Marcia Stefanick knows she will not get through this October day without hearing about monkeys. The Stanford University medical professor is addressing a major meeting of researchers and physicians at the National Institutes of Health, detailing the recent results of what everyone calls simply “The Study.” The Study is part of the massive Women’s Health Initiative, and the findings are not good news. The hoped-for health benefits of hormone replacement therapy, known universally as HRT, are not turning up. “It’s clear now that there is no cardiovascular benefit,” she tells her audience.

A physician approaches the microphone. He has a bone to pick: “In the monkey trials,” he says, “hormones reduce heart risk and atherosclerosis if the monkeys are started on hormones early enough. Don’t you think you would have found long-term benefits if the women in the trial had been younger and started hormones earlier? Are you aware of the monkey data?”

Stefanick, who has worked on most of the recent hormone trials, is struggling to conceal her annoyance. “Yes, I’m familiar with the monkey data,” she says evenly. She once again goes over her newest analysis of the WHI results, showing that younger women had more risks and fewer benefits than the average women in The Study. “We’ve got to get our arms around this: HRT does not provide cardiovascular protection. We were wrong. We were just wrong.”

Disconnected. It’s not surprising that doctors—and patients—are having difficulty getting their arms around these new findings, which also include elevated risk for invasive breast cancer. When the WHI’s safety-monitoring board pulled the plug on The Study last summer, some 6 million American women were using estrogen plus progestin, or combination HRT, to treat hot flashes and other menopausal symptoms and to prevent bone loss. But many also believed they were protecting themselves against the No. 1 female killer: heart disease. The post-Study reality represents “one of the biggest disconnects that has ever occurred in medicine,” says Peter Wilson of the Framingham Heart Study.

How this disconnect occurred is a story about the complex intersection of science, marketing, and individual choice. For nearly 40 years the disease-stopping power of hormones has been touted by a staggering array of individuals, ranging from some of the nation’s most-respected researchers to the world’s highest-paid celebrities—most recently supermodel Lauren Hutton and singer Patti LaBelle. Hormones have been promoted in doctors’ offices, in TV and magazine ads, in books, through

Why do we treat change of life as a medical disorder? The answer lies in the interplay of science and marketing
women’s organizations, at medical conferences, in medical journals. “Careers are built on this stuff,” Stefanick says later. “And there is a lot of money involved.”

Indeed, the Wyeth pharmaceutical company’s drug Premarin, the dominant estrogen product on the market, has consistently been among the top-selling drugs in the nation. In 2001, more than 45 million prescriptions were written for Premarin, and an additional 21.4 million were written for Prempro, the leading combination estrogen-plus-progestin pill and the drug used in the WHI study. Sales of Premarin products alone generated some $2.04 billion in sales in 2001.

Women’s potions. The idea that youth, health, sex, and vitality might be preserved with hormonal compounds, drugs, potions, even animal parts, has been around at least since the late 1800s, when injections made from the gonads of pigs, dogs, and other animals became popular in Europe. The 1899 Merck Manual, a drug reference book, lists a number of remedies for “Climaterica,” as menopause was called. “Often they contained heroin and opium, but they had a product called Ovariian, made from the dried ovaries of a cow,” says Barbara Seaman, author of a forthcoming history of HRT, The Greatest Experiment Ever Performed on Women.

The first estrogen, estrone, was synthesized in Germany in 1928, says Seaman. Stilbestrol, or DES, was made a decade later by a British scientist. Premarin, a mix of estrogens extracted from the urine of pregnant mares, was patented by Ayerst, Wyeth’s predecessor, and approved by the U.S. Food and Drug Administration in 1942. “By the end of World War II, estrogens were heavily promoted to gynecologists, and there were a huge number of products on the market—Premarin, DES, injections, elixirs made from estrogen and alcohol, pellets that were put under the skin, kind of a precursor to Norplant,” Seaman says.

Key to HRT’s growing popularity was the novel notion that menopause was a disorder requiring medical attention. In 1959, two Massachusetts doctors wrote one of the first papers describing “menopausal syndrome,” which they described as “hot flashes, fatigue, insomnia, and emotional lability, post-menopausal osteoporosis,” and an unfavorable lipid profile. All of these symptoms, they argued, could be reversed by simply replacing the body’s lost estrogen.

One of the most influential promoters of HRT was Brooklyn, N.Y., gynecologist Robert Wilson. In a 1962 article in the Journal of the American Medical Association, Wilson described his treatment with estrogen and progesterone of 304 women between the ages of 40 and 70. He predicted statistically that 18 women...
1962 Robert Wilson reports in *JAMA* that taking estrogen during menopause reduces breast and genital cancers.

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Elizabeth Barrett-Connor lobbied for controlled studies of HRT.

