover, across these studies, there was a significantly higher percentage of significant positive findings for the tests of verbal compared with visual memory performance with ERT (87).

2. Observational studies

a. Case-control studies. In general, case-control designs involve recruiting groups of postmenopausal estrogen users and nonusers from the general population who are, under ideal conditions, also matched for variables that may independently influence cognitive functioning such as age, level of education, and SES. The Rancho Bernardo cohort, assembled between 1972 and 1974, consisted of white, upper-middle-class women who were being followed for cardiovascular risk factors. Cognitive testing undertaken cross-sectionally between 1988 and 1991 on these women, who were an average of 77 yr old, found that performance on only one of 12 cognitive tests administered (verbal fluency) was significantly better in long-term estrogen users compared with never users (88). In another study, 72-yr-old estrogen users performed significantly better than the nonusers on a test of recall of proper names but not on recall of words, which were the only tests of cognition used (89). In a group of healthy, well functioning 65-yr-old women, the estrogen users performed significantly better on tests of short- and long-term verbal memory compared with the nonusers drawn from the same population (90) and, in another case-control study, 58-yr-old healthy estrogen users had overall higher scores on tests of memory and nonmemory tests compared with nonusers but the authors did not report significance for individual measures (91). Moreover, nine women treated with 17β-E_2, 2 mg/d, plus 2.5 mg or 5 mg progestin/d (drug unspecified) performed better on tests of LTM after 6 and 12 months of treatment compared with 10 women who had refused hormone treatment and served as controls (92).

In a cross-sectional study, men, estrogen users, and female estrogen nonusers were matched for age (mean of 72 yr), SES, and level of education (93). The men had higher free testosterone levels than either of the two groups of women; their plasma E_2 levels were not different from the mean levels of the female estrogen users and, in absolute terms, were 3 times higher than the plasma E_2 levels of the female nonusers. The 72-yr-old men and the age-matched female estrogen users also had higher Total and Forward Digit Span Scores compared with the 72-yr-old women who were not taking estrogen. When these subjects were tested 2 yr later when they were an average age of 74 yr, the differences in levels of testosterone and of E_2 reported above were still apparent (94). Moreover, the men and the female estrogen users had maintained their superior scores on the Forward Digit Span test compared with the nonusers, with the additional finding that the female estrogen users performed significantly better than the nonusers on Backward Digit Span, a test of verbal working memory.

Another case-control study investigated the possible effects of ERT on working memory, thought to be mediated by the prefrontal cortex. Thirty-five estrogen nonusers, 38 women on unopposed estrogen, and 23 women on a continuous regimen of estrogen plus a progestin (E+P) were included (95). Women in both estrogen groups performed better on tests of verbal and spatial working memory but not on a test of explicit memory. Interestingly, only the women on unopposed estrogen but not those on E+P did better on the Backward Digit Span test, thought to involve components of working memory.

A correlational study undertaken to investigate the relationships between plasma levels of sex hormones and aspects of cognitive functioning studied 39 highly educated, nondemented women whose average age was 78.8 yr (96). Higher E_2 levels were associated with better immediate and delayed verbal memory and retrieval efficiency, whereas low levels of E_2 were correlated with better immediate visual memory. A recent cross-sectional report on a subpopulation of the Baltimore Longitudinal Study of Aging cohort extended these findings by delineating the specific aspects of verbal memory most sensitive to estrogen (97). One hundred and three postmenopausal women who were receiving either oral or transdermal estrogen (44 of whom were also taking a progestin) were matched on education, health status, depressive symptoms, income, and general verbal ability with 81 women who had never received HRT. Estrogen-treated women performed significantly better on measures of verbal learning and memory than the nonusers, but scores did not differ between groups on neuropsychological tests that measured visual memory or spatial abilities. Moreover, the storage and retrieval of new information were the aspects of memory that were most profoundly enhanced by HRT.

In the Einstein Aging Study, 10 surgically menopausal women who were ever users of ERT (7 current users and 3 past users) were matched by age and years of education with 25 surgically menopausal women from the same cohort who had never received ERT (98). In these groups of women, whose average age was 75 yr, the ever users performed significantly better on tests of verbal memory, free recall, and constructional ability compared with the never users.

In a recent cross-sectional study, 31 estrogen users (mean age, 63 yr) and 16 nonusers (mean age, 70 yr) were tested with a battery of neuropsychological tests (72). After age, SES, and education were controlled for, the ERT users performed significantly better on tests of verbal fluency and working memory, but there were no between-group differences in contextual verbal memory.

Although the data from case-control studies also provide some support for the notion that estrogen selectively maintains verbal memory in women, they also show that cognitive functions other than verbal memory are associated with estrogen use in contrast to the specificity of estrogenic action seen in the RCTs. In general, the findings from the case-control studies are also less robust than those from the RCTs. This is not surprising because the ERT users in these case-control studies were self-selected, so that numerous biases likely affected the results. For example, women who choose to take ERT are usually healthier and have more years of formal education than women who do not take hormones

after the menopause (99). The importance of this statistic lies in the fact that a higher level of education is an independent protective factor with respect to cognitive aging (100). In view of the finding that older women are not always compliant with a prescribed hormone replacement regimen (81), it is also noteworthy that only a few of these case-control studies actually assayed levels of E_2 (93, 94). An additional confounder in most of these studies is that some included women who were also taking a progestin in addition to estrogen, and the data were analyzed together as the "estrogen" group. Although the possible effects of progestins on cognition have not been clearly elucidated, there is reason to believe that they may be different from and, possibly, opposite to those of estrogen, as will be discussed later in this article. Finally, although most investigators eliminated participants who were receiving psychotropic medications that could have affected cognitive function, few specifically inquired about a history of head injury or CNS diseases that likely would have affected cognitive function, especially in older populations. The possibility that these biases might have affected the findings must be considered.

