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Menopausal

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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Alternatives to Estrogen Use in Post-Menopausal Women

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INTRODUCTION

Many women are concerned about side-effects or potential risks from estrogen replacement therapy (ERT). Survivors of breast cancer are particularly fearful of risks of recurrent breast cancer. For women who choose not to take estrogen replacement therapy, alternative options for treatment of estrogen deficiency symptoms are needed. Therapeutic goals include the prevention of heart disease and osteoporosis¹ and relief of symptoms of urogenital atrophy, vasomotor instability, and neurocognitive dysfunction. Additional goals include a possible reduction in incidence of Alzheimer's disease, macular degeneration, colon cancer, and mandibular bone loss. In this review, we will compare the efficacy of estrogen with its alternatives for these various problems.

PREVENTION OF CARDIOVASCULAR DISEASE

Estrogen acts on the cardiovascular system by at least two different mechanisms: effects on serum lipid profiles and direct actions on blood vessels. Approximately 25% of the cardioprotective effect is due to lipid changes including increased HDL, decreased LDL, decreased Lp(a), decreased LDL oxidation, and decreased vascular LDL uptake.² The fact that estro-

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gens improve lipid profiles has been used as evidence that estrogens should prevent heart disease. In the Postmenopausal Estrogen/Progestin Intervention Trial (PEPI),³ 875 women received various estrogen/progestin regimens. Estrogen alone decreased LDL cholesterol levels and increased HDL cholesterol. Concomitant use of medroxyprogesterone acetate (MPA) with estrogen blunted the increase in HDL cholesterol but did not affect the reduction in LDL cholesterol. Triglyceride levels increased with either therapy when compared with placebo. Micronized progesterone exerted less of a negative effect on HDL than MPA. The remaining 65% to 75% of the cardioprotective effect of estrogen results from lipid independent effects on the heart and blood vessels. When delivered transdermally, estrogen does not substantially alter lipid levels.⁴ When given by this route, estrogen probably exerts its effects primarily by direct blood vessel and vascular actions rather than by effects on lipids.^{1,4}

Data from the Nurse's Health Study provide the strongest support for a cardioprotective effect of estrogen. The relative risk of developing heart disease in current hormone replacement therapy users was 0.60 for estrogen alone and 0.39 for estrogen plus a progestin. It was estimated that estrogen use continuously for 10 years would prevent 330 new cardiovascular

FROM THE EDITOR

David F. Archer, M.D.

Drs. Santen and Pinkerton have provided you with the rationale for use of various alternative therapies for women who have had or are concerned about breast cancer. Education of the consumer is a principal part of the physician-patient interaction. The following web sites are recommended. The consensus conference publication on alternative therapies is at www.hormone.org and is maintained by the Endocrine Foundation. Information on using and obtaining the breast cancer risk assessment tool developed by the National Cancer Institute can be found at www.nci.nih.gov or by calling 1.800.4.cancer.

Dr. Anthis indicates an increase in the occurrence to Type 2 diabetes mellitus. Active interventions should involve both diet and exercise, while the literature on hormonal intervention is limited. Several conditions associated with diabetes should make you consider hormonal therapy as an option for these patients.

Dr. Greene introduces us to the frontier of central nervous system research and hormonal therapy. His article describes the activation patterns and blood flow to various areas of the brain following the use of hormonal treatment. Implied in this paper is that blood flow reflects activation and maintains function. The role of hormones and brain function is only now being intensely investigated. How these changes reflect cognition remains to be seen.

Menopausal Medicine

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events in 50-year-old women and 660 events in 60-year-old women.⁵ The results of this non-randomized, observational trial could be attributable to a number of potential biases. For example, women in the United States who take estrogen may be self-selected for several factors that reduce the risk of cardiovascular disease – the “healthy woman” bias. For this reason, randomized, controlled trials are considered necessary to confirm that estrogens are in fact cardioprotective.

How do lipid-lowering drugs compare with estrogens in preventing heart disease? The ability of various agents to alter lipid levels is considered to be an “indirect endpoint” to predict efficacy in preventing heart disease. Two randomized studies have compared the effects of estrogen and the hMG Co-A (3-hydroxy-3 methylglutaryl-coenzyme A) reductase inhibitors (“statins”) on lipid levels (figure 1). In an Australian trial,⁶ continuous combined high-dose estrogen plus progestin (Premarin® 1.25 mg, medroxyprogesterone 2.5 mg) was compared with 40 mg of simvastatin daily. Both hormone therapy and simvastatin caused significant reductions in LDL cholesterol (24% and 36%, respectively), but simvastatin was more effective than hormone therapy ($p < 0.001$). Both treatments caused a significant increase (7%) in HDL cholesterol. Simvastatin

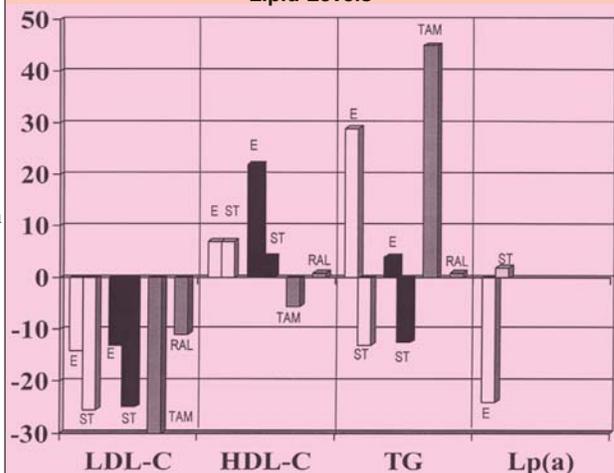
reduced triglyceride levels by 14%, and hormone therapy increased them by 29%. In a second direct comparison, Davidson et al⁷ reported the effects of conjugated 0.625mg/d estrogens alone, 20mg pravastatin alone, the combination and placebo for management of hypercholesterolemia in postmenopausal women. Conjugated estrogens reduced low-density lipoprotein cholesterol (LDL-C) levels by 13.5% and increased HDL-C (22.5%) and triglycerides (4.2%) (figure 1). Pravastatin reduced LDL-C levels by 25.4% and triglycerides by 12.1% while increasing HDL-C

increased slightly (3.7%). When the two approaches are compared, pravastatin diminished LDL-C to a significantly greater extent than estrogens, decreased rather than increased triglyceride levels, but caused a significantly lesser rise in HDL-C (22.5% vs. 3.7%). The relative contributions of LDL and HDL cholesterol to cardiovascular risk are incompletely understood. These results on lipid levels must be considered only surrogate endpoints to be considered while direct comparisons on cardiovascular endpoints are being studied.

