WOMEN'S HEALTH

The Vanishing Promises of Hormone Replacement

As the quality of epidemiological research improved, predictions that HRT would cut heart disease faded, whereas risks of cancer became clearer

"I'm glad I said yes to Prempro," a radiant-looking singer Patti LaBelle declares on a Web site praising the benefits of a popular family of hormone drugs, manufactured by Wyeth. But now, a study by the U.S. National Heart, Lung, and Blood Institute suggests that it's better to say "no" to those drugs—at least for long-term use. An interim safety review found that Prempro, a combination of estrogen and progestin often prescribed to postmenopausal women, increased the risk of invasive breast cancer, heart disease, stroke, and pulmonary embolisms. They reduced bone fractures and colorectal cancer, but not enough to outweigh the other risks.

Last week, the vast study came to a halt, and more than 16,000 participating women received a letter recommending that they stop taking their pills. The study, part of a huge research program called the Women's Health Initiative (WHI), stunned many supporters of hormone replacement therapy (HRT) and led many women taking the drugs—some 6 million in the United States alone—to call their doctors for advice. Thomas Clarkson, who studies hormone therapy at Wake Forest University in Winston-Salem, North Carolina, calls it the "9/11 of HRT."

But epidemiologists who have studied the issue for years say they're not so surprised. Some have long argued that the evidence supporting long-term hormone therapy was far from solid. There were almost no randomized controlled clinical trials—the gold standard in medicine—sorting out risks and benefits, says Diana Petitti, research director at Kaiser Permanente of Southern California in Pasadena. Yet the view that HRT prevented heart disease was so entrenched that during the planning for WHI, some argued that it would be unethical to deny some women the drug and give them a placebo. "Everybody was so convinced of the benefits," says Kay Dickersin, an epidemiologist at Brown University in Providence, Rhode Island, "I started wondering, 'Gosh, am I too skeptical?' "

The faith in hormone therapy remains strong even now, and the WHI results seem unlikely to end the debate. Already, some HRT proponents are criticizing the trial's methodology—arguing, for instance, that participants were too old to benefit. Besides, some doctors say, Prempro is only one of many hormone combinations on the market, and they intend to prescribe different ones.

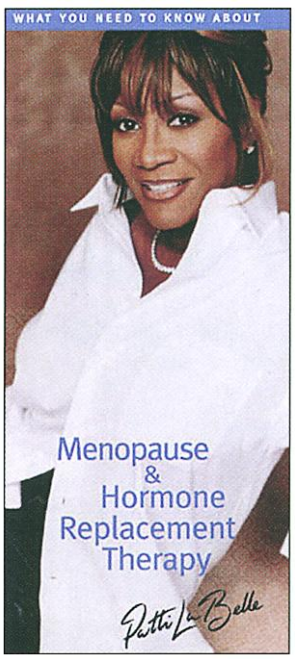
CREDIT: AAIUH

Fountain of youth

Treatments to replace a woman's dropping natural hormone levels after menopause have been around for about 50 years. Initially, many doctors prescribed estrogen alone, but evidence that this could cause uterine cancer prompted many to adopt a combination with a progesterone-like hormone. (Women who have had a hysterectomy usually get estrogen alone, and another part of WHI testing that regimen will continue.)

Scientists agree that HRT can help relieve short-term symptoms of menopause such as hot flashes and night sweats; nor is there evidence that such short-term use is harmful. It's the long-term risks and the fountain-of-youth promises that are in dispute. Earlier studies suggested that HRT could prevent osteoporosis and bone fractures, as well as cardiovascular disease and perhaps Alzheimer's disease and aging of the skin. Some nagging research data showed, however, that the treatment also caused a small but significant increase in breast cancer risk. And because there are other drugs for osteoporosis, the case for HRT hinged almost entirely on its powerful reduction of the risk of heart disease, a major killer.

The problem was that the evidence for this effect came from so-called observational studies, in which women who had decided to take the drugs were compared to those who did not. Such studies are considered less rigorous than randomized trials such as WHI, in which chance decides who gets a drug and who will take placebo. On the other hand, the data were backed by many "mechanistic" studies that showed a favorable effect on markers such as cholesterol levels and atherosclerosis.