b. Longitudinal studies. In recent years, several longitudinal studies have provided evidence for the role of ERT on cognitive aging in women. In the Baltimore Longitudinal Study of Aging cohort, the estrogen users (~65 yr old) made significantly fewer errors on the Benton Visual Retention Test (BVRT), a test of visual memory, compared with the never users in this repeated measures design (101). Whereas the number of errors on the BVRT increased with age for the never-treated women, it remained stable over time for the women who had been receiving ERT, suggesting that they had experienced less cognitive decline with increasing age. The BVRT was the only test for which repeated measures data were available in this study; therefore, it cannot be determined whether changes on verbal memory or on other aspects of cognition would have differed between groups with increasing age.

In an ethnically diverse, community-based epidemiological study of aging and dementia in northern Manhattan, New York, standardized tests of memory, language, and abstract reasoning were administered at baseline and at follow-up 2.5 yr later to women who were an average age of 74 yr at the time of testing (102). Women who had used ERT (a combination of current and past users) scored significantly better on all four neuropsychological tests at baseline. More important, perhaps, is that scores on tests of short- and long-term verbal memory improved over time in the ERT users, whereas they declined in the never users over the 2.5-yr time span between test sessions. Because a decrease in scores on this test would be expected with normal aging, these findings support the idea that ERT helps to maintain aspects of cognition in aging women.

In a homogeneous community in Utah, 2338 nondemented women whose mean age was 75 yr were administered the modified Mini Mental State Exam (mMMSE), an omnibus test of cognitive function designed to detect significant cognitive decline (103). Scores were higher among current ERT users compared with past and never users and higher also in past users compared with never users. The findings were significant even after controlling for other factors known to affect cognitive performance such as age, education, depression, and activity limitation.

The Study of Osteoporotic Fractures evaluated the effects of ERT on three measures of cognitive function in a diverse group of 9651 women aged 72 yr on average who were tested twice, 4–6 yr apart (100). Current and past ERT users had higher scores on the mMMSE compared with never users, and this was especially true for current users who were older and less educated. There was no apparent benefit of ERT on the Trails B or the Digit Symbol Substitution test, which measure visual scanning and perceptual organization, respectively. The methodological limitations of this cross-sectional study include the fact that more than 6% of the sample were depressed and 37% had a functional limitation. Although 21% of the current users were taking E+P, separate analyses to determine whether the progestin may have affected test scores differentially were not performed. Neither were tests of verbal memory and of verbal fluency, areas in which estrogen-treated women were shown to excel in previous studies, included in this investigation.

A second publication on the Study of Osteoporotic Fractures cohort reported on 116 women who developed breast cancer and on 309 women who did not develop breast cancer during the 6-yr study for whom both serum hormone levels and scores on the mMMSE were available (104). In this subsample, higher non-protein-bound and bioavailable E_2 levels were associated with a significantly lower risk of cognitive decline in these elderly women over the 6-yr period. The 33% attrition rate by the second test session was due to the death of 9% and the loss to follow up of 24% of the original sample. As in other longitudinal studies, women who were not available for testing after 6 yr were older, less educated, and had lower mMMSE scores at baseline than the women who returned for testing. Additionally, treatments are not reported for the 25% of the participants in this study who had breast cancer, and it is not known how the medical and surgical interventions for breast cancer they surely endured might have influenced the findings.

The Nurses' Health Study, an ongoing prospective cohort study begun in 1976 in Boston, reported results of the Telephone Interview of Cognitive Status and tests of verbal fluency and memory on 2138 women whose average age was 74 yr (105). The only difference between the groups at this one point in time was that the current ERT users scored better than the never users on a test of verbal fluency. There was also a trend of increasing scores on this test with increasing duration of hormone use. A separate analysis of women taking E+P compared with those on estrogen alone failed to change the results of the initial analyses. The reliability and validity of administering cognitive tests via telephone are not known.

The Kame Project is a longitudinal, population-based study of memory and aging designed to establish prevalence and incidence rates of dementia in older Japanese-Americans in Washington State (106). The Cognitive Abilities Screening Instrument (CASI), a measure of global cognitive function, was designed for this study and is said to yield scores on nine cognitive domains. The CASI was administered twice, 2 yr apart, to 837 women whose average age was 71 yr. Current

unopposed estrogen use was significantly associated with increased total scores on the CASI as well as with higher scores on tests of abstract reasoning and verbal fluency over the 2 yr. It is noteworthy that the beneficial association between ERT and cognitive changes in these elderly women was nullified by the concurrent administration of medroxyprogesterone acetate (MPA). Indeed, total CASI scores of women taking E+MPA actually decreased during the 2-yr period between test sessions. As in other longitudinal studies, women who were tested at baseline but who did not participate in the second test session 2 yr later were older, less educated, performed worse on the cognitive tests at baseline, and were more likely to be ERT nonusers.

