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Bioidentical Hormones: Sound Science or Bad Medicine

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BIOIDENTICAL HORMONES: SOUND SCIENCE OR BAD MEDICINE?

THURSDAY, APRIL 19, 2007

U.S. SENATE,
SPECIAL COMMITTEE ON AGING,
Washington, DC.

The Committee met, pursuant to notice, at 10:05 a.m., in room 526, Dirksen Senate Office Building, Hon. Gordon H. Smith presiding.

Present: Senators Smith and Craig.

OPENING STATEMENT OF SENATOR GORDON H. SMITH, RANKING MEMBER

Senator SMITH. Good morning, ladies and gentlemen. With the permission of the Chairman, Senator Kohl—he has asked us to proceed.

We thank you for attending today's hearing, "Bioidentical Hormones: Sound Science or Bad Medicine?"

As the title suggests, we are here today to closely examine the controversy surrounding the production and use of bioidentical hormones as an alternative to conventional hormone therapy.

The intent of this hearing is not to endorse one therapy over another. Rather, it is to ensure that the Federal Government is providing the information and oversight necessary so that consumers, women specifically, are able to make safe and well-informed decisions about their individual health-care needs.

From my review, it seems that the Federal Government and medical practitioners are playing a guessing game with women's health in the prescribing of hormone therapies. Today's hearing reflects my belief that women deserve better. I hope to get some answers today regarding the state of the science and the Federal Government's oversight role in this arena.

Over a decade ago, the National Institutes of Health set out to shed some light on the effect of hormone therapy on preventing heart disease in women through the largest research initiative ever undertaken of this kind: the Women's Health Initiative.

When evidence indicated that the health risks of the therapies studied in the WHI exceeded the benefits, the study was prematurely ended, scaring thousands of women away from traditional hormone therapy.

As an alternative, bioidentical hormones have become a popular and controversial option, not only for aging women, but for men and women of all ages seeking a route to the fountain of youth.

The sale of bioidentical hormone products are on the rise and have been promoted by such distinguished actresses as Suzanne Somers and major marketing campaigns in doctors' offices, pharmacies and the Internet touting bioidenticals as natural and, thus, safer alternatives to traditional hormone therapies.

There has been much debate in the scientific community, however, as to whether the science exists to support these claims. By the end of this hearing, I hope to have a clear understanding of whether additional federally funded studies are needed to address concerns regarding the safety and efficacy of these products.

Today, we will also address the regulatory issues relating to the manufacturing of these products, especially those that are custom-made or compounded in pharmacies.

I am particularly troubled that compounded medications are not routinely tested and are not accompanied by warning labels and risk indicators that are required for traditionally manufactured medications.

Further, there is a lack of information available to assist Congress in determining the proper roles of the Federal Government, the State Governments and the industry in regulating pharmacy compounding. That is why I have asked the Congressional Research Service to conduct a 50-State survey that will help me and my colleagues determine the best course of action going forward.

Ultimately, the Federal Government must do a better job of empowering consumers to make informed decisions regarding hormone therapies and compounded medications. But the current regulatory framework is hazy and creating confusion between the Federal Trade Commission, the Food and Drug Administration, and State boards of pharmacy, regarding who has ultimate regulatory responsibility.

I fear that lack of consistent and certain oversight has created an atmosphere ripe with opportunities for fraud and abuse. By the end of this hearing, I would like to have some confidence that the regulatory agencies are taking these issues seriously and have a concrete plan of action to address the committee's concerns.

On our first panel this morning, I am pleased that NIH will be testifying for the first time before Congress regarding the latest findings in the Women's Health Initiative study. Also on the first panel will be the FDA and the FTC, who will speak about the agencies' enforcement efforts.

Our second panel promises a lively discussion regarding the science of bioidentical hormones and the regulatory issues relating to pharmacy compounding. I look forward to that dialog.

With that, I will turn to my colleague, Senator Craig, from Idaho.

OPENING STATEMENT OF SENATOR LARRY CRAIG

Senator CRAIG. Well, to the Chairman and to you, the Ranking Member, let me thank you for bringing this hearing together.

I will ask unanimous consent that my full statement be a part of the record, Gordon. Let me say——

Senator SMITH. Without objection.

Senator CRAIG [continuing]. Just one thing.

