



LIFE EXTENSION

REPORT

THE INSIDER'S REPORT ON EFFORTS TO PREVENT AGING AND REJUVENATE THE AGED

NATURAL ESTROGEN Breakthrough In Hormone Replacement

By Terri Mitchell

Hormone replacement therapy (HRT) for men is a hot topic. Newsweek recently devoted front-page coverage to it.

Middle-aged baby-boomer males are apparently not happy about their sagging guts and descending erections. They are snapping up DHEA, testosterone, melatonin and growth hormone to gain muscle, endurance, and the vigor and vitality of youth.

Although you wouldn't have guessed it from the Newsweek article, women, too, are taking these hormones for similar reasons. But while hormone replacement therapy for men is a relatively new concept, women have been undergoing HRT for decades in the form of synthetic and semi-synthetic estrogen and progesterone.

A Revolution In Estrogen Replacement

While HRT for men is a fairly recent phenomenon, women have had decades of experience with various forms and dosages of estrogen.

And now a revolution is occurring in estrogen replacement therapy due to new data from years of

estrogens have long been associated



with adverse side effects and risks that are unacceptable to many women. It is now becoming clear that the problems of estrogen replacement therapy may be due more to form and dosage than to replacement per se.

It is no longer true that women have to choose between the unbearable symptoms of the menopause or adverse

side effects and the risk of cancer. The buzz at the recent scientific meeting of the **North American**

plant-derived estrogens, or phytoestrogens, is the way to go. Booths promoting these types of estrogens were wildly popular. Physicians descended on natural product booths, looking for answers to the questions their patients have been asking them about natural hormone replacement.

Benefits Of Estrogen Replacement

Estrogen replacement therapy has enormous benefits for women. **Dr. Frederick Naftolin** of Yale University and **Dr. Suzanne Woodward** of Wayne State University presented data at the Menopause Meeting about how estrogen regulates brain function. According to Dr. Naftolin, estrogen regulates autonomic function through the hypothalamus region of the brain. Memory, libido and aggression are regulated by estrogen through the temporal cortex/limbic system; and mood through the cerebral cortex.

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LIFE EXTENSION MAGAZINE is a practical handbook for people who want to stay alive and healthy. It features inside information about how to live longer now, innovative ideas about how to extend the human lifespan and bold visionary plans to achieve physical immortality. *LIFE EXTENSION* is published by The **LIFE EXTENSION FOUNDATION**, a non-profit membership organization dedicated to the extension of the healthy human lifespan.

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A new therapy for menopausal and postmenopausal women that features several potent plant extracts (phytoestrogens). The results of clinical trials with the new **Natural Estrogen**.