In the attempt to determine whether exogenous estrogen interacted with genetic factors to influence cognitive aging in women, 297 current estrogen users and 336 past estrogen users were administered the mMMSE annually within the context of the longitudinal Cardiovascular Health Study (107). The women were an average age of 72 yr at baseline. Over the 6-yr average follow-up, the mMMSE score of the never users declined significantly more than the average score of the current ERT users. Moreover, among apolipoprotein E-ϵ4 negative women, current estrogen use reduced the risk of cognitive impairment by almost half (hazard ratio = 0.59) compared with never users but did not influence the risk among ϵ4-positive women. Once again, the 23% of the original sample who failed to complete cognitive follow-up testing were older, less educated, and had lower mMMSE scores at baseline.

In the Duke Established Populations for Epidemiological Studies of the Elderly in North Carolina, 1907 women (average age, 73 yr) were tested at baseline using a brief cognitive screening test (The Short Portable Mental Status Questionnaire) and, again, 3 and 6 yr later (108). Although 20% of the cohort had used estrogen in the past, only 8% were taking estrogen by the 3 yr follow-up. When the analyses were corrected for demographic and health characteristics, the protective effect of ERT on cognitive decline was no longer significant. Two methodological limitations of this study are that only 5% of the sample were consistent long-term users of estrogen and that the survey screen measure used is not a targeted measure of memory or of any other cognitive function.

The Atherosclerosis Risk in Communities Study is a prospective investigation of the etiology and natural history of atherosclerotic disease in four communities in the United States. Of the 2121 women enrolled in the study, 669 were current estrogen users (mean age at baseline, 56.7 yr) and 1452 were never users (mean age at baseline, 59.2 yr) (109). Three cognitive tests were administered twice, 6 yr apart, during the second and fourth clinic visits. After adjustment for age, education, and duration of estrogen use, no associations were observed between estrogen use and 6-yr changes in cognitive functioning (verbal fluency, verbal learning, and psychomotor performance) in these middle-aged women.

Although the findings of these longitudinal studies do not allow causal inferences regarding the estrogen-cognition relationship, they nonetheless provide important information because they sampled large numbers of ethnically and economically diverse women. Some clear trends emerge from these data. All of the longitudinal studies (100–107) except for one (108), in which the average age of the women was greater than 65 yr at the time of their first neuropsychological test session, found that estrogen users performed better on cognitive tests and had significantly less deterioration over time compared with never users. In the recent Atherosclerosis Risk in Communities Study, which failed to find any protective effects of estrogen on cognitive aging (109), the average age of the estrogen users at follow-up was 56 yr. Because the deterioration in some aspects of cognitive functioning with normal aging has its onset after the age of 65 yr (31), the population sample in that study (109) was inappropriate for testing the association between estrogen use and cognitive aging.

Although the preponderance of findings from the longitudinal studies show that estrogen users performed better on cognitive tests and showed less deterioration in aspects of cognition with increasing age compared with the nonusers, it must be considered that these studies are replete with several sources of bias. Their subject samples reflect the common observation that women who take ERT after the menopause are younger, better educated, and generally healthier (99, 111–113). This is a particularly serious bias in studies of cognitive function and aging, because younger age and higher educational levels are themselves independent predictors of cognitive aging, and their effects would be confounded with a possible hormonal influence on cognition. Although most of the studies controlled statistically for age and education in their analyses, statistical adjustment cannot completely account for these sources of bias. A second and related problem is that, in five repeated-measures studies, the 25–33% of women who failed to return for cognitive testing were older, had less education, had lower mMMSE scores at baseline, and were more likely to be estrogen nonusers (100, 103, 106–107, 109). The characteristics of these women who failed to return for follow-up testing would have led to an underestimation of the strength of the associations that were found between estrogen use and the preservation of cognitive functioning.

A commonality among the longitudinal studies that reported on estrogen and cognitive functioning is that most were originally undertaken to study the effect of estrogen on other organ systems (*e.g.*, bone density, cardiovascular health). Because cognition was not a primary endpoint, many used the mMMSE as the sole measure of cognitive functioning. As mentioned earlier, the MMSE is an omnibus test of cognitive functioning that is generally used as a screening instrument to detect cognitive decline, and it is unable to distinguish performance between specific cognitive domains. Because the findings from the RCTs show that estrogen has its most profound effect on verbal memory, which was not specifically tested in any of the longitudinal studies undertaken to assess effects of ERT on other endpoints, it is possible that the true effects of estrogen on cognitive protection in their samples of elderly women may have been underestimated due to the lack of precision and specificity of the measuring instrument.

Logically, the longitudinal studies that tested women only once (88, 105) were able to provide only a comparison between the estrogen users and nonusers in their population and, interestingly, these studies found the weakest evidence

for a beneficial effect of estrogen on cognitive functioning in postmenopausal women. In contradistinction, studies that had two or more test sessions over a period of two or more years could not only compare absolute test scores between estrogen users and nonusers but were also able to address the clinically more important question of whether or not ERT helps to prevent deterioration in cognitive function with increasing age in women. Of the six studies that included two or more test times over the course of 2.5–6 yr in women aged over 65 yr (100–102, 106–108), five of the six reported that the cognitive test scores of elderly estrogen users either remained stable across time or decreased significantly less than the scores of the estrogen nonusers over time. Therefore, the weight of the currently available evidence from longitudinal studies suggests that cognitive aging may be prevented or attenuated by long-term ERT in postmenopausal women.