One of the expectations, I believe, that Americans have of their Government is, in part, to keep them safe. This is especially true in a protection from pharmaceuticals whose potential negative side effects outweigh their potential benefits. Americans want to know they can take a drug that is prescribed by their physician with the knowledge that this drug will treat or cure what ails them.

However, like all other governmental responsibilities, we must balance our obligation to protect with our responsibility to allow individual freedoms. That is a rather precarious balance at times that we especially try to achieve in the area of medicine, certainly in the area of pharmaceuticals.

So—I keep wanting to say, Mr. Chairman. Senator Smith—Gordon.

Senator SMITH. "Senator" works fine.

Senator CRAIG. OK.

That is why I think this hearing is important; that you come back to this issue, as you should, in an area where we may not be as aggressive or as responsible as we should be.

Thank you.

[The prepared statement of Senator Craig follows:]

PREPARED STATEMENT OF SENATOR LARRY CRAIG

Mr. Chairman, I know that we have a lot of witnesses that we want to hear from today, so I will be brief in my comments. First of all, I want to thank you for holding this hearing today. Bioidentical hormones are a part of the lives of many Americans and I think the questions surrounding them bear further examination. This hearing brings together a cross-section of issues: individual freedom to choose alternative therapies vs. ensuring drug safety.

One of the expectations that Americans have of their government is that we keep them safe. This includes protection from pharmaceuticals whose potential negative side effects outweigh their potential benefits. Americans want to know they can take a drug that is prescribed by their physician with the knowledge that this drug will treat or cure what ails them. However, like all other governmental responsibilities, we must balance our obligation to protect with our responsibility to allow individual freedom.

Many Americans utilize various alternative drug therapies or dietary supplements as a significant part of their health care regimen. They want the freedom to have more control of their health and to utilize what they believe are more natural drug treatments. It is important that we do not eliminate that option.

As Congress, our challenge is to strike the proper balance between these responsibilities. We must ensure drug safety without infringing upon personal freedom and choice.

When I first became aware of the concerns surrounding bioidentical hormones, my first inclination was to keep the government out of the issue. Women should have the freedom to choose natural treatments that may work better for them. However, as I have learned more about this issue a few items raised some red flags in my mind.

Many Americans, and I suspect many American women, are aware of the results of the National Institutes of Health (NIH) Women's Health Initiative relating to hormone replacement therapy. Unfortunately, the general public does not fully understand the nuances of the findings. The story people heard was that hormone replacement therapy was bad for you. And as the witnesses will testify, there was a significant drop in the number of women using hormone replacement therapy. How-

ever, as Dr. Wartofsky points out, many women went straight to what they thought were natural alternative treatments. Many women are not fully aware of the differences, and more importantly, the similarities between bioidentical hormones, compounded hormones, and those hormones used in the Women's Health Initiative. It concerns me that women who think they are choosing a natural alternative may not have all of the facts.

That is why this hearing is so important. Hopefully it will shed more light on compounded bioidentical hormones so that not just Congress, but consumers, are more educated about the products that are out there. With that said, I want to welcome our witnesses and I look forward to hearing from them.

Senator SMITH. Thank you, Senator Craig.

Our first panel consists of Dr. Jacques Rossouw, who is the chief of the Women's Health Initiative branch of the National Heart, Lung and Blood Institute at NIH. Dr. Rossouw will discuss findings from the Women's Health Initiative and its implications for the current approach to hormone therapy.

He will be followed by Dr. Steve Galson. He is the deputy director for the Center for Drug Evaluation and Research at FDA. We look forward to hearing about FDA's suggestions for legislative and regulatory initiatives.

Eileen Harrington is the deputy director of the Bureau of Consumer Protection at the FTC. Ms. Harrington will discuss the FTC's enforcement efforts regarding online sales of hormone products. We look forward to hearing FDA's future plans for oversight in the area.

So with that, Dr. Rossouw, take it away.

STATEMENT OF JACQUES ROSSOUW, CHIEF OF THE WOMEN'S HEALTH INITIATIVE BRANCH, NATIONAL HEART, LUNG AND BLOOD INSTITUTE, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD

Dr. ROSSOUW. I am pleased to appear before this——

Senator SMITH. Hit your button there on the microphone.

Dr. ROSSOUW. Yes.