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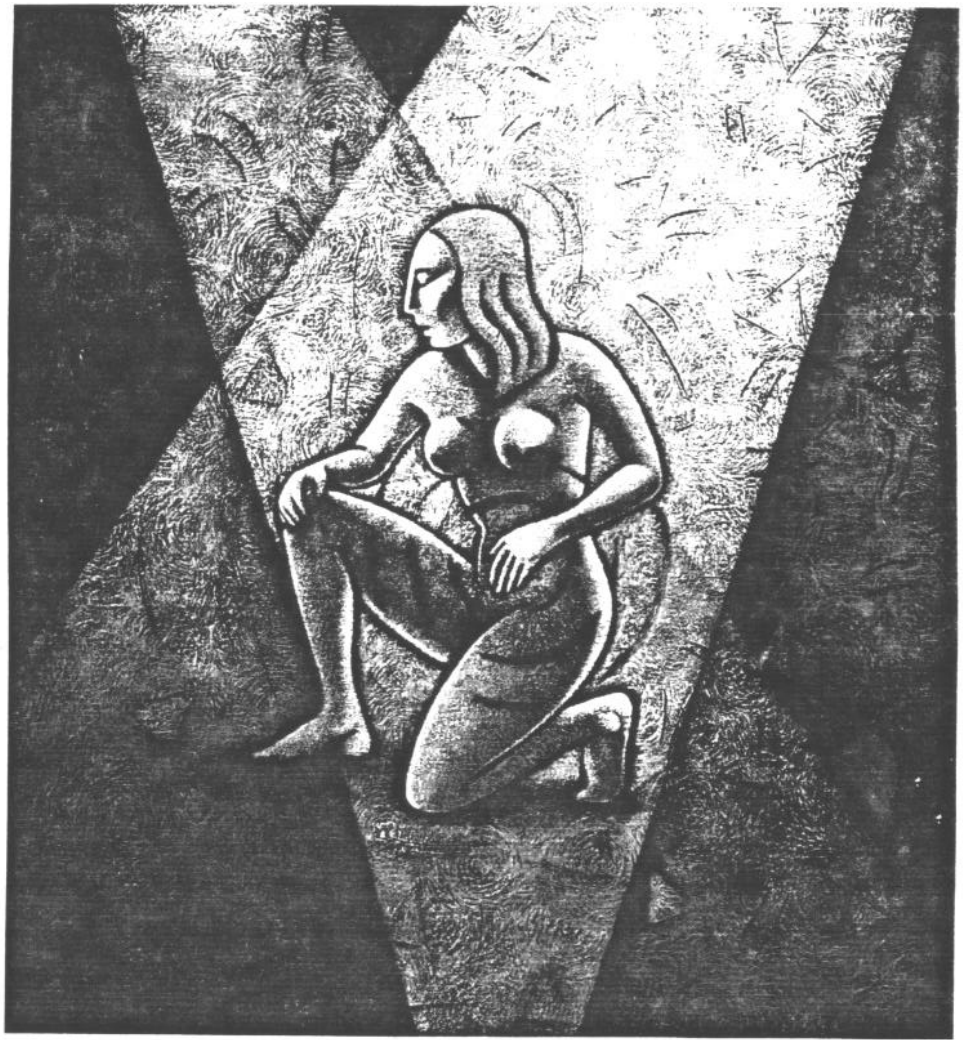
Dr. Woodward presented the results of her new study showing that “hot flashes” change sleep patterns due to their adverse effect on thermoregulation by the hypothalamus. This leads to decreased REM sleep. REM sleep is absolutely crucial for health. Studies in rats show that REM sleep deprivation causes profound dysregulation of body temperature, and eventual death.

One of the most important benefits of estrogen replacement therapy is its protection against heart disease, the No. 1 killer of women. In the **Lipid Research Clinics Program**, postmenopausal women who took estrogen were less than half as likely to die from heart disease. Women who already had heart disease who took estrogen reduced their risk of a heart attack by about 75%. Recent large-scale studies have verified the benefits of estrogen replacement therapy against Alzheimer’s disease and osteoporosis.

The Form Of Estrogen Is Crucial

Despite numerous benefits, some women have been reluctant to take supplemental estrogen because of their concern about adverse side effects, including cancer. Those days may soon be over. Data are accumulating that the negatives associated with estrogen replacement therapy are caused largely by the form in which it is given.

Like most substances in the body, estrogen works synergistically with other biochemicals. Giving estrogen alone is like installing four wheels on a car, but leaving off the tires. The results of the PEPI study published in the February 1996 issue of JAMA confirmed that some women given estrogen alone develop hyperplasia of the uterus, while those given progesterone in conjunction with estrogen do not. (Hyperplasia is a pre-cancerous condition).



Chemically-Altered Hormones

Drug manufacturers are largely responsible for the negative side effects associated with estrogen replacement therapy. It’s an old story: Drug company chemists take a natural substance, synthesize it and add a few chemical changes so that it can be patented as a new entity. The problem with this approach is twofold: 1) Synthetic single molecules are devoid of co-factors that enhance or modulate their activity; and 2) No matter how innocuous, chemically-altered substances are foreign to the body.

The makers of Premarin (the best-selling estrogen drug) like to refer to their product as “natural”. “Premarin” is short for “pregnant mares’ urine”. Premarin is made by

keeping artificially inseminated horses in stalls with collection bags strapped over their anatomy in order to collect their urine, which is then made into the drug. If the human consumption of horse urine is natural, then Premarin is natural.

The major side effects of Premarin include cancer and gallbladder disease. Among the “minor” side effects are urine breath, candidiasis, bleeding, depression, edema, hair loss, and vomiting. Women who add the synthetic progesterone “Provera” to their estrogen therapy expose themselves to additional side effects including blood clots in the brain and heart, insomnia, and skin disorders.