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who took menopausal estrogen had four or more times as great a risk of developing endometrial cancer as those who did not. Among women who took the hormone longer, cancer risk increased. Women who used the drug for seven or more years had nearly 14 times as great a chance of developing endometrial cancer as those who did not take estrogen. National cancer data also revealed that the incidence of endometrial cancer in the United States, particularly among middle-aged women, had skyrocketed between 1969 and 1973—up by as much as 150 percent.

There were those, of course, who did not believe that estrogen could cause endometrial cancer, and for months they wrote letters to NEJM and articles for other publications disputing the findings. Robert Kistner of Harvard Medical School was typical of the doubters: “I am convinced that estrogens per se are not a cause of endometrial cancer…” he wrote in a 1976 issue of Obstetrics and Gynecology. “We [OB-GYNs] refuse . . . to accept the conclusions of two recent papers and the Advisory Committee of the FDA.”

Kistner’s obstinacy aside, a major change in hormone-prescribing practice was already underway. In response to the string of NEJM pieces, Lila, Richard, and Robert Nachtigall of the New York University School of Medicine wrote a letter to NEJM about the endometrial cancer reports and about a clinical trial they’d been doing since 1965. In their study, they had prescribed another hormone—MPA, the progestin in Prempro—along with the estrogen. The idea of the combination was to mimic women’s natural menstrual cycle. They reported that the 84 patients on the combination HRT had remained free of endometrial cancer for 10 years.

Almost lost in the outcry over endometrial cancer was the first study showing an increased incidence of breast cancer in estrogen users. The 1976 study, by a young scientist named Robert Hoover, documented breast cancers among women in one private practice in Louisville, Ky. “At the time,” says Hoover, now at the National Cancer Institute, “it was the only piece about breast cancer and estrogen out, and it was a small study, only 1,800 women. My main conclusion, the thing that I wanted to get out there, was that all this stuff showing that estrogen protected against breast cancer was wrong.” The next thing he knew, he was testifying at a Senate hearing on the dangers of menopausal hormones.

Estrogen sales plummeted. By 1979, estrogen was approved only for treating hot flashes and vaginal dryness. “In 1979, there was no consensus in the scientific community that estrogens did anything more than that,” says Cynthia Pearson, executive director of the National Women’s Health Network. “Had the situation remained there, these would not be among the top-selling drugs in the U.S. There needed to be scientific reasons for these drugs to be prescribed.”

New campaign. One possibility was to promote hormones for prevention of bone loss. In 1985, Wyeth-Ayerst hired the public-relations firm Burson-Marsteller to conduct a campaign to create public awareness of osteoporosis, a bone-loss disease that affects 25 percent of postmenopausal women and leads to a high risk of fractures. The firm conducted a survey that concluded that 77 percent of women had never heard of the disease. The thrust of the campaign was to present osteoporosis as a devastating disease for which there was a remedy and to urge women to see their doctors. The campaign generated support for a National Osteoporosis Week, and, suddenly, articles appeared in Vogue, McCall’s, Reader’s Digest, and other magazines. The National Osteoporosis Foundation, founded in 1986, receives money from Wyeth and a number of other drug companies.

As pleased as hormone makers were with extending their potential market to women worried about bone loss, the claim they really wanted to make was for heart protection. Heart disease kills more women than any other illness, and if hormones were demonstrated to protect the cardiovascular system—and if the FDA would approve labeling for that purpose—then HRT could be promoted as a necessary treatment for all women. In 1985, they got some good news. The massive Nurses’ Health Study, run out of the Harvard School of Public Health, re-
ported that among its 32,300 post-menopausal women, hormone users had about half the rate of coronary disease as nurses who had never taken estrogen for menopause. Meir Stampfer, the lead author of the study, wrote that the data “support the hypothesis that the post-menopausal use of estrogen reduces the risk of severe coronary heart disease.”

But the science was getting murkier. In the same issue of New England Journal of Medicine, researchers at the Framingham Heart Study showed that women who took estrogen actually had a 50 percent higher coronary risk and twice as many strokes, blood clots, and related problems. The results were first questioned—the Framingham women were older, and therefore at greater risk, and some received high doses of estrogen—then forgotten.

Soon, researchers were churning out positive studies about hormones preventing heart attacks, atherosclerosis, and bone loss, while not increasing cancer, stroke, or blood clots. In fact, these observational studies showed that hormones reduced mortality from all causes—including accidents and homicides.

Some doctors wondered if these reports weren’t a little too good to be true. “I thought there were two or three very strong biases such that healthy women at low risk of heart disease were receiving the drugs and being studied,” says Elizabeth Barrett-Connor, professor at the University of California–San Diego and a veteran hormone researcher. “I knew all along that women taking estrogen were better educated, wealthier, and there was compliance bias—that is, people who are compliant in clinical trials, even with a placebo, have less disease.” The research seemed even less reliable when she realized that during many of the years covered in these studies, the standard Physicians’ Desk Reference suggested estrogen should not be prescribed to women with heart disease, hypertension, or diabetes. “So women with heart risks were not receiving the drugs,” Barrett-Connor explains.