I am pleased to appear before this committee. I am here to tell you about the Women's Health Initiative, which used conjugated equine estrogens. I will also briefly comment on other forms of estrogen therapy.

Recall that, prior to 1990, the main use of hormone therapy in post-menopausal women was to treat the symptoms of menopause and prevent osteoporosis. During the 1990's, there was increasing use for prevention of coronary heart disease. In fact, that was the standard recommendation at that time.

This recommendation was based on preceding observational studies indicating benefit for cardiovascular disease in particular in hormone users compared to nonusers.

NIH felt that this recommendation was an example where the policy was exceeding the science basis and mounted the Women's Health Initiative to test the very hormones—conjugated equine estrogens and medroxyprogesterone—which were suggested to be associated with benefit in preceding observational studies.

The expectation was that we would show benefit for hormone therapy—either estrogen alone or in combination with a progestin. What we found was that the estrogen alone and the estrogen with progestin did not protect against coronary heart disease.

In fact, for the combination therapy, the trial was stopped early because of an excess risk of breast cancer and heart disease and stroke and blood clots. These harms exceeded any potential benefits.

The estrogen-only trial was also stopped prematurely because of an increased risk of stroke and no benefit for the primary outcome of coronary heart disease.

As a result of these findings, the prescriptions for hormone therapy dropped by about 60 percent after 2002.

Now, because the primary findings were what they were—in a negative direction—certain questions then arose which would not have arisen if the findings had been as expected: that is, of benefit for coronary heart disease. But because there was no benefit, these secondary questions gained importance.

First of all, would the result have been different if the hormone therapy had been started at an earlier age, closer to the menopause? In the Women's Health Initiative, the age range was 50 to 79 because those are the women to whom hormone therapy was being prescribed for prevention of coronary heart disease. So that is what we tested. Would it have been different if most of the women had been closer to the menopause? First question.

Second question, would the result have been different and more beneficial if we had used a different kind of estrogen, such as estradiol, the estrogen produced by the human body?

So I want to get straight to the heart of the matter, if I may—pun intended—and direct your attention within your packet to these posters here, because to understand these questions one has to know a little bit about the science.

Atherosclerosis, which is the precursor of heart attacks and stroke, is an age-related disease. You can divide it into stages. Of course, that is artificial. I mean, it is a continuum. But for the purposes of understanding this, I have divided it into some stages.

There is the initiation phase, which occurs in the young adult. This is a process that involves the lining of the artery, the endothelium, and it then leads to fatty streaks.

At middle age, there is the increasing prevalence of raised lesions—progression to raised lesions.

From then onwards into old age, there is an increasing prevalence of complicated lesions, some of which will eventually rupture or erode, and a blood clot will form. This leads to the heart attack or stroke.

Now, these are age-related changes. Some of it is due directly to the aging of the arteries. Some of it is due to the increasing prevalence of risk factors, such as high blood pressure and high blood cholesterol as people age.

Now, we cannot stop aging. We haven't figured out how to do that. But we can treat the risk factors.

That is what we mean by "prevention." You are not preventing age, but you are treating the risk factors associated with age, and thereby you are preventing the complications of age. Or, you are not preventing them totally, but you are decreasing them.

So one example of such a prevention is lowering of the high blood cholesterol—lipid lowering. I will use the example of statins because there is an awful lot of data on statins. Statins will interfere

with every stage of the disease: from the initiation, to the progression, to the treatment of the complications—that is, people who have already had heart attacks.

Statins are effective at every stage, OK? So, therefore, one can assume that if you start statins at a young age and continue them lifelong, they will continue to have benefit. That is an assumption because that trial is not feasible, as it is also not feasible to do a really long-term lifelong trial of hormone therapy.

So statins represent a favorable or an acceptable prevention strategy. There are no known long-term complications.

The situation is different with estrogens, be they Premarin, conjugated estrogens or estradiol.

There is increasing evidence that estrogens, generally, may retard the earliest stages, the initiation, of atherosclerosis. There will be more evidence in the next coming years that may or may not be consistent with that idea. But at the moment there is reasonably good evidence that that is the case, including from the Women's Health Initiative, the recent publication.

However, once there are established raised lesions, established atherosclerosis, there is good evidence that estrogen in any form, be it conjugated estrogens or estradiol, does not prevent further progression. There is also good evidence that once there are complicated lesions, estrogens actually trigger events and make matters worse.