Other pharmaceutical non-urine-based estrogens start out as yams, but are “engineered” by chemists. They are known as “semi-synthetic” hormones. The problem with these

types of drugs is that they are so refined, that natural enzymes which aid the body in utilizing the drugs are completely lacking. This causes serious side effects, as huge amounts of the non-natural substance flood the body without mediating factors. In addition, as with cortisone, the body downregulates its own synthesis of natural hormones when flooded with synthetic ones. The body's inability to make cortisol-another steroid-after therapy with synthetic glucocorticoids like prednisone is well-known. It is interesting to note that synthetic cortisone was also originally made from yams. Anti-inflammatory and estrogenic substances seem to occur together in the same plants.

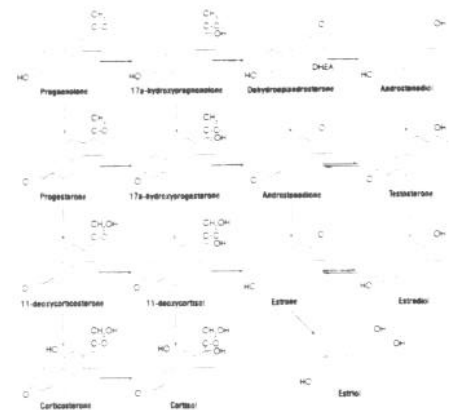
Another problem created by ingesting synthetic single hormones is that an imbalance of hormones is created. It is probably this imbalance that accounts for many of the side effects, including cancer. Estrogen causes the lining of the uterus to thicken; progesterone causes it to thin. The four-times

greater risk of endometrial cancer in women taking estrogen drugs versus not taking them, may be due to continuous "grow" signals of estrogen without the "stop" signals of progesterone.

Postmenopausal women are not only deficient in estrogen, they are deficient in progesterone and the androgen hormones (testosterone) as well. According to Lien, et al., there is a 50% decrease in androgen production after menopause (along with the 66% decline in estrogen). In some studies, estrogen plus androgen is more effective in increasing and maintaining bone density, and in lowering triglyceride levels. It is also interesting to note with regard to lipids, that according to a study by Crook, et al., Premarin increases triglycerides, while transdermal estrogen decreases triglycerides. This underlines the fact that all estrogens are not the same, and estrogen alone is not the answer.

Botanical Sources of Estrogen

In countries where botanical sources of estrogenic hormones are consumed, women do not experience estrogen-related side effects, nor do they suffer the severe menopausal symptoms experienced by women who consume a Western diet. This knowledge has led to an explosion of plant-based estrogen and progesterone products on the American market. Unfortunately, many of these products do not contain enough hormone to do any good. And many do not provide hormones in a form that can be utilized by the body.



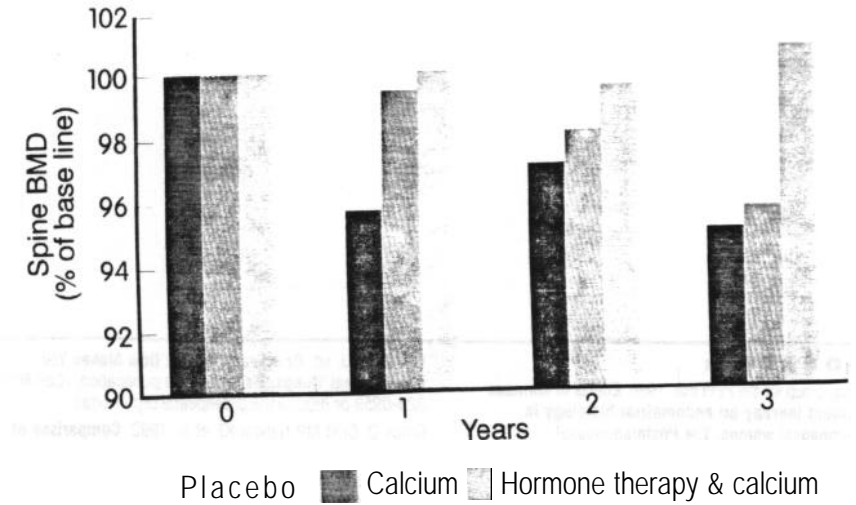
Biochemical Pathways of Steroid Hormones

All steroids are synthesized from cholesterol, a type of alcohol synthesized in the liver and found in fats, nerve tissue, and other organs of the body. Cholesterol is a sterol, hence the moniker "steroid." Plant sterols are known as phytosterols.