VI. Imaging Studies on Estrogen and Cognition

The development of functional neuroimaging technologies presented new opportunities to investigate whether estrogen influences cerebral circulation and brain activation in ways that might impact on cognitive functioning in women. A functional MRI study in healthy young women found an enhanced perfusion in cortical areas involved in cognitive functions during the phase of the cycle when estrogen levels were high (114). When postmenopausal women were given ERT or placebo for 21 d, to examine brain activation patterns during the performance of verbal and nonverbal working memory tasks with functional MRI, increased activation in the inferior parietal lobule during the verbal task only in estrogen-treated women suggested that estrogen may mediate the short-term storage of verbal material (115).

The neuroimaging techniques of single photon emission tomography (SPECT) and positron emission tomography (PET) allow the study of cerebral blood flow (CBF), neurotransmitter function, and glucose metabolism as a function of estrogen levels, and there is some evidence that estrogen modulates all of these endpoints. Using PET, regionally specific variations in glucose metabolism occurred during different phases of the menstrual cycle in healthy young women (116). Twelve estrogen users and 16 nonusers from the Baltimore Longitudinal Study on Aging cohort were tested twice, 2 yr apart using PET (117). Regions of increased regional CBF occurred over time in the estrogen users, particularly in the hippocampus, the parahippocampal gyrus, and temporal lobe regions that form a memory circuit. Estrogen users performed better than nonusers on a standardized test of prospective memory but not on the delayed memory activation task performed during the PET imaging procedure. These findings on changes in CBF in postmenopausal estrogen users are consistent with an earlier report that found that sex hormones modulated CBF during the performance of cognitive tasks (118). When SPECT was used to evaluate CBF in postmenopausal estrogen users and nonusers, an improvement in CBF occurred in temporal and parietal regions of the brain in the estrogen users (119).

Although the findings from these neuroimaging studies provide some support for the conclusion that estrogen modulates CBF and glucose metabolism in regions of the brain that underlie specific cognitive functions, others have failed to confirm the positive hormonal effect on CBF (120). The inconsistencies may be due to the small sample sizes of some studies, to the fact that data from women taking unopposed ERT and those taking E+P were folded into a "users" group and analyzed together (117), or to an inappropriate choice of cognitive tests used during imaging. At the present time, it is possible to conclude only that ERT is associated with different patterns of brain activation in some regions of the brain that subserve memory and other cognitive functions, but the theoretical and clinical significance of the differences await clarification.

VII. Estrogen and AD

A. Case-control and cohort studies

The most common cause of dementia is AD, whose earliest symptom is the inability to learn and recall new information followed by a progressive loss of other cognitive abilities. Typically, these symptoms of dementia begin insidiously in the seventh decade of life or later and progress gradually over a period of 5–15 yr before death. Several lines of evidence suggested that ERT might prevent or delay the onset of AD in women. First, findings from basic neuroscience that estrogen has a salutary effect on many of the brain structures and functions involved in the neuropathology of AD (such as the degeneration of neurons in the basal forebrain, the source of cholinergic projections to cortical, hippocampal, and amygdala regions) provided biological plausibility for this hypothesis (see Ref. 121 for a review). Second, although the sex difference in the incidence of AD had been in dispute, a recent meta-analysis found a significantly higher incidence of AD in women compared with men [odds ratio (OR) = 1.56] while correcting for greater female longevity (122). Finally, the findings that ERT protected the very aspects of cognition in healthy, elderly women that deteriorate most profoundly in patients with AD (memory and learning) raised the possibility that ERT might protect against AD in women.

In 1998, Yaffe *et al.* (123) performed a meta-analysis of 12 studies that addressed the effect of estrogen on cognitive function (70, 71, 73–75, 77, 79, 82, 88–91) and 10 studies that addressed the effect of estrogen on the risk for developing AD (124–133). They found an overall 29% decreased risk of AD in estrogen users compared with nonusers. The two prospective cohort studies that reported a significantly reduced risk of AD in estrogen users are particularly compelling because they avoid both recall and prescribing-practice bias (132, 133). Two studies documented a positive association between longer duration of ERT and the degree of AD risk reduction (129, 132).

Since the 1998 meta-analysis, three more case-control studies and one more prospective study have been published. In the Italian Longitudinal Study on Aging, ERT was associated with a reduced prevalence of AD in 2816 women (OR, 0.24; 95% CI, 0.07–0.77) (134). A case-control study from The Netherlands found a similar inverse association between ERT and early-onset AD in women (adjusted OR, 0.34; CI, 0.12–0.94) (135) and a third case-control study performed in the United

States also found a significant inverse association between estrogen use and the risk of AD (OR, 0.42; 95% CI, 0.18–0.96) (136). In the latter study, a significant trend of decreasing risk of AD among estrogen users with increasing duration of use was also evident.

Recently, new findings from The Cache County Study, a longitudinal investigation of the prevalence of AD and other dementias in a single county in Utah became available (137): 2930 women (mean age, 74.5 yr) and 2691 men (mean age, 73 yr) who showed no evidence of cognitive impairment were first assessed with the MMSE at baseline between 1995 and 1997. Of these, the cognitive status of 1801 women and 1322 men was reassessed between 1998 and 2000 and these subjects were found to be free of dementia. Forty-two percent of these women had never used HRT and 57% were either past or current HRT users. Duration of HRT use was classified as either less than 3 yr of use, 3–10 yr of use, and more than 10 yr of use. In the female nonusers, the incidence of AD increased after age 80 yr and considerably exceeded the incidence among men of similar age (adjusted HR, 2.11; 95% CI, 1.22–3.86). Women who used HRT had a significantly reduced risk of AD compared with nonusers (adjusted HR, 0.59; 95% CI, 0.36–0.96). Importantly, the risk of AD was found to vary with duration of HRT use, so that a women's gender-specific increase in risk disappeared entirely with more than 10 yr duration of hormone treatment. Moreover, almost all of the HRT-related reduction in the incidence of AD risk reflected former use of HRT; current HRT use was not protective unless duration of treatment exceeded 10 yr. These findings are consistent with those of three other longitudinal studies, which also found a lower incidence of AD in women with longer duration of estrogen use (129, 132, 136).

