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Scientists Find Compound to Explain Hormone-Heart Disease Connection

By **RON WINSLOW**
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Scientists say they have found a biological mechanism that helps explain why hormone-replacement therapy failed to prevent heart disease in some participants of the controversial Women's Health Initiative study.

Researchers at University of Texas Southwestern Medical Center in Dallas have discovered that a compound related to cholesterol can block the hormone estrogen from performing functions in blood vessels that keep them healthy and free of disease that can lead to heart attacks.

Much previous research has found that estrogen benefits the heart, but confidence in that premise was shaken in 2002 when a major Women's Health Initiative study of hormone-replacement therapy in postmenopausal women was halted after data indicated the regimen increased the risk of coronary disease.

The findings caused an uproar, and thousands of women undergoing hormone replacement to alleviate menopause symptoms stopped taking the medicine. Subsequent findings show those who were younger and much closer to the onset of menopause when they began taking replacement hormones actually experienced no increased heart risk. The latest report offers a possible explanation for why some women are at heightened heart risk and others aren't.

The culprit identified by the Texas team is a molecule called 27-hydroxycholesterol, or 27HC, a byproduct created as the body processes cholesterol. The researchers found in experiments in mice that 27HC and estrogen target the same receptors in blood vessels.

When estrogen is present in normal amounts and 27HC levels are low -- as is typically the case in women before they enter menopause -- the hormone successfully latches onto the receptors, triggering actions that protect the heart, the researchers found. But when estrogen falls, as it does during menopause, 27HC is able to beat the hormone to the targeted receptors and block its beneficial effects.


"As long as estrogen is there, you have protection," says David J. Mangelsdorf, a Howard Hughes Medical Institute investigator at UT Southwestern whose laboratory made the discovery. "If you lower the concentration of estrogen or inhibit its action, that increases the risk for cardiovascular disease." A report on the finding is being published in the October issue of *Nature Medicine*, which posted it on its Web site yesterday.

Participants in the Women's Health Initiative began taking estrogen, on average, 13 years after the onset of menopause. Dr. Mangelsdorf says his findings suggest that in the interim, 27HC had taken over the estrogen receptors, setting in motion processes that gave cardiovascular disease a foothold in the blood vessels. "Estrogen is a protector, it's not therapeutic," he says. "You can't give it to cure something that's started."

Dr. Mangelsdorf's work was supported by the National Institutes of Health, Howard Hughes Medical Institute and a private philanthropy.

Donald McDonnell, a researcher at Duke University Medical School who has collaborated with Dr. Mangelsdorf but wasn't involved in the *Nature Medicine* paper, says the report "brings a new perspective" to the findings of

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the Women's Health Initiative study and "a very plausible [scenario] that has been tested out in the best [animal] models we have available." It is also consistent with recent closer examination of that study.

The findings don't mean women should consider hormone therapy to prevent heart disease, but they are consistent with current advice that starting the therapy near the onset of menopause to treat its symptoms doesn't appear to increase heart risk. Dr. Mangelsdorf says his report offers a reason why women who have high cholesterol and have been in menopause or off hormone therapy for a few years aren't good candidates to start taking estrogen, though he says any decision should be made in consultation with a physician familiar with the science.

JoAnn Manson, one of the principal investigators of the Women's Health Initiative, agrees the new findings provide "intriguing" insight into results of the study.

For instance, she wondered about a finding from the big study in which women with high cholesterol were more likely to have worse outcomes on hormone-replacement therapy than those with low cholesterol. Since high levels of 27HC reflect high levels of cholesterol in the blood, the new report offers an explanation for that result, she says.

"Their overall finding ties together very nicely with the clinical-trial results," says Dr. Manson, who is chief of preventive medicine at Harvard University-affiliated Brigham and Women's Hospital in Boston. "This could help fit pieces of the puzzle together."

While 27HC counteracts estrogen in the cardiovascular system, another paper, published online this past Thursday by the journal *Molecular Endocrinology*, describes how the compound acts in a different and deleterious way in breast tissue, activating estrogen receptors that promote tumor growth. Duke's Dr. McDonnell is senior author of that study. Dr. Mangelsdorf is a co-author.

"Those are two properties that are very undesirable in a compound that targets the estrogen receptor," says Dr. Mangelsdorf. "If you had a compound that could inhibit 27HC [in both settings], you'd have a very interesting drug."

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