So estrogens do not represent a good prevention strategy. We cannot assume that if you start it early, and there is potential benefit, that that benefit will persist into older age.

Again, that is an assumption. We cannot do that trial. But knowing what we know, that would be a very far stretch of the imagination to imagine that if you start it early and use the right estrogen, you will get a different outcome than we found in the Women's Health Initiative.

So, again, we don't think that there is any essential difference between estradiol and conjugated equine estrogen as far as heart disease is concerned. We don't believe that this window of opportunity is anything but a window into the present. There is a reasonably safe period to use hormone therapy close to the menopause, but it is not necessarily a window into the future if you start then and persist that that benefit will persist.

With that, I will close and thank the committee for addressing them on this very important issue to women's health. I am happy to entertain questions.

[The prepared statement of Dr. Rossouw follows:]

Testimony
Before the
Special Committee on Aging
United States Senate

The Women's Health Initiative

Statement of
Jacques Rossouw, M.D.
Chief, Women's Health Initiative Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
U.S. Department of Health and Human Services

For Release on Delivery
Expected at 10:00 a.m.
Thursday, April 19, 2007

I am pleased to appear before this Committee in my capacity as the chief of the Women's Health Initiative (WHI) branch of the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health (NIH), an agency of the Department of Health and Human Services. I am here to tell you what we have learned from the WHI about menopausal hormone therapy using conjugated equine estrogens and to briefly comment on other forms of estrogen therapy.

During the second half of the 20th century, estrogen was shown to relieve common menopausal symptoms such as hot flashes and night sweats. Subsequent clinical trials showed that estrogen also prevents bone loss. Based on these findings from rigorous scientific studies, menopausal hormone therapy was approved by the Food and Drug Administration (FDA) and became well accepted for treatment of menopausal symptoms and for prevention of osteoporosis. Most of the prescriptions for menopausal hormone therapy were written by gynecologists and family doctors for women experiencing symptoms shortly after the onset of the menopause transition. A smaller number were for older women to prevent osteoporosis.

However, for many years estrogen was also used under circumstances where there was no definitive proof of efficacy. One idea that was promoted and became part of popular lore was that the ebb of estrogen levels after the menopause represented a disease-like condition or "estrogen deficiency" that needed to be treated using "estrogen replacement". Many thought that such replacement would keep a woman "forever young." In the mid-1980s, another potential reason to use menopausal hormone therapy emerged from observational studies: prevention of coronary heart disease. Women taking menopausal hormone therapy appeared to have a lower risk of heart disease, though a higher risk of breast cancer, than women who did not take hormones. Given that heart disease is far more common than breast cancer, many researchers thought that the benefit from menopausal hormone therapy would outweigh the risk.

Based on these observations, along with evidence suggesting that estrogen improves blood cholesterol levels, several professional bodies recommended that menopausal hormone therapy be considered for the prevention of heart disease, especially in high-risk women (e.g., those with existing heart disease or high blood cholesterol levels). Unfortunately, however, observational studies have limitations, one of the most important being that they do not establish causality. In this case, it was impossible to tell whether the women who took hormones had better heart health because of the menopausal hormone therapy -- or whether the women who chose ("self-selected") to take hormones were simply healthier to begin with. Nevertheless, as a result of the new recommendations, hormones were increasingly prescribed to older women for the express purpose of lowering blood cholesterol and preventing heart disease.

Recognizing that practice recommendations related to menopausal hormone therapy were outpacing the scientific evidence, the NIH undertook two clinical trials of hormone therapy as part of the WHI, a long-term effort begun in 1991 to identify strategies for preventing heart disease, breast and colorectal cancers, and osteoporosis in postmenopausal women. Participants were randomly assigned to menopausal hormone therapy or placebo, so self-selection for hormone therapy was not an issue. By design, the trials used the same hormones and the same doses that were associated with the apparent benefit reported in the observational studies mentioned above. They enrolled more than 27,000 women, ranging in age from 50-79 years. Those who had a uterus were assigned to take either a pill containing estrogen and progestin (0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate--Prempro) or a placebo; those who had undergone a hysterectomy were assigned to take either an estrogen pill (0.626 mg of conjugated equine estrogen--Premarin) or a placebo.