Overall, the findings from the case-control and cohort studies show a 20–70% reduction in the risk of AD in women who use ERT and also provide some evidence that estrogen users who develop AD do so at an older age (132, 138). A meta-analysis of observational studies on estrogen use and AD found a summary OR of 0.71 (95% CI, 0.53–0.98) for estrogen-treated women (123), and a more recent meta-analysis that applied inclusion criteria for grading internal validity of studies found a summary OR of 0.66 (95% CI, 0.53–0.82) for AD in estrogen users (139). Although this implies that estrogen use in postmenopausal women provides a 29–41% decreased risk of developing AD, it is important to acknowledge that, like the longitudinal studies on estrogen use and cognition in healthy, elderly women, these studies on ERT and the risk for AD are replete with possible biases that suggest caution in their interpretation. For example, not only do estrogen users tend to be healthier in general, but they also tend to have more years of formal education and to be younger than nonusers. As discussed earlier, these biases, which were indeed evident in the ERT users in several of these case-control and cohort studies, are themselves independent protective factors with respect to the development of AD. Therefore, any conclusion that ERT protects against or delays the onset of AD will be strengthened by data from RCTs.

B. Treatment studies of women with AD

During the 1980s, several small, uncontrolled trials using ERT for the treatment of women with mild-to-moderate AD found improvement on some, but not all, measures of dementia (140–141). Each study had a sample size of less than 10 women, administered ERT for 6 wk, and lacked control groups. When 15 women with AD were given CEE, 1.25 mg/d, for 6 wk and compared with 15 untreated controls matched for age and dementia severity at baseline, ratings on one dementia scale improved in the estrogen-treated women (142). However, a between-group analysis was not conducted at posttreatment.

C. Randomized controlled treatment studies of estrogen and AD

In the first true RCT of ERT and AD, 14 women with AD were randomly assigned to treatment with either CEE, 1.25 mg/d, or placebo for 3 wk (143). The estrogen group had improved scores on one dementia scale but not on two others. These findings are complicated by the fact that some of the estrogen-treated women also received a progestin in this small study. Nonetheless, these findings were confirmed in another RCT in which 12 women with mild-to-moderate AD randomly received either a 17β-E_2 transdermal patch, 0.05 mg/d, or a placebo patch for 8 wk (144). A significant increase in scores occurred on tests of attention and verbal memory in the estrogen-treated but not in the placebo-treated women. The estrogen-induced enhancements on tests of attention and verbal memory were no longer evident several weeks after the termination of treatment, indicating that the beneficial effects of ERT did not endure after treatment was withdrawn.

In a third RTC, 50 women with mild-to-moderate AD received either CEE, 1.25 mg, or placebo daily for 12 wk (145). Neither primary nor secondary outcome measures showed any benefit of ERT on cognitive performance, dementia severity, mood, or cerebral perfusion in this well controlled drug trial.

Recently, results of two multicenter RCTs on ERT and cognitive functioning in women with AD have become available. In the Alzheimer's Disease Cooperative Study, women with AD who had had a hysterectomy were randomized to receive treatment with CEE, 0.625 mg/d (n = 42), CEE, 1.25 mg/d (n = 39), or a placebo daily (n = 39) for 12 months (146). Although there was a benefit of CEE, 0.625 mg/d, on MMSE scores after 2 months of therapy, it did not persist with continued treatment. The authors concluded that ERT for 1 yr failed to slow disease progression or to improve global, cognitive, or functional outcomes in women with mild-to-moderate AD.

In the second RCT, 42 women with mild-to-moderate AD were randomly assigned to treatment with CEE, 1.25 mg/d, or placebo for 16 wk (147). After 4 and 16 wk of treatment, no differences between the treatment groups were apparent in scores on the primary outcome measure, the clinician-rated global impression of change, or on the caregiver-rated functional status measure.

Although the earlier, small, uncontrolled studies on the

use of estrogen for the treatment of women with AD were encouraging, the more recent, methodologically rigorous RCTs on larger sample sizes failed to confirm their early promise. At the present time, there is no reason to believe that ERT, in doses conventionally used to treat healthy postmenopausal women, is an effective treatment for women with AD. However, there is a suggestion that the efficacy of ERT in women with AD may lie in its potentiation of other agents used to treat AD. When tacrine (an acetylcholinesterase inhibitor) or placebo was administered randomly to women with AD, a *post hoc* analysis found that the 14% of the sample who were estrogen users and had received tacrine improved more on tests of cognitive function than the estrogen nonusers treated with tacrine (148). The potential efficacy of estrogen as adjunctive therapy with other drugs that affect acetylcholine metabolism merits further study in RCTs due to its potential clinical significance.