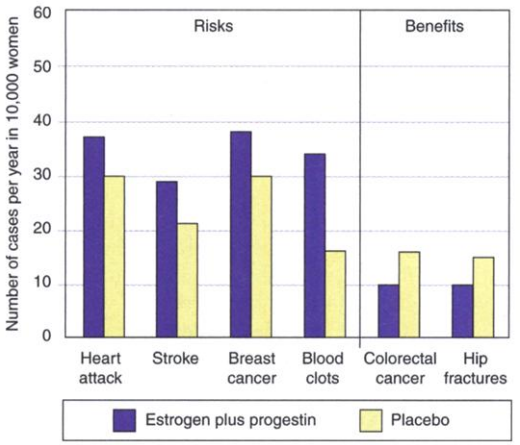
Poster girl. Wyeth recruited Patti LaBelle to promote hormone drugs.

Citing this research, Wyeth tried in the 1990s to get HRT approved as a treatment to prevent cardiovascular disease. The U.S. Food and Drug Administration rejected the application, and the company agreed to fund a disease-prevention trial, the Heart and Estrogen/Progestin Replacement Study (HERS). It enrolled women who already had heart disease—the group in which an effect would be easiest to demonstrate.

Deborah Grady, an epidemiologist at the University of California, San Francisco, and a HERS investigator, says she had high hopes when the trial began. "The evidence was pretty darn convincing," she says. But the first HERS results caused a shock in 1998: HRT increased, rather than decreased, the risk of heart attacks in the first years of the trial and had no overall beneficial effect after 4.1 years. But some HRT proponents argued that it might still benefit women who had survived the initial phase of therapy. That glimmer of hope was dashed in a follow-up study, HERS-II, published in *The Journal of the American Medical Association* (*JAMA*) on 3 July: It showed no long-term benefit. After HERS, says Grady, it seemed unlikely that WHI, which enrolled healthy women, would produce favorable results.

She was right. In 2000 and 2001, preliminary analyses by an independent panel suggested a modest increased risk of heart attacks and stroke; WHI participants were informed by letter. And on 31 May, the panel decided that the trial should be stopped altogether, as the risk had passed a preestablished threshold. (The analysis was published in the 17 July issue of *JAMA*.) "It's simple now," says Grady. "The harm outweighs any benefit."

But the trial still poses a huge question for public health: How did more than 50 observational studies show benefits for HRT that were not real, leading researchers and doctors astray? One likely explanation, says Elizabeth Barrett-Connor of the University of California, San Diego, is a process called selection bias. Women who decided to take the drugs were already healthier and saw doctors more often than did those who didn't receive HRT. When the HRT users had better outcomes, researchers credited the drugs. Jacques Rossouw, who led the WHI team—which will spend several more years following up the women and analyzing data—says they



Bottom line. Risks of HRT outweighed benefits, according to a U.S. government study.

are planning to look into the discrepancy.

Other analysts, unwilling to discard long-term HRT, say there are different ways to explain the data. Clarkson, for instance, argues that studies in cynomolgus monkeys indicate that a real benefit occurs only if HRT is started as soon as natural hormone levels begin to drop (for most women, in their 40s) and is sustained from then on. A benefit in the WHI study was unlikely, he says, because most women started taking pills too late. Stanley Birge, a geriatrist at Washington University in St. Louis, argues that a reduction in Alzheimer's might not have shown up because the women were followed up for an average of only 5.2 years. He says it's "tragic" that the trial was ended "prematurely."

So what's the future of HRT? Most agree that Prempro will no longer be widely prescribed for long-term prevention. But some epidemiologists believe that doctors, nudged by skilled marketing, will continue prescribing other HRT combinations, lower doses, or therapies that use progestin intermittently. Birge, for one, thinks the study results say little about these alternatives, and he is advising women who consult him to keep taking their pills.

Ideally, says Birge, each alternative should be tested in a rigorous WHI-style trial. In the meantime, "I just don't think it's fair to withhold the potential benefits" of HRT, he says. But Barrett-Connor says this view is upside down: "When you're giving drugs to healthy people to prevent disease, there has to be evidence that they work," she says. "You shouldn't just start giving them until they're shown to be harmful."