When the trials began, many researchers expected that, after the 8 years, menopausal hormone therapy would be shown to:

- reduce heart disease
- have no effect on stroke
- increase blood clots
- increase breast cancer
- decrease hip fractures
- and decrease colorectal cancer.

Although researchers anticipated some adverse effects, they believed that the overall benefits of menopausal hormone therapy would be shown to outweigh the risks. Instead, the trial of estrogen plus progestin was stopped in 2002 after just over 5 years because of increased risks of heart disease, stroke, blood clots, and breast cancer due to menopausal hormone therapy and because these risks exceeded the benefits from reduced risks of hip fractures and colorectal cancer. The trial of estrogen alone was stopped in 2004 after almost 7 years because estrogen increased risk of stroke and did not benefit heart disease. The estrogen alone trial also showed that the hormone increased blood clots and decreased hip fractures, but had no effect on breast or colorectal cancer. Subsequently, investigators conducting an ancillary study found that both hormone preparations increased the risk of memory problems and dementia in women aged 65 and older.

As a result of WHI findings, professional bodies altered their recommendations, and the FDA required a "black box" warning that menopausal hormone therapy should not be used for the prevention of heart disease or dementia. The drugs remain approved for moderate to severe hot flashes or night sweats, vaginal atrophy, and the prevention of osteoporosis, but with cautions to use the lowest doses for the shortest

amount of time needed to achieve the desired effect. The FDA requires all formulations of menopausal hormone therapy to carry the same language.

After 2002, the number of women using postmenopausal hormone therapy fell from about 16 million to about 6 million in 2006, a decline of more than 60%. The main use of menopausal hormone therapy has reverted back to the short-term treatment of moderate to severe hot flashes and night sweats, symptoms that are most prevalent in the years immediately surrounding onset of menopause, although, in a small proportion of women, they persist for much longer. Evidence from national databases indicates that the drop in menopausal hormone therapy use occurred in women below 60 years of age as well as in older women, and anecdotal evidence from gynecologists and from news stories suggest that many younger women with hot flashes and night sweats forego menopausal hormone therapy because they fear its adverse health consequences.

Although the WHI showed that menopausal hormone therapy is not effective for preventing heart disease in women generally, there has been much interest in learning whether certain groups of women (e.g., younger women or women closer to menopause) may experience less harm or even some benefit in terms of disease outcomes. Several WHI publications have touched on the topic, and, in general, have suggested that while the risk of stroke due to menopausal hormone therapy is not affected by age or time since menopause, the risk of heart disease may not be increased in younger women or those close to menopause who take hormones.

In an attempt to provide more definitive information to guide treatment choices, the WHI investigators recently published analyses of the combined trial data that examined various subgroups of women. The results suggest that women who begin menopausal hormone therapy within 10 years of menopause may have less risk of coronary heart disease due to the therapy than women farther from menopause.

Women who began treatment more than 20 years after menopause experienced a significant increase in risk. There was a similar non-significant trend for total mortality. As before, menopausal hormone therapy did not reduce the overall risk of heart disease, and increased stroke risk regardless of years since menopause. Further exploratory analyses also suggested that the increased risk of heart disease in older women due to hormones occurred primarily among those with persistent moderate to severe hot flashes. Women with these symptoms were also more likely to have risk factors for heart disease such as high blood pressure, high blood cholesterol, diabetes, and excess weight.

The more detailed analyses provide some reassurance to women who begin menopausal hormone therapy within 10 years of entering menopause that short-term treatment (up to 4 or 5 years) of hot flashes and night sweats is not accompanied by an increased risk of heart disease. However, even women who begin menopausal hormone therapy soon after menopause need to be screened and treated for cardiovascular risk factors such as high blood pressure and to have regular mammograms. The findings should further discourage menopausal hormone therapy in women who are more distant from menopause. In these women, particularly those with hot flashes and night sweats, the focus should be on identifying and treating cardiovascular risk factors. The overall findings are consistent with current recommendations and may aid in their implementation by encouraging doctors and patients to focus on the appropriateness of menopausal hormone therapy based on an individual's situation and medical history. According to the current recommendations, menopausal hormone therapy should not be used for prevention of heart disease, but can be used for the short-term treatment of menopausal symptoms.