VIII. Selective ER Modulators (SERMs) and Cognition

Because they have tissue-selective effects as both estrogen agonists and antagonists, the possible influence of SERMs on brain function and on cognition in postmenopausal women has aroused considerable interest. Raloxifene, a SERM that binds with high affinity to the ER, prevents bone loss, favorably alters the serum lipid profile, and does not stimulate breast tissue (149, 150). On the other hand, raloxifene increases the incidence of hot flashes in postmenopausal women, suggesting that it may act as an estrogen antagonist at the level of the hypothalamus (149, 150). In a RCT, 143 women with established osteoporosis received either placebo, raloxifene, 60 mg/d, or raloxifene 120 mg/d (151). After 1 yr of treatment, no differences in performance were apparent between the three treatment groups on a computerized battery of neuropsychological tests. The failure to find significant differences between raloxifene and placebo on cognitive functioning was recently confirmed in a RCT whose duration of treatment with either raloxifene or placebo was 3 yr (152). At the present time, therefore, there is no evidence from humans that raloxifene positively influences aspects of cognition in women. Similarly, performance improved on a test of spatial working memory in aged, ovariectomized monkeys when they were treated with ethinyl E_2, but not when they were treated with raloxifene (153).

IX. Modulators of the Estrogen-Cognition Relationship

In addition to age and years of education, several other factors can modulate the association between estrogen and cognitive functioning in women. Variables that can act as the major confounders of studies in this area include the influence of estrogen on mood, the concomitant administration of progestins with ERT, and the pharmacokinetics of various estrogen formulations.

At the present time, there is a considerable amount of evidence that estrogen enhances mood in women. It now seems clear that, although physiological doses of estrogen given to postmenopausal women alleviate depressive symptoms, or dysphoria (82, 154–156), these doses are without significant effect on the more profound mood disturbances that fulfill diagnostic criteria for a major depressive episode (157, 158). Although large, supraphysiological doses of estrogen are somewhat effective for the treatment of a clinical depression (159), the import of this finding is more theoretical than clinical, both because of the side effects that accrue to these large doses of estrogen and because the efficacy and favorable side effect profiles of current second-generation antidepressant drugs has solidified their use as first-line treatment for major depression. Nonetheless, in a recent RCT, six of seven perimenopausal women with a major depression (85%) and 19 of 24 perimenopausal women with minor depression (79%) had a full or partial remission of their depressed mood when treated with 0.05 mg/d of transdermal E_2 compared with the 22% who improved with a placebo patch (160). The finding that associated depressive symptoms such as disturbed sleep, increased appetite, lack of energy, and emotional detachment were unaffected by ERT suggests that although estrogen has antidepressant properties, physiological doses are not sufficiently effective for use as a sole agent to successfully treat the syndrome of clinical depression.

The serotonin-deficit hypothesis is still the most prominent biological theory of the etiology of depression and, notably, estrogen affects the serotonin system in numerous ways. For example, estrogen increases the rate of degradation of monoamine oxidase, the enzyme that catabolizes serotonin (15), and also affects intraneuronal serotonin transport (161). Both of these mechanisms would serve to increase serotonin availability in the synapse, thereby enhancing mood. In contradistinction, P increases the amount of monoamine oxidase, thereby decreasing the concentration of brain serotonin (15). Indeed, in a RCT, the addition of a progestin (MPA) to an estrogen replacement regimen attenuated the beneficial effect of estrogen on mood in a dose-dependent manner (156). These findings were similar to those of two nonblinded trials (162, 163), as well as to those of a meta-analysis of sex hormones and mood (164). Because depression is associated with a reduction in concentration and attention, which would compromise performance on cognitive tests, the ability of P to attenuate the beneficial effect of ERT on mood underlines the importance of including only women on unopposed estrogen in studies of estrogen and cognition. At the very least, studies with mixed hormone groups containing unopposed estrogen users and E+P users need to analyze data from those two groups separately. Unfortunately, the vast majority of the case-control and longitudinal studies on healthy, elderly women and on those with AD failed to do so. Because estrogens and progestins affect mood differentially, it is also necessary to include a reliable measure of mood in studies of estrogen and cognitive functioning, the scores of which should be used as covariates in the analysis of the cognitive data to discount the possibility that a change in cognitive functioning occurred secondary to a change in mood in estrogen-treated women.

There is also reason to believe that P may have a direct, negative effect on cognition. The decrease in apical dendritic spine density in the CA1 area of the hippocampus that occurs

during the estrous phase of the rat cycle was prevented by the administration of RU-486, a P receptor antagonist (12). This suggests that the estrogenic enhancement of dendritic spine density, thought to be a protective factor for cognitive aging, is opposed by P. Indeed, in the Kame longitudinal study (106), whereas scores on a global measure of cognitive functioning improved over time in elderly women taking unopposed ERT, scores actually worsened during the same time frame in those treated with a combined E+P regimen. In a recent SPECT study, the duration of ERT correlated positively with the density of cortical cholinergic terminal concentrations, and the effect was attenuated in women who were also taking a progestin along with estrogen (165). This is the first evidence from humans that progestins may adversely influence cholinergic neuronal integrity. Adding to the complexity of this issue is that different classes of progestins, such as MPA and micronized P, have differential effects on some aspects of metabolism, such as lipoprotein lipid cholesterol, when administered with estrogen (166). This raises the possibility that different progestins might also affect brain function differentially. Although a definitive study on progestins and cognitive function in women has not been performed, currently available evidence strongly suggests that findings from studies that had mixed groups of women treated with unopposed ERT and with E+P, and in which the data were analyzed together, need to be interpreted with caution.