No surprise, then, that women taking the drugs had less heart disease.

A muddle. Barrett-Connor convinced the National Institutes of Health to begin the first of the clinical trials in 1987, the Postmenopausal Estrogen/Progestin Interventions Trial, or PEPI, a study of the effects of hormones on key heart disease risk factors, such as lipids, blood clotting, and weight gain. Completed in 1990, PEPI showed that while HRT reduced some risks—such as LDL, or “bad cholesterol”—it increased others, such as fats called triglycerides. So Barrett-Connor went to NIH to propose a trial to evaluate whether hormones would prevent further heart attacks in women who’d had them.

But NIH had even bigger plans: Under its first female director, cardiologist Bernadine Healy (now a senior writer at U.S. News), the agency was about to launch a really large clinical trial on women’s health—covering heart disease, breast and colon cancer, bone fractures, and the role of hormone therapy, diet, vitamins, and calcium in preventing these diseases. This effort, the Women’s Health Initiative, was past due. Women were increasingly concerned about HRT and breast cancer, particularly after a 1989 report by NCI’s Hoover and a group of Swedish scientists. Not only did estrogen increase breast cancer among the 23,000 Swedish women studied, but the progestins in combined HRT, widely used in Sweden, appeared to have made cancer rates higher. The Swedish study was a bombshell, widely covered by the media. It was the first evidence that progestins, added to HRT to protect the uterus, might increase breast cancer.

Following the breast cancer study, Wyeth was eager to begin promoting Premarin for prevention of heart disease. Based only on the observational studies, the company asked the FDA to approve a label change to include heart disease prevention in women without a uterus and asked both Barrett-Connor and Stampfer to testify. Stampfer’s team was preparing a 10-year follow-up study showing that “current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as stroke.”

1970 Medical journals are running the Wyeth advertisements—“Treat her with Premarin. Keep her on Premarin.” Almost 14 million prescriptions are dispensed.

1972 All in the Family’s Edith Bunker, 47, shocks her husband and the nation with the news that she’s menopausal. Archie’s response: “If you’re gonna have a change of life, you gotta do it right now. I’m gonna give you just 30 seconds.” The groundbreaking episode wins an Emmy.

1973 A clinical trial of men taking Premarin to prevent heart attacks and strokes is stopped when it turns out that the subjects were having more heart attacks and blood clots.
as in mortality from cardiovascular disease” with no increase in stroke.

At an FDA advisory committee meeting in June 1990, Barrett-Connor reviewed the observational studies and told the committee: “I would do the trial.” She did not support the label change. Stamper, however, threw the weight of Harvard and the Nurses’ Health Study behind Wyeth’s request: “I believe that the data are quite substantial in showing a protective effect of estrogens for heart disease, and I believe that it is a cause-and-effect relationship.” He added that a clinical trial would be difficult and was unnecessary, since women with heart disease were those likely to benefit most from hormones.

The advisory committee was swayed. With only one member dissenting, they voted to allow Wyeth to list heart protection on Premarin’s label. “I couldn’t believe they approved it,” says Barrett-Connor. “I was shocked.”

“Pocket veto”? Though the FDA usually acts on the decisions of its advisory committees, this time the whole issue of label change seemed to vanish. Philip Corfman, former executive secretary to the advisory committee, says that Linda Golden, the FDA’s medical officer assigned to the label change, recommended it not be approved. “If they got approval on a restricted basis for women without a uterus, they’d promote the hell out of it for everyone,” Corfman says. Corfman thinks someone in the FDA hierarchy “exercised a pocket veto.” Whatever happened, a year later Bruce Burlington, then deputy director of the FDA’s Office of Drug Evaluation, explained to a Senate committee why the label change had been withheld: “The studies that are available [on Premarin’s cardiovascular effects] do not constitute randomized, prospective clinical trials that offer hard data.”

About this time, Wyeth was fighting off a challenge to its hegemony in the hormone market from generic hormone products. Premarin had lost its patent protection in the 1970s. Several smaller companies did offer generic estrogens after Wyeth’s patent expired, but in 1990 Wyeth told the FDA that the generics on the market released estrogens in the bloodstream more quickly than Premarin, and it launched a campaign to get them off the market. Wyeth argued that if the biochemistry of Premarin were not duplicated precisely, a generic would be ineffective, even dangerous. In May 1997, the FDA rejected an application for a generic by Duramed Pharmaceuticals, saying it could not show the same rate of absorption. Duramed solved the absorption problem, only to be foiled again. Wyeth enlisted several women’s groups—some of which received money from Wyeth—and the help of Sens. Barbara Mikulski, Patty Murray, and Olympia Snowe to urge the FDA to reject Duramed’s application. Wyeth claimed that any generic version of Premarin must include several inactive ingredients. The FDA agreed, denying Duramed’s approval.