Primary prevention of heart disease:

The observational studies reviewed above and particularly the nurses health study suggest a cardioprotective effect of estrogens. With respect to the statins, the AFCAPs/TexCPS study examined the effect of 20 mg daily of lovastatin (or 40 mg per day if LDL cholesterol remained above 110 mg/dl) vs. placebo.⁸ The study involved 5,608 men and 997 women without a prior history of cardiovascular disease and with average LDL cholesterol and below average HDL cholesterol levels. Overall, the relative risk of first coronary event was 0.63 after an average follow-up of 5.2 years in patients receiving lovastatin. This group also had a decreased relative risk for myocardial infarction, unstable angina, coronary revascularization procedures, coronary events, and cardiovascular events.

Figure 1. Effect of Estrogens, SERMs, and Statins on Lipid Levels



Comparative effects of estrogens, selective estrogen receptor modulators, and statins on lipid levels. E=estrogen preparation, ST=“statin” preparation, TAM=tamoxifen, RAL=raloxifene. When the bars are together without a space, this indicates a direct “head-to-head” comparison of one therapy with another. When the bars are separate, this indicates a trial which studied a single agent. The dark shaded E vs. ST trial represents that of Darling. The lightly shaded E vs. ST trial is that of Davidson et al. The TAM trial is that of Love et al,³⁵ and the RAL trial is that of Delmas et al. LDL-C=LDL cholesterol; HDL-C=HDL cholesterol; TG=triglyceride; Lp(a)=lipoprotein (a). This figure compares available data from multiple studies and does not exclusively represent direct comparisons in the same study. Interpretation of the data must take into consideration the limited nature of available information and the need for direct comparisons of all available therapeutic modalities.

Secondary prevention of heart disease:

Non-randomized studies suggest that HRT use in women with established CVD reduces risk of death and future cardiovascular events. Surprisingly, the randomized, prospective HERS trial⁹ could not confirm this beneficial effect. This study involved 2,763 women, mean age 66.7, with severe coronary heart disease (CHD) who used continuous combined estrogen (conjugated equine estrogens .625 mg) and progesterone (medroxyprogesterone acetate MPA 2.5 mg) or placebo, with 4.1 years of follow-up. The HRT group showed an increase in CHD and mortality at year one when compared to those using placebo. With continued use, it appeared that a beneficial effect of HRT developed over time, with fewer deaths in years four and five. However, at the end of five years on study, the number of deaths, heart attacks, and CHD rates did not differ between the two groups. The early death rate may represent a prothrombotic effect of estrogen or that the lack of differences between groups may be due to a detrimental effect of medroxyprogesterone acetate, the progestin used in the hormone group. Nonetheless, the HERS study has called into question the efficacy of estrogens for secondary prevention. Definitive data regarding estrogens and primary prevention will probably become available with completion of the Women's Health Initiative.

Recent non-controlled but prospective studies show different results from those reported in the HERS trial. Sullivan et al compared survival after coronary bypass surgery in women receiving and not receiving estrogen. The 10-year survival rate in estrogen users was 81.4% compared with 65.1% in non-users.¹⁰ Another study examined women after atherectomy in whom estrogen inhibited the rate of re-stenosis. The mean loss in minimal luminal diameter was -0.13 mm in estrogen users at six months following the procedure and -0.46 mm in non-users ($p=0.0006$).¹¹ Clearly, longer term prospective randomized trials comparing estrogen/non-MPA progestin combinations with placebo are needed. In the meantime, the efficacy of estrogens for secondary prevention of heart disease is unknown.

Randomized, prospective, controlled trials demonstrate that the "statins" reduce new cardiovascular events by approximately 30% with favorable side-effect profiles. Unfortunately, too few women have been included in these trials to be certain about

differential effects in women. Nonetheless, when results from men and women were combined,^{12,13} it was found that simvastatin produced highly significant reductions in the risk of death and morbidity in patients with CHD followed for a median of 5.4 years, relative to patients receiving standard care. Over the median follow-up period of 5.4 years, one or more major coronary events occurred in 622 (28%) of the 2,223 patients in the placebo group and 431 (19%) of the 2,221 patients in the simvastatin group, for a highly significant 34% risk reduction with $P<.00001$. Thus, the addition of simvastatin 20-40 mg daily to the treatment regimens of CHD patients, with characteristics similar to those of postmenopausal women, should be beneficial.

Conclusions: These non-"head-to-head" comparisons of the "statins" with HRT for primary and secondary prevention allow conclusions that can only be considered tentative. Improvement of survival of 30% with the "statins" has been clearly shown with randomized controlled trials. With estrogens, the only randomized trial for secondary prevention does not show survival benefit. For primary prevention, no such trials have been completed but observational studies report a 30% to 50% improvement in survival. Based upon this analysis, it is reasonable to consider the "statins" appropriate estrogen alternatives for the primary or secondary prevention of heart disease.

OTHER AGENTS FOR PREVENTION OF CARDIOVASCULAR DISEASE

Lipid effects have been demonstrated with several other hormonally active agents but to date, a significant reduction of cardiovascular events has not been shown. Tamoxifen appears to decrease LDL cholesterol, to reduce lipoprotein (a), and to increase triglycerides. Available data do not provide statistically significant evidence that tamoxifen reduces cardiovascular events but studies are not of sufficient size. Randomized studies with raloxifene¹⁴ demonstrate reductions in total cholesterol of 6.6% and LDL by 10.9%; both lipoprotein (a) and fibrinogen are reduced with no change in HDL or triglycerides. This compares to an increase of 10.6% in HDL and an increase in 10% in triglycerides with HRT. Raloxifene also exerts direct effects on the cardiovascular system in rabbits. However, in ovariectomized placebo-treated cynomolgous monkeys,¹⁵ neither vasoactive effects nor protective effects

against atherosclerosis were seen at either low or high doses of raloxifene. A large randomized study (RUTH) is currently examining the effects of raloxifene on cardiovascular events in women.

Animal studies and early human studies are suggestive that soy/isoflavones show an estrogen-like effect on coronary artery reactivity.¹⁶ A meta-analysis¹⁷ of the effect of soy on cholesterol in humans revealed that 47 g daily of soy was associated with a 12.9% decrease in LDL, 9.3% decrease in cholesterol, and no change in HDL, with the greatest effect seen in those with the highest pretreatment cholesterol.

PREVENTION AND TREATMENT OF OSTEOPOROSIS

For women with objectively diagnosed osteopenia or osteoporosis using the DEXA scan, initial recommendations include calcium intake up to 1,500 mg, and vitamin D if needed. Bone formation is stimulated by a combination of gravitational and weight-bearing forces such as the low repetitive muscle activity combined with weight load found in walking, jogging, or low-impact aerobics.