A third modulating factor that is likely to have affected the findings in these studies on estrogen and cognition is related to the different drugs, doses, and routes of administration of the many estrogen compounds used. The majority of investigations on estrogen and cognitive functioning reviewed here have sampled women who were predominantly taking CEE (Premarin, Wyeth-Ayerst Laboratories, Inc., Philadelphia, PA), although some used other forms of oral estrogen, whereas other studies administered estrogen transdermally, transcutaneously, or intramuscularly. Although little attention has been paid to the differences in the pharmacokinetics and route of administration of various estrogen preparations, the work of Steingold *et al.* (167) provides reason to believe that differing characteristics of various estrogen preparations could critically influence the findings of studies on estrogen and brain function. They investigated, *in vivo*, the influx from the microvasculature into the brain, the uterus, and the liver of all commercially available classes of estrogens available in the United States for replacement therapy in 1986. In the brain, there was an 80–100% extraction of E_2, estrone, and ethinyl E_2, but only a 6.5% extraction of estrone sulfate. On the other hand, the mean extraction of all estrogen preparations by the liver was high, indicating that the hepatic microvasculature was freely permeable to all compounds, including estrone sulfate. It must also be considered that orally administered E_2, but not ethinyl E_2, undergoes substantial hepatic metabolism to less active forms (168), so that parenteral routes of administration, which avoid the initial hepatic metabolism, may allow more estrogen to be available to the brain.

Second, route of administration modulates responses to ERT. Indeed, it is widely accepted that oral estrogen preparations induce greater beneficial effects on serum lipoproteins than transdermal estrogens, which circumvent first-pass liver metabolism (169). Although it is likely that route of administration also influences brain levels of estrogen in treated, postmenopausal women, no information is available for humans because of the obvious problem of measuring levels of estrogen in the brain; however, the future development of an estrogen ligand that can be used in imaging studies may eventually be able to provide information on the differential availability of various estrogen compounds to the brain.

It must also be considered that certain components of oral CEE have specific beneficial effects on brain function. For example, equilenin, a component of CEE, was more efficacious than E_2, estrone, and estriol for cortical nerve growth *in vitro* (170), and 17α-dihydroequilenin, another component of CEE, increased the density of dendritic spines on hippocampal neurons (171). This could imply that CEE would induce the greatest benefit on cognition because of the uniqueness of its neuroactive components. Although there is clearly much to be learned concerning the availability to and the influence of different estrogen formulations on the brain, it should be acknowledged, for the present, that these heretofore ignored pharmacological issues are likely responsible for some of the inconsistency in the extant literature.

At the present time, it cannot be determined what dose of estrogen would endow the cognitive benefits seen in many of the studies reviewed above, because there is not a single, systematic dose-response study available. It is difficult to glean dose-response information from the extant studies because remarkably few investigators actually measured serum levels of estrogen at the time of neuropsychological testing, thereby failing both to confirm their subjects' compliance with the treatment regimen and to provide an estimate of the potency of the specific estrogen preparation they used. Inasmuch as 0.625 mg CEE/d or its equivalent has conventionally been the standard replacement dose for postmenopausal women, the majority of participants in the case-control and longitudinal studies were actually receiving that dose, although doses in those studies ranged from 0.3 mg to 1.25 mg CEE. Clearly, dose-response studies are needed in this area to determine the minimally effective dose required to protect aspects of cognitive aging in postmenopausal women.

X. Summary and Conclusions

The evidence that estrogen influences neuroanatomical and neurophysiological aspects of CNS function implicated in cognition is compelling and provides a high degree of biological plausibility for the notion that estrogen would have a beneficial effect on cognition in women. Cognition is a complex, multidimensional set of intellectual functions whose component processes are subserved by distinct but interrelated brain areas. The established quantitative differences in some cognitive skills between the sexes, coupled with evidence from studies of individuals with genetic disorders that caused them to be exposed to abnormal levels of the sex hormones during prenatal life, led to the hypothesis that estrogen would have its most pronounced beneficial effect on those cognitive skills in which females typically

excel, such as verbal memory and learning and fine-motor skills. Although the specificity of the estrogenic effect on memory holds true for the RCTs that examined mainly the acute postoperative phase in surgically menopausal women, in the observational studies of older women, it seems that the estrogenic effect is more diffuse and encompasses other aspects of cognition in addition to verbal memory.

Several experimental models have been used to investigate whether estrogen affects aspects of cognition in women. In some, but not all, of the menstrual cycle studies, performance on tasks of verbal memory and fine-motor skills was better, and that on tests of visual and spatial ability was worse, during the midluteal phase of the cycle when both estrogen and P levels are high. However, considerable variability exists across studies, perhaps because few actually measured circulating levels of hormones to verify cycle phase or considered that P might oppose the influence of estrogen. Because the effect size of the differences in cognitive scores between menstrual phases are small and unlikely to be clinically significant, the importance of these findings lies in their demonstration that fluctuations in hormone levels during the normal menstrual cycle are associated with measurable differences in cognitive function in healthy young women.

Most of the work on estrogen and cognition has been carried out in postmenopausal women whose ovaries have become atrophic. RCTs of the efficacy of ERT on cognition that measured serum levels of hormones and used a comprehensive battery of standardized neuropsychological tests consistently found that ERT enhanced verbal memory and learning in postmenopausal women but was without effect on visual memory and spatial abilities. Although the results of the case-control and the longitudinal studies on estrogen and cognition in postmenopausal women generally show that estrogen users perform better on tests of verbal memory and learning compared with nonusers, the findings are less robust and less consistent than those from the RCTs, probably because of the biases associated with self-selected estrogen users, and the failure to control for concomitant progestin use, to assay serum levels of estrogen, and to include neuropsychological tests that measure the specific cognitive domains of interest. Nonetheless, taken together with the findings of the RCTs, the results of the case-control and longitudinal studies provide converging evidence that ERT protects aspects of cognition that normally deteriorate somewhat with normal aging (31).