Cholesterol contains the backbone structure of all steroid hormones called the perhydrocyclopentanophenanthrene ring.

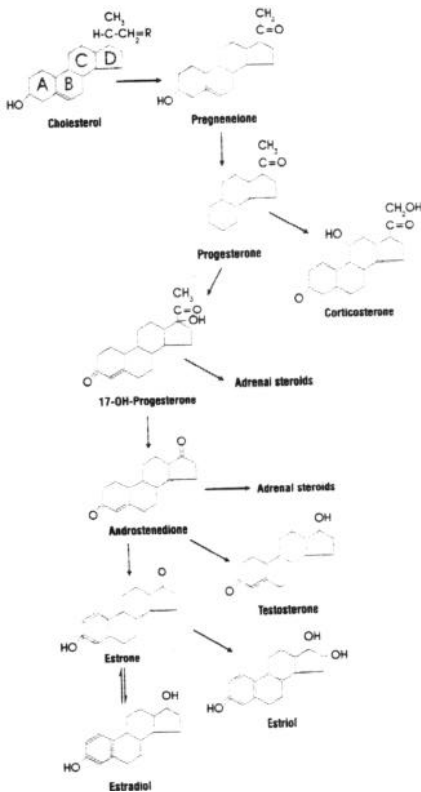
Side Effects of Premarin (source: 1996 PDR)

- Endometrial cancer
- Breast cancer (high doses for prolonged periods)
- Gallbladder disease
- Fluid retention
- Uterine bleeding
- Uterine fibroids
- Hypercalcemia and renal insufficiency (prolonged use)
- Candidiasis
- Breast tenderness and enlargement
- Nausea, vomiting, abdominal cramps, bloating, jaundice
- Chloasma (abnormal pigmentation of skin)
- Loss of hair, hirsutism
- Skin eruptions
- Steepening of corneal curvature, intolerance of contact lenses
- Headache, migraine, dizziness, mental depression, chorea (muscle twitching)
- Increase or decrease in weight
- Reduced carbohydrate tolerance
- Aggravation of porphyria (disturbance in metabolism of porphyrin)
- Edema
- Changes in libido
- Blood clots
- Enlargement of benign tumors of the uterus



The annual rates **of change in bone mineral density in the lumbar spine after menopause.**

Based on the findings of Aloia JT, Vaswani A., Yeh JK, et al. Calcium supplementation with and without hormone replacement therapy to prevent postmenopausal bone loss. Ann Int Med 1994, 120:97- 103



Biosynthesis of Estrogens Through Progesterone

can be synthesized and broken down evenly along the biochemical pathways. When a co-factor (such as an enzyme) is missing, hormones will be biochemically converted down alternate pathways, resulting in an overabundance of some hormones and a deficit of others.

In addition, studies on the phytoestrogen genestein show that it inhibits the growth of breast cancer cells in vitro. Premenopausal women may benefit from the protective effects of phytoestrogens against breast cancer, fibroids, and osteoporosis. Any woman 35 years of age or older should consider **NATURAL ESTROGEN** therapy for its **bone-building benefits**.

Unlike drugs which deliver only one hormone, **NATURAL ESTROGEN** contains a natural blend of estrogens, progesterones, and testosterone which are carried into the body along with co-factors such as enzymes that allow the body to utilize them. Unlike synthetic estrogen, no case of cancer has ever been associated with the use of phytoestrogens.

Dr. Gushleff and others believe that **NATURAL ESTROGEN** may even protect against estrogen-mimicking chemicals (2, 3, 7, 8-tetrachlorodibenzo-p-dioxin) which lodge in fatty tissue such as the breast. Some scientists believe that these chlorine and pesticide-related chemicals are responsible for the explosion of breast cancer that is occurring (breast cancer is the No. 2 killer of women, after heart disease).