Estrogen therapy reduces bone resorption and is used to both prevent and treat osteoporosis. The PEPI trial¹⁸ revealed that HRT improved bone mineral density by up to 4% in the lumbar spine and 2% in the hip at three years. Data regarding fracture risk reduction with estrogens derives almost exclusively from observational studies. One clinical trial of transdermal estrogen therapy in 75 postmenopausal women with osteoporosis observed for one year revealed a relative risk of vertebral fractures of 0.39 compared to placebo.¹⁹ A series of 20 studies²⁰ revealed a risk reduction ranging from 80% to no effect in some studies. The reduction appears to average approximately 50%. The analysis of Grady et al estimated a lifetime reduction of vertebral fracture of 50% and hip fracture of 30% with long-term use of estrogen.² A prospective cohort study (The Study of Osteoporotic Fractures)²¹ among 9,704 women 65 and older, found the relative risk for nonspinal fractures for women on estrogen to be 0.66. Current users experienced a reduced relative risk of hip fracture of 0.60. For women who started estrogen within five years of menopause, the RR was 0.29 for hip fracture and 0.50 for all non-spinal fractures. More precise comparisons must await further studies. New studies suggest that some women may need

only 0.3 mg of estrogen to maintain bone density, but no fracture data is available.

FRACTURE AND BMD DATA WITH ALENDRONATE

It is important to consider how effective the bisphosphonates are in comparison with estrogen. The most commonly used bisphosphonate, alendronate, appears to exert an anti-resorptive potency similar to that of estrogen when used at low dose (5 mg) (figure 2). The Early Postmenopausal Intervention Cohort (EPIC)²² study of recently menopausal women included placebo, alendronate (2.5 or 5 mg/day), and open-label estrogen/progesterone. Patients receiving placebo plus calcium lost bone. Those receiving either 2.5 or 5 mg of alendronate/day increased bone mass between 1% to 2% over baseline but not to the same extent as the estrogen/progesterone group at 2% (figure 2). With measurement of total body bone density at two years, estrogen/progesterone improved bone density almost 2%, while 5 mg of alendronate increased this parameter 1% and 2.5 mg of alendronate maintained baseline levels compared with a 2% loss with placebo. Thus for prevention of bone loss, both estrogen/progesterone and 5 mg of alendronate are effective, with slightly better responses with estrogen/progesterone.

Dose response studies indicate that 10 mg of alendronate may be more efficacious than 5 mg daily.²³ At the end of three years, BMD was higher in patients treated with 10 mg/day alendronate than in

patients receiving placebo by (mean \pm SE) $8.8 \pm 0.4\%$ at the lumbar spine, by $5.9 \pm 0.5\%$ at the femoral neck, and by $7.8 \pm 0.6\%$ at the trochanter. Although no head-to-head comparison studies have been conducted, it would appear that 10 mg of alendronate daily would result in a similar or greater increase in bone mass than that seen with estrogen therapy.

No direct comparative data to evaluate the reduction of fracture risk with estrogen vs. bisphosphonates are yet available. Three multi-center, double-blind, placebo-controlled studies provide compelling evidence of the vertebral anti-fracture efficacy of alendronate. The first²⁴ involved 994 postmenopausal women with osteoporosis who received either placebo for three years, alendronate 5 mg/day for three years, alendronate 10 mg/day for three years, or alendronate 20 mg/day for two years and then 5 mg/day for third year. BMD increased in patients receiving all alendronate dosage regimens and decreased in patients receiving placebo. Vertebral fractures occurred in 6.2% of patients receiving placebo and 3.2% of patients receiving alendronate; this represented a 48% reduction in numbers of women sustaining fractures ($P < 0.04$). Two or more new vertebral fractures occurred in 4.2% of patients receiving placebo (15 of 355) and 0.6% of patients receiving alendronate (3 of 526), a risk reduction of 87%. Nonvertebral fractures occurred in 60 of 590 women receiving placebo and 73 of 1,012 receiving alendronate. The cumula-

tive incidences (placebo vs. alendronate) were 12.6% and 9%, a 29% reduction in risk compared with placebo ($P < 0.05$).

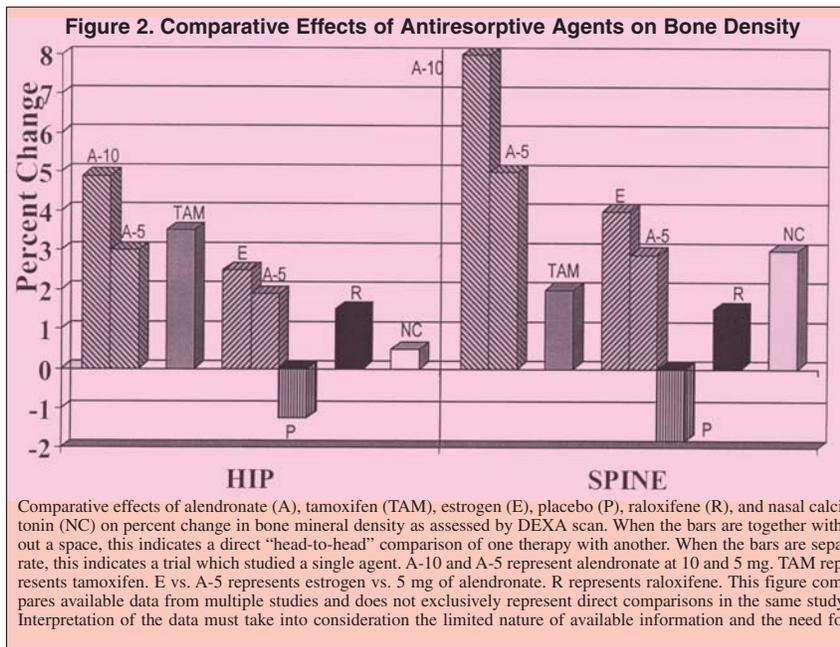
In the Fracture Intervention Trial (FIT),²⁵ 2,027 women with one or more vertebral fractures at baseline and reduced BMD were randomized to receive either placebo ($n = 1,005$) or alendronate ($n = 1,022$) 5 mg/day for two years, 10 mg/day in year three. After three years, BMD increased significantly by 6.2% above placebo at the spine and by 4.7% above placebo at the total hip region. The rate of new clinically apparent vertebral fractures decreased by 47% compared to placebo. Similar decreases were seen in the frequency of hip and wrist fractures but not for other types of fractures.

A follow-up examined women without pre-existing vertebral fractures. Women received 5 mg daily of alendronate for two years followed by 10 mg daily thereafter.²⁶ Only those with osteoporosis responded with a significant reduction of clinically evident fractures. The radiologically detected fractures were reduced by 44% in the total group of women taking alendronate (relative risk 0.56; 95% CL 0.39-0.80). Subgroup analysis demonstrated a significant reduction in those with a baseline bone density T score of > 2.5 SD and close to a significant reduction in those with scores of -2.5 - 2.0 (relative risk 0.54 (95% CL 0.28-1.04).

These trials suggest that alendronate is effective at preventing vertebral and non-vertebral fractures when compared to placebo, and 10 mg appears to be the most effective dose. Although hip fractures were reduced, the number of actual fractures was small.