Overall, although 71% of the studies that examined the effect of estrogen on cognitive functioning found significant beneficial effects on one or more neuropsychological tests of cognition (87), the potential clinical importance of these data lie in determining the magnitude of the effect. When effect sizes were calculated for the scores on the memory measures of studies for which the necessary information was available (26% of the RCTs and 70% of the observational studies), the median effect size for the memory measures in the RCTs was 0.681 (range, 0.276–1.111) and 0.492 (range, 0.137–1.631) for the observational studies that compared estrogen users to nonusers (87). The median effect size for the nonmemory cognitive measures was 0.425. In accordance with conventional methods of quantifying effect sizes, the effect of estrogen on memory in the RCTs is considered to be medium to large, whereas that of the observational studies as well as that of the nonmemory tests of cognition is a medium effect size (172).

Case-control and cohort studies show that ERT use is associated with an approximately 30-40% decrease in the incidence of AD in elderly women. There is also some evidence that estrogen-treated women who eventually develop AD do so at an older age, suggesting that ERT may delay the onset of AD in women who are destined to develop it for genetic and/or environmental reasons. Although these studies also suffer from numerous and significant methodological limitations, their findings are remarkably consistent in demonstrating a protective effect of ERT with regard to the development of AD. The same is not true, however, for the treatment studies of women diagnosed with probable AD. Two recent, well controlled RCTs of women with mild-to-moderate AD both failed to show that treatment with estrogen either improved cognitive function or prevented the deterioration in aspects of cognitive function that predictably occur during the course of this degenerative disease.

Accumulating data are beginning to suggest that there may be a critical period during the immediate postmenopausal years for the protective effect of ERT on cognition. For example, elderly women who initiated ERT at the time of menopause had less cognitive decline than nonusers, whereas the incidence of cognitive decline was not different in women with more recent exposures (100). Likewise, the recent Cache County longitudinal study found a reduced risk in AD among former users of ERT but not among current users unless they had taken estrogen for more than 10 yr (137). Others have suggested that the withdrawal of estrogen at the time of menopause may lead to increased brain susceptibility to pathological processes so that treatment with ERT during the immediate postmenopausal period may be protective (173). Although there is no direct evidence in support of that idea, the finding that women who initiated ERT around the time of menopause had a lower risk of AD compared with never users, even when ERT had been terminated more than 20 yr before the assessment of AD risk, suggests that the initiation of ERT in the immediate postmenopausal period may provide the most protection against AD (102). Not only do these findings suggest that there may be a critical window to optimize the efficacy of ERT with regard to its protective effects on cognitive decline and/or AD but also imply that the beneficial effects of early treatment are enduring. However, confidence in these conclusions is attenuated by the fact that the evidence in their support comes from observational and not from controlled studies, which weakens their value for the formulation of clinical recommendations for treatment.

In summary, the weight of the evidence from extant studies provides support for the idea that ERT helps to maintain aspects of cognition in healthy postmenopausal women that normally deteriorate somewhat with aging. Based on the available evidence, it is also reasonable to conclude at this time that ERT significantly reduces the incidence of AD while bearing in mind that the support for this conclusion rests exclusively on the findings of observational studies. However, once probable AD has been diagnosed, physiological doses of estrogen are apparently without effect on the de-

terioration of cognition that is induced by the neuropathological processes that underlie this disease.

Unfortunately, the caveats that temper these general conclusions on the effect of estrogen on cognitive functioning in women are numerous and relate to biases inherent in the populations studied, the use of other drugs that affect CNS function, the use of inappropriate measuring instruments, and the variety and doses of estrogen formulations used. Some of these limitations will be addressed by the Women's Health Initiative (WHI) Memory Study, a randomized, controlled, multicenter trial in the United States that is prospectively assessing, over the course of 9 yr, the effect of ERT on dementia risk and progression in more than 8000 women over the age of 65 yr (174). In addition, the WHI Study on Cognitive Aging, an ancillary study to the WHI Memory Study, is a 6-yr longitudinal assessment of cognitive outcomes in 2900 women randomly assigned to receive either ERT, ERT plus progestin, or placebo. However, in May, 2002, the estrogen-progestin arm of the WHI study was halted because the global index statistic summarizing the balance of risks and benefits after 5.2 yr of treatment supported risks exceeding benefits (175). Specifically, the WHI study found a significantly increased risk of cardiovascular disease, venous thromboembolism, deep vein thrombosis, and nonsignificant increases in stroke and in invasive breast cancer in the combined estrogen-progestin group compared with placebo. Hip and vertebral fracture rates and colorectal cancer rates were significantly lower in the hormone-treated women compared with those who had been randomized to placebo, and there was no difference between the groups in all-cause mortality (175). The estrogen-alone arm of the WHI is continuing because the balance of overall risks has not outweighed the benefits thus far. The findings from the estrogen-alone arm of the WHI Study on Cognitive Aging, due in 2005, will provide more definitive evidence on the putative protective effect of estrogen on memory in healthy elderly women. At that time it is hoped that more information will be available to evaluate the complex array of risks and benefits of ERT to formulate treatment recommendations for each individual woman.

Acknowledgments

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