Dosage Schedule For Natural Estrogen

Just one capsule of **NATURAL ESTROGEN** equals one 0.625 tablet of Premarin. With hormones, "one size does not fit all". Women should undergo testing before therapy is begun to determine baseline hormone levels, and again after therapy

has begun. **NATURAL ESTROGEN** should be taken cyclically: three weeks on and one week off, beginning on the 5th day of the cycle for premenopausal women, and any day for postmenopausal women.

Although patients can go "cold turkey" from synthetic estrogen to **NATURAL ESTROGEN** without any adverse effects, Dr. Gushleff suggests that women who have been using estrogen drugs gradually wean themselves off. The following program is suggested:

1st month: NATURAL ESTROGEN every other day

2nd month: NATURAL ESTROGEN 2 days in a row

3rd month: NATURAL ESTROGEN 3 days in a row, continuing until synthetic estrogens are eliminated completely

NATURAL ESTROGEN enhances the assimilation of hormone precursors DHEA and pregnenolone through its enzymatic action. Women who are taking these supplements may reach adequate levels of estrogen quicker than women who are not taking them.

How To Obtain Natural Estrogen

NATURAL ESTROGEN can be purchased in bottles of 60 caplets for the retail price of \$38.00. When a member buys four bottles of **NATURAL ESTROGEN** during our currently running **SUPERSALE**, the price is only \$22.28 per bottle. When ten bottles are purchased during the **SUPERSALE**, the cost is reduced to members to the super-low price of just \$19.58 per bottle.

You can order your supply of **NATURAL ESTROGEN** by calling 1-800-544-4440 or by sending your check to:

**Prolongevity Ltd.
10 Alden Road, Unit 6
Markham, Ontario L3R 2S1
Canada**

Calcium and Vitamin D3 augment estrogen's ability to prevent osteoporosis. In a study published in the **Annals of Internal Medicine**, optimal bone retention occurred in women given 1,700 mg. of calcium plus 400 IU of vitamin D3 per day, along with estrogen and progesterone. **Life Extension** recommends that women take this dosage along with **NATURAL ESTROGEN** to augment its anti-osteoporosis effects.

Calcium and vitamin D3 are found in the **Mineral Formula For Women** and can be ordered by calling: 1-800-544-4440 or by using the order form in the back of the magazine.

How To Get Tested For Your Hormone Levels

Being treated for the symptoms of the menopause or as a means of preventing heart attacks, osteoporosis, Alzheimer's disease, and other disorders should be done under the care of a physician- either a gynecologist or endocrinologist.

Hormone testing is desirable as a means of determining your need for estrogen, progesterone, testosterone, DHEA, and other hormones. The traditional method is blood testing. Blood tests can be ordered through your physician or through The Foundation, under the authorization of The Foundation's medical director.

We suggest that, before you start to take **NATURAL ESTROGEN**, you should be tested for total estrogen (estradiol, estrone, estriol). You should then be re-tested every 3 months thereafter, until you establish stabilized estrogen levels. This should be done regardless of whether you are already taking an estrogen drug. If you substituting **NATURAL ESTROGEN** for an

RESOURCES :

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ESTROGEN AND ALZHEIMER'S DISEASE

Another study showing the benefit of estrogen replacement therapy against Alzheimer's Disease (AD) will be published in the *Journal of Neurology* within the next six months. The study shows a 56% reduction of risk of getting AD with estrogen therapy. Four-hundred and seventy-two women took part in the study conducted at **Johns Hopkins University**. Some were studied for as long as 16 years. The results confirm research done at the **University of Southern California** on 8,877 women (only 138 had AD) which showed that the risk of Alzheimer's in women who took estrogen was less, and that the more estrogen they took, the better. That study also found that duration of use was a positive factor, as well. Both of these studies conflict with a study from the **University of Washington** published in 1994, showing no effect of estrogen therapy on AD.

Estrogen can improve the mental scores of Alzheimer's patients. In a Japanese study of 7 patients with

mild-to-moderate dementia, **estrogen improved both cognitive function and ability to carry out daily activities in 6 of 7 patients.** Four patients improved greatly; two moderately; and one patient didn't improve. When estrogen therapy was stopped, the scores got worse.

The same group of researchers studied another group of 15 patients, with the same results. In addition, they measured blood flow and took EEGs of the patients' brains. They found that **estrogen replacement therapy increased blood flow to the frontal cortex and motor areas.** Improvements in brain waves were also apparent.