FRACTURE AND BMD DATA WITH CALCITONIN

Nasal calcitonin is approved for treatment of osteoporosis in women who are five or more years postmenopausal. It is not effective in preventing bone loss in early postmenopausal women. A randomized double-blind trial of approximately 230 postmenopausal women with osteoporosis in each group received either placebo or three doses of nasal calcitonin (100, 200, and 400 IU/day) for three years. An increase of 1.0% to 1.5% over baseline in lumbar spine but not other skeletal sites was seen at the end of year one (significant) with no dose response apparent. Statistical significance over placebo was lost in years two and three.



Overgaard et al²⁷ studied the effects of intranasal salmon calcitonin on fracture rate in a two-year, double-blind, placebo-controlled trial of women aged 68 to 72 years randomized to receive 50, 100, or 200 IU calcitonin or placebo daily plus 500 mg calcium supplement. For the 162 women completing the study, spinal BMD increased by 1% in the placebo group and by 3% in the group receiving 200 IU calcitonin. By one method of detection, fractures occurred in seven patients receiving placebo and five receiving calcitonin; by the second method, fractures occurred in six patients receiving placebo and four receiving calcitonin. Although a decreased number of fractures was seen, pooling of all doses was not preplanned and the small numbers of fractures leave uncertainty.

Four-year interim results²⁸ from the five-year multi-center PROOF study (Prevent Recurrence of Osteoporotic Fractures) have been presented. 1,255 postmenopausal women with established osteoporosis were randomized to receive either placebo, or Salmon Calcitonin nasal spray (100, 200, or 400 IU/day) plus 1,000 mg of calcium and 400 IU of vitamin D. At four years, there was a 36% reduction in relative risk of new fracture with 200 IU compared to placebo ($p=.020$). A reduction of 18% and 23% in new fractures was seen among those treated with 100 IU or 400 IU compared to placebo. The mean increment in BMD over baseline for placebo, 100 IU, 200 IU, and 400 IU was 0.7, 1.2, 1.2, and 1.6 percent respectively. The increases in lumbar spine BMD were statistically significantly increased in all treatment groups compared to placebo over baseline and at two years compared to placebo, and up to three years for the 400 IU. Nasal calcitonin spray appears to reduce the risk of new vertebral fractures in postmenopausal women with established osteoporosis. The data suggest a protective effect on hip fractures but the study is not adequately powered to detect differences in hip fracture rates. At four years, a 51% reduction in hip/femur fractures was noted in the 200 IU dose but the numbers are small, 1.3% (4/315) of patients in 200 IU group vs. 2.6% (8/305 of patients) in the placebo group.

FRACTURE AND BMD DATA WITH SERMS (TAMOXIFEN AND RALOXIFENE)

Studies in postmenopausal women using tamoxifen for prevention of breast cancer have shown average increases in BMD of

1% to 2% per year. Premenopausal women show a transient bone loss for the first two years with tamoxifen, felt to be due to the antiestrogenic effect of tamoxifen. In the Tamoxifen Breast Cancer Prevention Trial, a nonsignificant reduction in fractures was observed.

Three large randomized placebo-controlled osteoporosis prevention trials¹⁴ with raloxifene demonstrated significant increases in bone mineral density of 2% over placebo in hip, spine, and total body. Compared to placebo, there is between a 2% to 2.5% increase in spine, total hip, and total body ($P<0.001$ for all comparisons). Raloxifene increased total-body bone mineral density from 1.8% to 2.5% over placebo after 24 months. This effect was similar to that seen with conjugated equine estrogens and medroxyprogesterone acetate or 5 mg of alendronate per day. In the total hip, the raloxifene group improved to a greater extent than those given placebo (1.8% to 2.3%). The effect was similar in magnitude to that observed in women receiving conjugated equine estrogens and medroxyprogesterone acetate or 5 mg of alendronate. The effects were greater than effected by 200 IU of nasal calcitonin or tamoxifen.

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial is a multi-center, double-blind, controlled study of 7,705 recently postmenopausal (average 4.5 to 5 years) women with osteoporosis (mean age 66.5) treated with raloxifene (60 mg or 120 mg) or placebo. All received 500 mg of calcium and 400 to 600 IU vitamin D. Interim analysis at three years²⁹ shows significant effects on vertebral fracture prevention of 38% in women with prevalent fractures and 52% without prior fractures.

Comparison among therapeutic agents for treatment of osteoporosis (figure 2):

For women with documented osteoporosis, there are no direct comparisons of effectiveness of different agents. Ten mg of alendronate has been shown to increase density in the lumbar spine by 5% to 7% and femoral neck by 4% to 6%. Estrogen alone or with progesterone increased bone density by 2% to 5% in the lumbar spine and by 1% to 6% in the hip. Nasal calcitonin at 200 IU improved bone density 2% to 3% at two years in lumbar spine. Raloxifene increased BMD 2% to 3% per year, and tamoxifen 1% to 2%. We have long-term epidemiologic data about the effect of estrogen on prevention of osteoporosis but are lacking prospective controlled data for estrogen and long-term data about alen-

dronate, nasal calcitonin, and raloxifene.

Head-to-head comparisons of various agents in preventing fracture are non-existent. Efficacy is estimated by comparing results from different trials. Epidemiologic studies suggest a relative reduction of fracture rate of 55% with estrogen use, even for women over 70. For alendronate, the decrease in lumbar spine and hip fractures is 50%; for nasal calcitonin, the decrease in lumbar fractures is 36%; and for raloxifene, 38% to 52%. Based upon these data, one can conclude that alendronate, nasal calcitonin, and raloxifene could serve as alternatives for estrogen for prevention and treatment of osteoporosis.

UROGENITAL ATROPHY

Vaginal moisturizers and lubricants do not completely relieve symptoms. In one study, a vaginal moisturizer, Replens, reduced vaginal pH to 4.8, compared to estrogen at 4.4, and reduced atrophy in 60% of patients compared to 100% with estrogen. Various doses of vaginal estrogen have been used in an attempt to achieve local control of symptoms without systemic absorption. In one study, plasma estrone and estradiol levels were measured in women receiving vaginal Premarin® with increases in doses from 0.3-2.5 gm per day. Systemic levels of estradiol increased up to 60 pg/ml, a level comparable to that seen with oral Premarin®. However, the lowest dose (0.3 gm/day) produced complete maturation of vaginal mucosa with only minimal increases in plasma estrone and estradiol. In a recent study, no increase in plasma estrone was observed over baseline after six months of use. Disadvantages of the vaginal method involve irregular application intervals, bolus absorption and low absorption capacity of a fat-based vehicle, necessitating use of emollient (which results in stickiness and messiness and compliance issues).

Newer methods of delivering estrogen locally into the vagina without systemic absorption include a vaginal estrogen ring device (Estring) and low dose vaginal creams currently being tested and developed. The vaginal ring provides nearly complete relief of symptoms with minimal systemic absorption. Four percent of women had endometrial thickness greater than 5 mm measured by ultrasound compared with 10% using the vaginal cream. Three percent experienced vaginal withdrawal bleeding from the ring compared to 21% using vaginal cream. Preliminary data support the possibility that very low doses

of estradiol given vaginally can achieve local vaginal effects without systemic absorption of estradiol.

