



# Forever Smart

## Does estrogen enhance memory?

By KATHLEEN FACKELMANN

**T**outed in the 1950s as an elixir that would keep postmenopausal women forever feminine and vilified in the 1970s as a cause of cancer, estrogen replacement therapy has had a checkered history.

Yet doctors now know that this drug provides many benefits to women who have gone through menopause. Estrogen shields women from the potentially crippling bone loss of osteoporosis and can slash their risk of heart disease.

Despite the huzzahs given this therapy of late, however, many older women don't take estrogen, perhaps because of a lingering fear of cancer. There's little doubt that estrogen, when taken by itself, magnifies the risk of endometrial cancer. Yet doctors can mitigate this cancer threat by giving estrogen in combination with another hormone called progesterone.

That strategy has done little to assuage another cancer worry, though. Researchers know that a woman's cumulative exposure to her own body's estrogen increases the risk of breast cancer. Unfortunately, studies on the link between estrogen pills and breast cancer have produced conflicting results.

Several research teams, however, now add some more good news to the complex risk-benefit picture of estrogen replacement therapy. Their data suggest it boosts short-term memory and the ability to learn new tasks. In addition, one team suggests that estrogen replacement therapy may counter depression.

"Estrogen has been shown to influence several areas in the brain that are involved in cognition and behavior," says researcher Uriel Halbreich of the State University of New York at Buffalo.

At the same time, a California team reports data hinting that estrogen replacement therapy shields — at least partially — against Alzheimer's disease,

a degenerative disorder of the central nervous system (see sidebar).

**I**s menopause a disease or simply a natural consequence of aging?

Proponents of the disease model point out that at the turn of the century, most women didn't live long past menopause: In fact, only 5 percent of women lived beyond their 50th birthday. However, most U.S. women alive today can expect to spend one-third of their life in that estrogen-deficient state.

Menopause is a dramatic event. Ovarian production of estrogen declines from as much as 300 micrograms per day to almost nothing. Yet postmenopausal women still manufacture up to 20 micrograms of estrogen per day in the liver and fatty tissue.

Women prescribed estrogen replacement therapy have a choice of natural or synthetic estrogen. The most popular product, Premarin, is estrogen derived from the urine of pregnant horses.

With antibiotics, improved diets, and the everyday miracles of modern medicine, humans have expanded their life span. "In a way, we've created this phenomenon of old age," says psychologist Barbara B. Sherwin of McGill University in Montreal.

The theory behind estrogen replacement therapy is that women should be able to avoid the numerous undesirable consequences of menopause, including osteoporosis and hot flashes. Sherwin and other researchers believe it makes sense to supply in pill form the estrogen the body stops manufacturing.

**A**s one ages, it takes longer to remember names and other facts once retrieved without hesitation. While memories of long ago remain sharp, an older person may have difficulty recalling a new telephone number.

Sherwin knew that some research on animals suggested a link between estrogen and memory. In rats, for example, estrogen increases the amount of an enzyme necessary for synthesis of acetylcholine, a neurotransmitter that plays a key role in memory. She wondered whether older women could improve their memory by taking hormone therapy.

Diane L. Kampen, also at McGill, and Sherwin began to study this question by

recruiting healthy women age 55 and over who had completed menopause at least 2 years earlier. The duo ended up with 28 women in estrogen replacement therapy and 43 who were not.

To test verbal memory, the researchers read a short prose passage to each recruit. Immediately, and then after a 30-minute delay, the volunteers had to remember as much as they could about the material.

Estrogen users recalled more of the text than nonusers on both tests, the Canadians report in the June 1994 *OBSTETRICS & GYNECOLOGY*. "In our hands, estrogen enhances verbal memory and helps maintain the ability to learn new material," Sherwin says.

How big a difference is it? Sherwin says it's not a huge effect, but it's enough that estrogen users' performance in the laboratory remains higher than their peers'. In real life, Sherwin says, the difference might come down to this: A postmenopausal woman who starts taking estrogen might recall telephone numbers, instructions, or directions with greater ease.

So estrogen won't turn the postmenopausal woman into a human calculator. On the other hand, who couldn't use a little memory boost now and then? How many times have you gone to a party, been introduced to someone, and then failed to remember the person's name a minute later?

A recent study suggests that hormone replacement treatments may prove an antidote to such forgetfulness. In this study, Jerome Yesavage of the Stanford University School of Medicine and his colleagues decided to study the relationship between estrogen replacement therapy and the ability to recall a name or a specific word.

The team began its study with 72 women between the ages of 55 and 93 who were taking estrogen and 72 women in the same age group who were not. None of the women appeared senile.

To test the women's ability to recall a name, the researchers showed each recruit black-and-white slides of six male and six female faces. The team matched each photo at random with a common first and last name. The women studied each face and the corresponding name for 1 minute. The researchers later shuffled the photographs and projected the faces in random order. The recruits had

to write down the name they associated with each face.

Estrogen users performed significantly better than their peers. The researchers discovered that women taking estrogen got 36 percent of the names right, while their counterparts recalled only 26 percent correctly.

The team also administered another simple memory test. It gave recruits a list of 16 common words and asked them to memorize as many as possible in 4 minutes. Later, the women had to write down, in order, the test words they could remember.

On this task, estrogen users did slightly better than nonusers. However, the improvement did not reach statistical significance. The researchers report their finding in the September 1994 *JOURNAL OF THE AMERICAN GERIATRICS SOCIETY*.