Taking a different route, Duramed submitted a new drug application, per-
formed clinical trials, and got its product, Cenestin, approved. But the story doesn’t end there. According to an antitrust lawsuit filed in 2000 by Duramed, Wyeth tried to prevent consumers from getting access to the competing drug. The suit says Wyeth tried to prevent health plans and pharmacy benefits managers—which control drug purchases by over 70 percent of Americans—from adding Cenestin to their formularies. Wyeth entered into contracts with pharmacy benefits managers that offered valuable discounts and rebates on the condition that they offer Premarin and not Cenestin, the lawsuit alleges. Wyeth, in its court filings, denies any anticompetitive behavior, arguing that consumers can still get Cenestin even when it is not on formularies. It also says that its contracts are short term, and therefore, do not constitute restraint of trade.

During its struggle over the generics, Wyeth began marketing Prempro, its new one-pill HRT. The company was funding a four-year heart disease prevention trial, the Heart and Estrogen/Progestin Replacement Study (HERS), and had high hopes. If HERS proved hormones prevented heart disease in high-risk women, it would strongly suggest that HRT protected healthy women’s hearts as well. About a year into the trial, the safety-monitoring board met to review the data. “It was already clear that there was a great deal of difference between the two groups,” says Deborah Grady, director of the Women’s Health Clinical Research Center in San Francisco and a principal investigator of HERS.

Stunning result. Though they were labeled only “A” and “B,” one group had experienced significantly more heart attacks, blood clots, and pulmonary embolisms than the other. “The board asked us to unmask the data,” says Grady. “Where we thought the group that had the lower rate of heart events would be the hormone group, it was the opposite, the placebo. We were dumbfounded.”

The HERS investigators discussed stopping the trial. “By the second year,” Grady recalls, “it was clear we had no hope of showing any benefit, and we were kind of in territory we never expected to be in—continuing the trial to see how dangerous this stuff could be.” In 1998, the HERS investigators reported their findings: HRT did not reduce the rate of coronary heart disease events in women with heart disease, and it increased serious blood clots and gallbladder disease. There had been a 50 percent increase in cardiovascular events in the first year of HERS that leveled off, but there was no benefit from HRT.

The results from HERS shocked the medical community. And the bad news just kept coming. David Herrington, a cardiologist at Wake Forest University School of Medicine, reported that HRT did not slow the progression of atherosclerosis, as many had hoped it would. About the same time, WHI Acting Director Jacques Rossouw wrote the first of two letters to participants describing an increase in heart attacks, strokes, and blood clots that were occurring among HRT users. Faced with the added burden of invasive breast cancers, The Study came to halt last summer.

But there are the monkeys to fall back on, which some hormone advocates still do. Says Stamper: “You know that monkeys that were given hormones early had substantial cardiovascular protection, whereas if they waited until a few years after menopause to give the monkeys hormones, they didn’t see the protection. In the WHI trial, they enrolled older women past menopause, so it’s possible this could explain the differences. . . . I’m not disputing the results of the WHI. I’m just saying that in the monkey trials, the timing mattered a lot.”

Elias Zerhouni, the director of NIH, captured the current state of the hormone debate when he said, “Often in science the reaction to a new finding is directly proportional to the strength of the dogma it overturns. People are still in denial of the theory of relativity, too.”

With Susan Headden, Katy Kelly, the U.S. News library staff, and Nancy Cohen in Northampton, Mass.

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**1995**

Prempro, the first estrogen-plus-progestin HRT pill, is approved by the FDA.

**1998**

The first major placebo-controlled trial of HRT shows that the hormones do not help women who have already had a heart attack and, in fact, caused more heart attacks, strokes, and other cardiovascular events.

**2000**

The Women’s Health Initiative tells study participants that some women are experiencing heart attacks and strokes and offers them the chance to drop out.

Model and Wyeth posterwoman Lauren Hutton is featured in a *Parade* magazine cover story saying that if she could keep only one piece of her health and beauty regimen, it would be estrogen.

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**2001**

More than 11 million women use a Premarin product.

**2002**

The Women’s Health Initiative combined HRT study is stopped because of continuing heart events and an increased risk of invasive breast cancer. Doctors are urged to prescribe HRT only for short-term relief.

A study of nearly 1,900 women suggests that HRT may help forestall Alzheimer’s.

Soul diva Patti LaBelle (paid by Wyeth) sings the praises of HRT.

**2020**

Some 60 million American women will be in or through menopause.