VASOMOTOR INSTABILITY

The use of a placebo consistently reduces the number and severity of hot flashes by about 25%. Vitamin E induces a statistically significantly greater reduction of hot flashes than observed with placebo with a 30% improvement over basal symptoms. Clonidine given by transdermal patch relieves symptoms further to about 40% of base line. Megestrol acetate at a dosage of 40 mg daily appears to be as effective as estrogen, with an 80% level of control of hot flashes (figure 3). The SSRI (Selective Serotonin Reuptake Inhibitor) drugs may show a decrease in hot flashes over placebo. Studies which have used phytoestrogens for relief of hot flashes show conflicting results, varying from little effect to a significant reduction, to a reduction in the severity but not frequency of hot flashes.

CNS SYMPTOMS

For symptoms of sleep disturbance, trazodone or benzodiazepines and hypnotics have been used. Depression should be identified and treated with antidepressants and mood stabilizers. More research is needed to identify the frequency and severity of these symptoms and the use of non-estrogenic medications such as St. John's Wort.

SAFETY AND SIDE EFFECTS OF ALTERNATIVES TO ESTROGEN

The choice between estrogen and its alternatives requires consideration of the wide range of benefits and risks of each. The additional beneficial effects of estrogen

over the alternatives identified in this review include a potential reduction in incidence or severity of Alzheimer's disease, macular degeneration, colon cancer, mandibular bone loss, and osteoarthritis. The risks of estrogen are well known. Regarding the "statins," creatine phosphokinase levels and renal and hepatic function have been altered and myopathy induced. Reports of gastrointestinal symptoms including erosive esophagitis have been reported with alendronate although no significant differences have been found in controlled studies compared to placebo. The nasal form of calcitonin has few side effects – nasal discomfort or ulceration, nausea, facial flushing, and diarrhea – and, like subcutaneous calcitonin, may have an analgesic effect on bone pain.

Use of the SERMs as alternatives to estrogen provides the potential of preventing breast cancer. Raloxifene decreases breast cancer risk by 50% to 70% over a three-year period. Preliminary data from over 7,000 women who participated in preliminary trials shows a 71% reduction of breast cancer and a decrease in endometrial cancer in the raloxifene group.²⁹ No data are yet available on long-term rates of breast cancer with raloxifene, its use in women at high risk for breast cancer, or its use in woman with prior breast cancer. Uterine thickness was unchanged from placebo with no stimulation of atrophic endometrium. Side-effects include leg cramps and a 2.5 increased relative risk of DVT and increases in vasomotor symptoms. No effect was seen on vaginitis, migraine, headache, anxiety, or emotional lability. Very few data are available on cognitive function, mood, or memory.

Tamoxifen is now approved for prevention of breast cancer in women at high risk.

The Tamoxifen Prevention Trial,³⁰ a prospective, randomized, blinded, controlled study of 13,000 high-risk women, found a 45% decrease in development of breast cancer after 4.5 years of treatment. Risks include increased risk of uterine cancer, cataracts, and blood clots. The absolute excess of deaths from endometrial cancer was

about one or two per 1,000 (corresponding to an annual excess of about 0.2 per 1,000). Although this trend may well be real, the absolute excess was not large.³¹

CONCLUSION

Breast cancer survivors, women with an absolute contraindication to use of estrogen, and those fearful of taking ERT are candidates for alternatives to systemic estrogen therapy. The statin drugs appear as effective as estrogen for the primary and secondary prevention of heart disease, and the antiresorptive agents (bisphosphonates, calcitonin, raloxifene, tamoxifen) are useful to treat or prevent osteoporosis. Hot flashes respond to vitamin E, clonidine, megestrol acetate, and SSRI drugs but not as effectively as to estrogen. Urogenital atrophy responds to vaginal lubricants and moisturizers but also not as effectively as to estradiol. Low-dose vaginal estradiol may allow vaginal maturation with only minimal systemic estrogen absorption. Affective disorder symptoms can respond to the SSRI drugs. Each patient needs to be evaluated for individual symptoms and treated with appropriate alternatives to use of systemic estrogen.

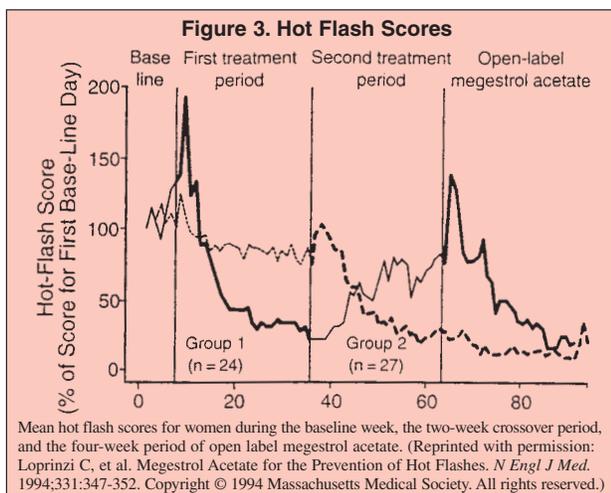
* For full review and complete bibliography, see Pinkerton JV, Santen RJ. Alternatives to the use of estrogen in postmenopausal women. *Endocrine Reviews*. 1999;20:308-320.

Dr. Santen has revealed the following potential conflict of interest: Board of Advisors - Eli Lilly.

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Diabetes Mellitus in Postmenopausal Women

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INTRODUCTION

Diabetes mellitus is very common in postmenopausal women. An estimated 15 million Americans have type 2 diabetes mellitus.¹ With the 1997 changes in diagnostic and screening guidelines published in the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus,² it is likely that more previously unrecognized cases will be discovered (table 1). Management of menopausal issues in the patient with diabetes requires special consideration. The goals of hormonal and non-hormonal treatments of menopause are two-fold; to improve climacteric symptoms and to potentially prevent the development or slow the progression of disease states such as osteoporosis and cardiovascular disease. Special attention should be given to the possible interaction between therapies for menopause and management of the diabetic women.

Type 2 diabetes is associated with two basic physiologic defects. The primary defect appears to be resistance to insulin action at the target tissue.³ The other contributing mechanism is an abnormality in insulin secretion. Insulin resistance and the resultant hyperinsulinemia and hyperglycemia lead to the long-term complications associated with type 2 diabetes. Any therapy used in diabetic women to treat menopausally related changes should not adversely affect carbohydrate metabolism.