The beneficial effects of estrogen on Alzheimer's and other dementias has been known for at least ten years, but researchers are just beginning to unravel how it works. Research suggests that estrogen may protect in several ways. A study conducted at the **Max Planck Institute of Psychiatry** shows that

17-beta estradiol can protect mouse neuronal cells from oxidative stress caused by glutamate, H₂O₂, and amyloid beta protein (the protein which accumulates in the brains of Alzheimer's patients). **17-beta estradiol** also blocked DNA degradation caused by glutamate.

Another way estrogen may affect the brains of Alzheimer's patients is through its effects on blood vessels. The positive effects on blood flow noted in the Japanese study may be the result of estrogen's ability to dilate blood vessels. Researchers have discovered that vascular smooth muscle cells have estrogen receptors, which means that estrogen modulates blood vessels. This effect is at partially responsible for estrogen's protection against heart disease.

Estrogen receptors have also been discovered on certain types of brain cells. **When estrogen is added** to neurites in cell culture, they grow **dramatically**. Some of the most exciting Alzheimer's research is aimed at uncovering the nature of the **beta amyloid protein** which builds up in the brains of AD patients. **"Beta amyloid plaques"** are one form of abnormal structures in the brains of AD patients. The other is **neurofibrillary tangles**", composed of "paired helical filaments"-twisted accumulations of skeletal-like structures.

Amyloid beta comes from a precursor protein called APP. This protein is snipped apart by chemical scissors known as enzymes. APP is snipped into different types of amyloid proteins. AD patients have too much APP 770, which may lead to increased soluble amyloid beta. Although the relationship between amyloid protein and estrogen is not clear, studies published offer tantalizing clues about what causes AD.

Three possible explanations for the increased levels of amyloid beta protein have been suggested by researchers: **1) overexpression of the protein; 2) faulty processing of**

the protein; or 3) lack of enzymatic degradation of the protein. APP is cut in the amyloid beta area by two enzymes, α -secretase and β -secretase. If α -secretase cuts APP no beta amyloid results, and there is increase in soluble APP. A group of researchers from Cornell, Rockefeller and Columbia reported in the *Journal of Biological Chemistry* that under certain conditions estrogen increases soluble APP which suggests that estrogen has something to do with enhancing the enzymes which cut APP?

This very exciting research suggests that enzymes play a major role in the build-up of amyloid beta protein in AD. Researchers in Japan are zeroing in on the exact enzyme-related mechanism that malfunctions in Alzheimer's patients. They have discovered that enzyme inhibitors secreted by a type of brain cancer are identical to one of the amyloid precursor proteins. In other words, **Alzheimer's patients may be making too much of a protein which either inhibits the degradation of amyloid beta or cleaves the precursor protein towards making amyloid beta.**

A study just published in *Molecular and Chemical Neuropathology* confirms that the amyloid beta protein precursor interacts with the enzyme, trypsin. This underlines the importance of enzymes in AD. The authors of the study wrote that, **"this scenario supports our previous suggestion that degenerating neurons, including those surrounding focal points of degeneration such as amyloid deposits, are in a state of proteolytic imbalance."** In other words, **the molecular scissors are snipping too little, allowing a build-up of protein in the brain which interferes with proper function.**

Another group has been investigating the paired helical filaments which create AD tangles. **Drs. Virginia M-Y Lee and John Q. Trojanowski** and their group believe that enzymes called phosphatases are disrupted in AD. As in the build-up

of beta amyloid, faulty degradation mechanisms may be at work.

Dr. Claudia Kawas, who is one of the authors on the new estrogen study, is part of another group investigating the role of **corticotropin-releasing factor (CRF)** in AD. CRF is decreased in AD patients. The factor has been linked to memory and learning in rodents. The group believes that CRF is being deactivated in AD patients by another protein. The other protein is binding to CRF. The group believes that drugs can be developed to keep the binding protein from tying up CRF.

For now, estrogen is the most proven treatment for AD. While it is not known how estrogen works, a picture is emerging that links it to enzymes which are crucial in regulating proteins produced by cells in the brain. A study published in 1989 showed that estrogen can cause phosphorylation, which is further evidence of its enzyme-regulating effects.

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