The problem is that final answer might never come, because most agree that a study as large and costly as WHI is unlikely to be repeated. Currently, one other trial of Prempro is under way: the Women's International Study of long Duration Oestrogen after Menopause (WISDOM), a huge study that started 18 months ago. So far, the study has enrolled about 5000 out of the 22,000 women scheduled to participate in the United Kingdom, Australia, and New Zealand, says Madge Vickers of the U.K.'s Medical Research Council, one of the study's leaders.

Although many epidemiologists would love to see the trial completed, some wonder if that will happen: It could be difficult or even unethical to enroll more volunteers, now that U.S. women have been warned against taking HRT therapy. WISDOM's data-monitoring panel was scheduled to meet this week after *Science*'s deadline to recommend what should happen next. **–MARTIN ENSERINK**

MARINE SCIENCE

Researchers Plunge Into Debate Over New Sub

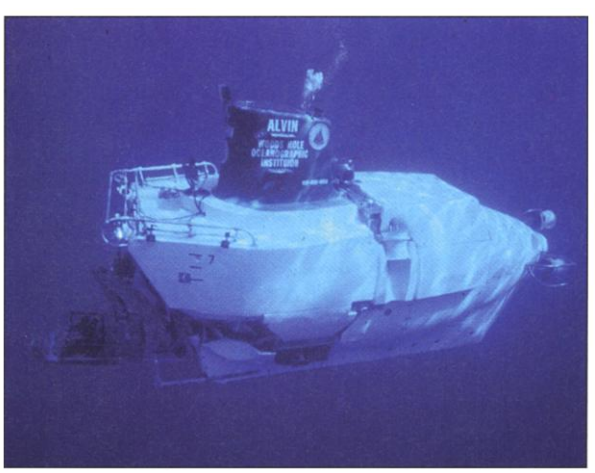
With its mainstay deep-sea submarine aging, U.S. marine scientists are talking about a replacement. There are lots of ideas but no consensus

U.S. marine scientists are thinking deep thoughts about a new research submarine. But there is fierce debate about how deep it should go—and whether humans should go along for the ride. "The idea of building a new human-operated vehicle is a polarizing issue; you hear strong views from all sides," says Marcia McNutt, head of the Monterey Bay Aquarium Research Institute in Moss Landing, California.

Competition for a slice of the nation's $400 million ocean research budget is always heated. But the contest has been sharpened by the aging of the 35-year-old *Alvin*, one of the world's few deep-water piloted submersibles (see table) and a mainstay of U.S. researchers. Although *Alvin* could last another decade, maintenance costs are mounting. So the National Science Foundation (NSF) and other agencies have asked the sub's operator, the Woods Hole Oceanographic Institution (WHOI) in Massachusetts, to design a more capable model by early next year.

Some researchers say a new *Alvin*, estimated to cost at least $20 million, doesn't need to go as deep as the current model, whereas others are pushing to go even deeper than planned. Another faction, to which McNutt belongs, argues that the money might be better spent on building some new, improved robotic craft. Meanwhile, members of Congress, a White House oceans panel, and a National Academy of Sciences group studying ocean exploration are preparing to wade in with their own ideas. "It's going to be a very energetic discussion," predicts James Yoder, director of NSF's ocean sciences division.

The sparring comes amid growing interest in exploring Earth's watery inner frontier. NSF and some international partners, for instance, are already pushing plans to build automated sea-floor observatories that would need tending from submarines. Other nations, such as Japan, are considering new deep-water submarines. And Congress has asked the academy panel to study ideas for an international ocean-exploration program that would take scientists into uncharted waters (*Science*, 24 May, p. 1386).



Sunken treasure. Scientists hope that a successor to *Alvin* would be more capable than existing piloted submersibles.

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Such trailblazing has been *Alvin*'s forte since 1967. The stubby craft—which carries two scientists and a pilot—has made more than 3700 dives, giving researchers a glimpse of everything from historic shipwrecks to the evolving edges of continental plates. Among its greatest hits: retrieving a hydrogen bomb accidentally dropped into the Mediterranean Sea in 1966, discovering chemical-fed tubeworms and other chemosynthetic creatures huddled around deep-sea hydrothermal vents in 1977, and surveying the