Little is known about the effects of hormone replacement therapy (HRT) on carbohydrate metabolism in diabetic women. The PEPI trial enrolled 875 women who had normal carbohydrate metabolism and found that women assigned to active treatment had a slight decline in their fasting glucose levels, and an increase in their glucose levels taken two hours after a 75 gram glucose challenge when compared to placebo controls.⁴ The Atherosclerosis Risk in Communities study found that fasting glucose and fasting insulin both decreased slightly in non-diabetic women on estrogen replacement therapy (ERT) or HRT.⁵ Several studies comparing the

impact on carbohydrate metabolism of estrogen delivered orally, vs. transdermally, have not shown any negative impact on fasting glucose or fasting insulin levels by either delivery system in the non-diabetic women.^{6,7} Overall the data in non-diabetic women support no worsening of carbohydrate metabolism and possibly some minimal improvement in insulin resistance on HRT.

Few studies have directly examined the impact of ERT or HRT on glycemic control in the postmenopausal women with type 2 diabetes. In one six-week prospective randomized trial involving 40 women receiving either ERT or placebo, the results showed improvement in the HbA1c levels, insulin sensitivity, and suppressibility of hepatic glucose production in the women in the active treatment arm.⁸ In another trial involving 25 diabetic women randomized to receive HRT or placebo for three months, blood glucose and HbA1c both decreased with active treatment.⁹ Although these trials involved small numbers, the results are encouraging. In a recent large-scale chart review involving the charts of 14,601 type 2 diabetic women from the Northern California Kaiser Permanente Diabetes Registry, the use of HRT was significantly associated with lower HbA1c levels.¹⁰ If this trend can be supported by larger, long-term prospective trials, then HRT might be considered adjunctive therapy for diabetic menopausal patients. At this point it is prudent to monitor glycemic control closely when starting a diabetic woman on HRT.

The prevention of heart disease after menopause is an important consideration for all women, but particularly for the women with type 2 diabetes because diabetes increases coronary heart disease incidence and increases the predisposing risk factors for heart disease, including abnormalities in plasma lipids.¹¹ Diabetic patients have higher levels of both triglycerides and LDL cholesterol and lower HDL cholesterol.¹² Additionally, hypertriglyceridemia is associated with an increased risk of coronary artery disease

in patients with type 2 diabetes.¹³ There have been no prospective large-scale trials looking at the impact on cardiovascular disease in diabetic women treated with HRT. Any risks or benefits of HRT in diabetic women must be extrapolated from data available in non-diabetic women. One cross-sectional population study which did not record dose or route of delivery of estrogen showed that diabetic women may have an exaggerated hypertriglyceridemic response and a blunted response to the HDL-raising effects of estrogen.¹⁴ If this is the case, then diabetic women may not expect to achieve the same potentially protective changes in serum lipids that have been documented in non-diabetic women.

Further complicating the issue of HRT in diabetic women are the results of the HERS trial. HERS was a large, prospective placebo controlled trial evaluating HRT as secondary prevention for coronary heart disease (CHD) in older (average age 66.7) non-diabetic women with established CHD. The group actively treated with HRT did not show a benefit over placebo with the primary end-points of CHD deaths and non-fatal myocardial infarctions over an average follow-up of 4.1 years.¹⁵ Interestingly, the women in the HRT treatment arm did show favorable improvements in their serum lipids including a 14% reduction in their LDL and an 8% increase in their HDL. Their triglycerides however increased by 10%. The HERS trial did not include women with type 2 diabetes; but since many women with type 2 diabetes have CHD, the results are relevant and should be considered when deciding to initiate a patient with type 2 diabetes and CHD on HRT. There are currently on-going large-scale trials in non-diabetic and diabetic women, includ-

ing the Women's Health Initiative (WHI), which will hopefully further clarify the issue of HRT and its impact on CHD.

Osteoporosis is a disease process that is common in postmenopausal women and increases in incidence with age. Because

type 2 diabetes and osteoporosis are commonly seen conditions, it is important to understand any possible impact one would have on the other. The effects of type 2 diabetes on osteoporosis have been controversial, with some studies reporting decreased bone mass in type 2 diabetics, some reporting normal findings, and still others reporting increased bone mass.¹⁶ Type 2 diabetics have been felt to be somewhat protected from osteoporosis owing to their tendency toward obesity which

“Because type 2 diabetes and osteoporosis are commonly seen conditions, it is important to understand any possible impact one would have on the other.”

is protective against bone loss. In addition, the presence of increased adipose tissue may result in metabolically active steroid hormones which may protect against bone loss.¹⁷ It is clear that postmenopausal diabetic women do have a decline in bone mineral density with age and years since menopause.¹⁸ Additionally, bone mineral density in women with type 2 diabetes is negatively correlated with years since diagnosis of diabetes. Women with diabetes of greater than 15 years have a 10% decrease in bone mineral density compared to age-matched controls.

Another factor to consider in the evaluation of osteoporosis in the diabetic postmenopausal patient is that diabetic complications such as retinopathy, neuropathy, and angiopathy influence the fracture risk independent of bone mass. Although no randomized prospective studies have addressed the prevention and management of osteoporosis in diabetic women, a reasonable approach should include measuring a baseline bone mineral density in perimenopausal diabetic patients considering HRT and recommendations for adequate exercise and calcium supplementation in all women with diabetes. A baseline bone mineral density in the diabetic patient could be used to make therapeutic choices regarding prevention or treatment of existing osteoporosis.

The management of menopause is an

Table 1: Criteria for the Diagnosis of Diabetes Mellitus

1. Symptoms of diabetes plus casual plasma glucose concentration >200mg/dl OR
2. FPG>126mg/dl. Fasting is defined as no caloric intake for at least 8 hours OR
3. 2hPG>200 during an OGTT. (Using 75 grams of glucose dissolved in water)

important aspect of any women's health care, but when a woman has type 2 diabetes as a co-morbidity there are several issues that should be considered when deciding on a management strategy. First, all women seeking treatment for menopause should be questioned about their risk for type 2 diabetes. In any patient over 45 who has not been screened in the last three years for type 2 diabetes with a fasting blood glucose, this should be done. Women in high-risk groups (positive family history or obesity) should be screened annually. Secondly, all women with type 2 diabetes should be counseled about all their options for treatment of menopausal symptoms and complications. The decision to treat with conventional HRT, a selective estrogen receptor modulator (SERM), or other therapy must be individualized for each patient based on menopausal symptoms, bone density, family or personal history of cardiovascular disease, current serum lipid profile, the patient's personal preference, and likelihood of compliance. In patients with baseline triglycerides of >300dl/ml, care should be taken in initiation of HRT as there is a risk of a significant increase in triglycerides after starting oral HRT. Raloxifene, a SERM, may be an alternative, as it has not shown an increase in triglycerides in non-diabetic patients.¹⁹ Additionally, transdermal estrogen appears to have a neutral effect on triglycerides and may be an option in the patient with hypertriglyceridemia. All type 2 diabetic women who begin treatment with HRT or a SERM should be monitored closely for changes in glycemic control and serum lipids. A lipid panel including a fasting triglyceride level and a HemA1C after three months of therapy seems prudent. Finally, all type 2 diabetic women treated with HRT or not who complain of irregular vaginal bleeding should be evaluated carefully. This evaluation should include endometrial sampling if necessary because diabetes puts women at a four-fold increased risk of endometrial cancer.