"The implication of this finding, if real, is tremendous — estrogen replacement therapy may confer some protection against memory loss," says epidemiologist Trudy L. Bush of the University of Maryland School of Medicine in Baltimore, who wrote an editorial in the same issue of the journal.

Bush, however, contends that this study, although carefully conducted, is limited. First, she points out, the boost in the ability to remember names is small. Of the dozen names, women on estrogen therapy could remember an average of four. The nonusers recalled about three.

She wonders if some factor other than estrogen use might explain the slight increase in performance enjoyed by those on estrogen therapy. Bush says estrogen users may be healthier than women who do not take the treatment and that better health may explain the improvement in their test scores.

"Right now, the data are pretty weak," Bush says. "I think we need an awful lot more work before we can say anything with any degree of certainty."

**C**an estrogen reverse some of the ravages of aging? A study by researchers in New York shows that estrogen replacement therapy improves reaction time, verbal ability, mental alertness, and other thinking abilities in postmenopausal women.

Halbreich and his colleagues recruited 34 postmenopausal women who were not taking estrogen and 24 women of childbearing age. The team gave both groups a battery of tests measuring a range of cognitive abilities. The researchers also measured performance on complex cognitive tests. For example, the women took a simulated driving test in which they had to make quick decisions about a variety of road hazards.

In general, the postmenopausal women performed less well than their younger counterparts, Halbreich says. The older women's scores were not abnormal, they

simply showed the older women weren't as quick to respond as the younger ones, Halbreich adds.

The researchers then gave the older women estrogen replacement therapy for 60 days. When the team administered the tests again, they found the older women did significantly better on certain tests, including the simulated driving exercise. Indeed, after estrogen therapy, some of the older women posted test scores indistinguishable from the younger women's, Halbreich says.

The researchers also discovered that performance correlated with the amount of estrogen: The higher the concentration of estrogen in the blood, the better the test scores. Halbreich presented the group's results this July at the International College of Neuropsychopharmacology meeting in Washington, D.C.

The findings suggest "a beneficial role of estrogen replacement therapy on some aspects of cognitive functioning," he concludes.

Halbreich cautions, however, that the boost in test scores could be a placebo effect — an improvement not related to the therapy itself — because the older

women knew they were getting estrogen. So he and his colleagues plan another study, this one to include a control group of postmenopausal women who will not receive treatment.

The Buffalo-based team also has data hinting that estrogen may help improve mood in older women. Previous research had indicated that postmenopausal women with low concentrations of estrogen may be more vulnerable to depression, perhaps because of a deficit in a neurotransmitter called serotonin. Halbreich's data suggest that estrogen modulates serotonin in older women and thus may help regulate mood.

Although estrogen replacement therapy might help ward off depression in older women, it cannot, by itself, banish this disorder, the researchers caution.

The history of estrogen replacement therapy is littered with promises of turning back the clock. Little wonder, then, that researchers remain cautious about these new findings regarding estrogen and thinking ability.

"I think it's hopeful research," Bush says. "But I think we should proceed cautiously." □

## Alzheimer's link to estrogen

While some researchers pursue the tantalizing lead that estrogen may enhance memory in healthy older women, others ponder the sex hormone's role in Alzheimer's disease.

A California team, for example, suggests that estrogen may protect against Alzheimer's, a neurodegenerative disorder of aging characterized by progressive memory loss, mood changes, confusion, and physical deterioration.

To look for such a link, Annlia Paganini-Hill and Victor W. Henderson of the University of Southern California School of Medicine in Los Angeles turned to a retirement community called Leisure World Laguna Hills. The researchers mailed a health survey to 8,877 female residents in June 1981 and then kept track of the deaths in the community.

The researchers noted that 2,529 female residents died between 1981 and 1992. Of that group, 138 women had Alzheimer's disease, senility, or dementia listed on their death certificate. Most suffered from Alzheimer's disease, Paganini-Hill says.

For each of these women with Alzheimer's, the team picked out four controls, women who had died during the same period but did not suffer from any type of dementia.

The team then looked at each woman's menstrual history, as recorded on the original survey. They noted whether she had undergone estrogen replacement therapy. When the researchers com-

pared the women who had Alzheimer's disease to the controls, they discovered that women on estrogen developed Alzheimer's less frequently than nonusers.

When the team calculated the relative risk, it found that estrogen users show a 30 percent lower risk of developing Alzheimer's disease than women who do not use this drug. "That would be a substantial reduction if it's confirmed by other studies," Paganini-Hill says.

Furthermore, the team found that women taking the highest doses of estrogen had the lowest risk of this dementia. Paganini-Hill and Henderson describe their findings in the Aug. 1, 1994 *AMERICAN JOURNAL OF EPIDEMIOLOGY*.

The findings hint, but do not prove, that estrogen may be able to prevent Alzheimer's disease. As menopause shuts down the ovaries' production of estrogen, some women may not receive sufficient estrogen from other sources, the team speculates. That deficiency could somehow trigger the changes associated with Alzheimer's disease, Paganini-Hill says. She notes that previous studies have demonstrated estrogen's effect on the brain's cholinergic system, which is crucial for memory, learning, and other cognitive abilities.

Next, the California team wants to find out whether estrogen can slow the mental deterioration seen in women who already suffer from Alzheimer's.

— K. Fackelmann