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Measurement of Estrogen's Effects on the Brain Using Modern Imaging Techniques



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INTRODUCTION

The brain is one of the most enigmatic organs in the human body. Most of us like to conceptualize it as a living computer. However, that metaphor fails in application. Even the most basic computer can be easily separated into "hardware" and "software." The brain however does not provide for such a clear distinction. There is a complex inter-relationship of form and function.

In July 1990, President George Bush signed a congressional proclamation declaring the 90s to be the "Decade of the Brain." Resulting from the aging of the Baby Boom generation, the last decade has seen a 47% rise in the number of women reaching the menopausal age range. The US Census Bureau anticipates this number to peak around 2010 with approximately 22 million US women in the 45-54 year age range. Associated with this "aging of America," we have seen a dramatic increase in neurodegenerative diseases like Alzheimer's disease. In women's health-care, we are well aware that women are two to three times more likely to develop dementia than age-matched men. Several large prospective placebo controlled trials like the Women's Health Initiative Memory Study are currently investigating the impact of hypoestrogenism on the aging process. Although this information will be invaluable in assisting us in making recommendations to our patients, it is years away from reaching a level of practical application. We therefore must seek other means of studying the brain and aging in order to provide us with interim data and design

future studies to further investigations of the central nervous system.

One of the limiting factors in understanding the brain is having tools that allow us to study it. New techniques have emerged that provide greater insight into investigating the brain and its functions. This manuscript will summarize the current imaging studies useful in studying the central nervous system and the information they have revealed on the impact that estrogen has on this vital organ system.

Previously, neuroscientists were limited to invasive studies or imaging studies with limited resolution. Combining these techniques with electro-physiologic research helped establish the brain's functional compartmentalization. These data were reinforced by clinical studies of known brain lesions. However, it was not until the advent of the CT scan and the subsequent development of the MRI that neuroscience rapidly progressed. More recent studies have focused on issues surrounding cerebral blood flow and metabolism.

Brain function is dependent upon blood flow. Unlike many organ systems, the brain does not have the physiologic reserve to use other fuel sources or metabolic pathways to serve during times of stress or deprivation. Specifically, there is believed to be a coupling mechanism in cerebral cir-

culatory physiology that relates the following phenomenon: (1) blood flow increases with increased neuronal activity, and (2) blood flow increases during tissue hypoxia.¹ Therefore, the healthy brain monitors its needs and adjusts blood flow distribution accordingly.

Using Magnetic Resonance Imaging (MRI), areas of previous vascular injury appear as "white matter hyperintensities." The areas of these white matter lesions correspond to the anatomic area of the brain effected. The Austrian Stroke Prevention Study followed 210 menopausal women for over 10 years. Seventy of the women were on estrogen replacement therapy (ERT) and 140 had never used estrogen. Each patient had yearly MRI studies and a battery of neuropsychologic testing. This study demonstrated that women using ERT had a lower rate and smaller area of white matter hyperintensities. There was an inverse relationship between total white matter hyperintensity and the duration of

estrogen use. The conclusion was that ERT was associated with better cognition and a lower rate of unsuspected ischemic brain injury.²

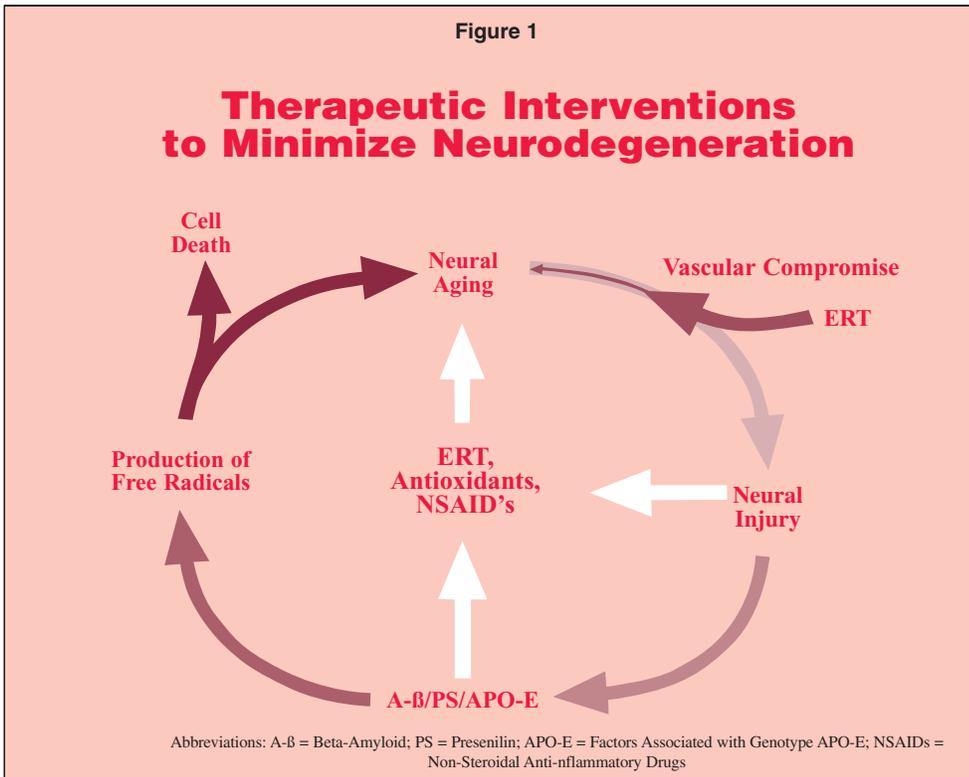
"Recent studies have extended the relationship of brain vasculature and functioning by using advanced imaging tools to measure blood flow distribution."

Cacciatore et al³ used color Doppler imaging to study estrogen's effects on the major vessels supplying blood to the brain. They followed 57 post-menopausal women for one year. Measurement of carotid pulsatility index was obtained to assess the resistance of the brain to flow. They found that during the course of their study there was a progressive decrease in vascular resistance. This translates into an increase in blood supply to the brain during estrogen replacement, presumably facilitating better functioning.

They also found that the women who were most remote from the onset of menopause demonstrated the most dramatic improvement in cerebral blood flow.

Recent studies have extended the relationship of brain vasculature and functioning by using advanced imaging tools to

measure blood flow distribution. Within the brain, different tasks have been localized to specific regions. Single photon computed tomography (SPECT) is a non-invasive imaging modality that measures blood flow distribution. Radioactive trace elements are administered to the test subject. A gamma camera and computer then quantify the circulation in a regionally specific fashion. Okhura et al⁴ were the first to perform such a study on post-menopausal women before and during estrogen replacement therapy. Their group performed SPECT imaging on 14 menopausal women before and during estrogen replacement therapy. By the third week of twice daily 0.625 mg conjugated equine estrogen therapy, they demonstrated a significant mean percent increase of 29.3 ±



10.2% in whole cerebral blood flow and $29.5 \pm 10.4\%$ in whole cerebellar blood flow. There was no change in the control group.

Our group was performing similar research around the time of this publication. However, we were using a SPECT imaging technique that facilitated rapid image acquisition. This technique made it reasonable for us to study brain blood flow during hot flash episodes.⁵ Our study confirmed that hypoestrogenic women had reduced circulation to the central nervous system compared with estrogenized controls. During hot flash episodes, hypoestrogenic women have measurable further decreases in cerebral circulation. In fact, these women had vascular changes typically seen in patients with mild to moderate Alzheimer's disease.⁶

Our investigation also demonstrated that conjugated equine estrogen therapy augmented cerebral blood flow and normalized its distribution similar to that of premenopausal controls. Further, ERT relieves the vasoactive events known as hot flashes. It has been reported by Baxter et al that women have whole brain glucose metabolic rates that are 19% higher than those of men.⁷ It thus stands to reason that women might be more susceptible to physiologic events that result in circulatory compromise. Therefore, this might provide a reason for the gender disparity that seems to make hypoestrogenic women more susceptible to Alzheimer's dementia.

Since SPECT imaging maps vascular data in a regionally specific fashion, it can be correlated (in general) fashion with known anatomic data. In our study, it was apparent that the left temporal, parietal, and pre-frontal regions of the brain were most susceptible to vasoactive compromise. Interestingly, this supports the studies on cognition and estrogen replacement which repeatedly demonstrate that short-term memory and verbal memory seem to be most susceptible to menopausal deterioration. Comparatively, these are also some of the earliest clinical signs of Alzheimer's disease.

As the link between hypoestrogenism and Alzheimer's disease seems to be growing stronger, we have proposed that hot flashes might contribute to neurodegenerative changes. These vasoactive events might be an initiating event analogous to the initial damage that results in coronary artery plaque formation. Specifically, hot flush episodes could create physiologic

stress in the form of a vascular insult which could result in cerebral ischemia and free radical formation (figure 1). Each individual hot flush episode is unlikely to be of any clinical significance. However, taken collectively, hot flushes might result in enough damage to initiate a cascade of events resulting in accelerating neurodegenerative changes.

Functional imaging studies are techniques for studying brain metabolism rather than just blood flow. Positron Emission Testing (PET) and functional Magnetic Resonance Imaging (fMRI) are the two modalities most widely used for these purposes. In these analyses, test subjects are given a metabolic substrate, generally either radiolabeled glucose or oxygen, and then instructed to perform a prescribed task. A camera then determines the location and quantity of the metabolites. These studies can demonstrate which areas of the brain were being activated and to what extent in order to complete the prescribed task. Results are then compared to control cases.

The Baltimore Longitudinal Study on Aging⁸ was the first to use this technique to investigate brain activity in menopausal women. This is a prospective study of normal aging initiated by the National Institute on Aging in 1978. From their cohort of 514 postmenopausal women, 32 have had annual PET scanning and neuropsychological testing for nine years. Fifteen of these subjects are ERT users and 17 are nonusers.

They demonstrated that ERT users performed better on verbal ($p < 0.05$) and figural ($p < 0.02$) memory than nonusers. These cognitive differences were matched by differences in the brain activation patterns between the two groups. The exact significance of these differences cannot be determined using this technique, but their existence indicates that estrogen affects metabolism as well as circulation.

PET imaging of women with Turner's Syndrome has also provided insight into the relationship of estrogen and cerebral function. Turner's Syndrome (TS) is the

complete or partial deletion of one of the X-chromosomes. Affected women have premature ovarian failure and thus produce little or no estrogen. Murphy et al⁹ performed a PET study on 16 TS patients (mean age: 26 years) and compared their results to 13 healthy controls (mean age: 28 years). They found that the TS women had significant brain hypermetabolism relative to the controls. They also found an "X-chromosome dosage effect" in: (1) language ability, (2) left temporal and parietal metabolism, and (3) brain asymmetry test scores. The impact of ERT on these observations or their effects on long-term brain functioning is not yet known.

Functional MRI is also being employed to study estrogen and the brain. Shaywitz¹⁰ et al performed a prospective crossover study on 46 postmenopausal women. Their study design had patients randomly assigned to a 21-day treatment with conjugated equine estrogens or placebo and then crossed over following a 14-day washout period. They demonstrated that estrogen

clearly effects brain activation. Specifically, based on the regions of activation, estrogen seems to affect the organization of memory by demonstrating a significant impact on specific regions of the frontal lobe. Their study did not demonstrate any measurable effects on cognition. This investigation's inability to measure any significant outcome effect on cognition could be a result of its design or duration.

Finally, now that it has been clearly shown that estrogen has physiologic impact on the brain, several investigations are underway to measure differential effects of vari-

ous estrogenic compounds. Specifically, one research group has performed a randomized double-blinded crossover study using PET scan imaging to compare data from a group of women treated with conjugated equine estrogen to data from the same women treated with raloxifene. Thus far, they have demonstrated that the same women clearly have different brain activation patterns on one therapy vs. the other.¹¹

"Finally, now that it has been clearly shown that estrogen has physiologic impact on the brain, several investigations are underway to measure differential effects of various estrogenic compounds."

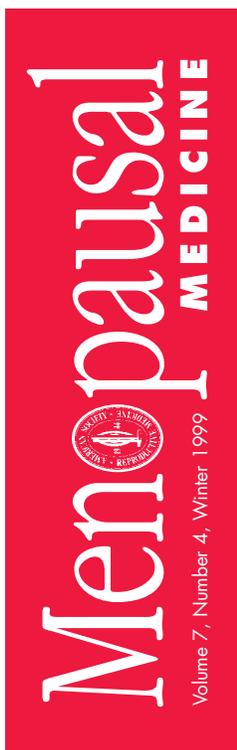
This study was not designed to judge effectiveness of one product vs. the other and does not lend itself to that sort of interpretation. It is clear however that they do influence metabolism of the brain differently. This is not surprising when one couples this data with the SPECT data on hot flushes and the well-known clinical observation that SERMs (selective estrogen receptor modulators) often result in exacerbation of these vasoactive events. An area for further investigation will be the comparison of SERMs and various estrogen preparations on regional cerebral blood flow. This area of research might facilitate us in our clinical recommendations for women with various mental health questions and concerns.

As we now complete the "Decade of the Brain," we can acknowledge that we have learned much about how to study the brain but we still have many unresolved questions. It is therefore more important now than ever before that we continue to investigate ways to facilitate healthy neurologic aging in women. It is hoped that with these new imaging tools, we will be able to collect data that will guide us in our rec-

ommendations as we await with anticipation the results of important ongoing clinical trials. These advanced imaging studies might even provide greater insight into the pathophysiological process of neurodegenerative diseases in menopausal women.

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