Researchers are still interested in following up on results from animal and laboratory studies supporting the hypothesis that menopausal hormone therapy may

slow the earliest stages of arterial disease. Upcoming trials, including some supported by NIH, will test whether hormones given at a younger age can forestall development of the earliest stages of atherosclerosis. However, even if the results show a benefit or lack of harm among younger women, they should not be taken to mean continuing to use hormones as the women grow older would be safe. As women age, they are increasingly more likely to develop artery disease, and the point at which any potential benefit of menopausal hormone therapy becomes outweighed by the risk of harm is not yet known. Addressing the remaining issues would require a trial of about 30,000 women close to the menopause, randomly assigned to take menopausal hormone therapy or placebo and followed for 20 years. Such a trial would not be feasible due to serious ethical concerns about the risk of stroke, blood clots, and breast cancer among participants, technical issues such as poor long-term adherence to menopausal hormone therapy, and the prohibitive cost. Finally, to the extent that the motivation for pursuing a large trial would be a desire to prevent cardiovascular disease among women, it should be noted that further deployment and improvement of existing prevention strategies, such as the identification and adequate treatment of known risk factors, offers far better potential for safely and effectively reducing cardiovascular disease burden.

Another important question arose after publication of the main WHI findings: Would the results have been different if other types of hormones, such as estradiol or progesterone, had been used instead of conjugated equine estrogens? First, it should be reiterated that the hormones tested by the WHI were chosen because they were the same ones that appeared to be beneficial in early observational studies -- and, even so, the results of the WHI trials and the early observational studies were quite different. Second, it should be noted that trials using oral estradiol have been conducted in women with existing disease, and they have uniformly showed a lack of cardiovascular benefit.

One small trial using oral estradiol found a slight benefit for slowing the thickening of the arteries that supply blood to the brain. However, trials using such surrogate outcomes rather than clinical disease outcomes are not definitive.

A separate but related issue is whether the method used to administer menopausal hormone therapy affected the WHI results. In the human body, estradiol and progesterone are released directly into the bloodstream, whereas when the hormones are given by mouth, they must first pass through the liver, where a large amount of hormone is rendered inactive. Most of the proteins involved in blood clotting, lipid metabolism, and inflammation are manufactured in the liver, and oral estradiol in particular has profound effects on all of these molecules. Therefore, the action of oral hormones in the liver may contribute to adverse cardiovascular effects. On the other hand, estradiol given transdermally is distributed throughout the body, has minimal, if any, effect on molecules involved in blood clotting, lipid metabolism, and inflammation, and may have direct and potentially beneficial effects on the normal arterial lining. Some of the surrogate outcome trials will use non-oral routes of administration, and may provide additional information about whether the route of administration affects the outcome of menopausal hormone therapy.

Thank you for the opportunity to address these issues of great importance to women. I would be pleased to answer any questions the committee may have.

Senator SMITH. Thank you, Doctor.

Steve Galson.

STATEMENT OF STEVE GALSON, DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, ROCKVILLE, MD

Dr. GALSON. Thank you. Mr. Chairman and members of the committee, I am Dr. Steven Galson——

Senator SMITH. You need to hit your microphone.

Dr. GALSON. OK. I am Dr. Steven Galson. I am the director of the Center for Drug Evaluation and Research at FDA, and a Rear Admiral and Assistant Surgeon General in the United States Public Health Service.

I am really very pleased to be here to discuss FDA's role regarding the compounding of so-called bioidentical hormone products.

FDA has increasingly seen these products prepared and marketed by pharmacists as part of a practice called drug compounding. FDA regards traditional drug compounding as combining or altering of ingredients by a pharmacist in response to a licensed practitioner's prescription, which produces a medication tailored to an individual patient's needs.

Traditional pharmacy compounding enhances patient treatment with individually tailored drugs when a health-care provider decides that an FDA-approved drug is not appropriate for that particular patient's care.

Traditional compounding may involve reformulating a drug, for example, by removing a dye or preservative in response to a patient allergy. Or it may involve making a suspension or a suppository form for a child or an elderly patient who has difficulty swallowing a tablet.

Sometimes, however, the risks associated with compounded drugs outweigh their benefits. Improper compounding has caused patient harm and death.

Although many pharmacists are well-trained and well-equipped to compound certain medications safely, not all pharmacists have the same level of skill and equipment, and some products may not be appropriate in the first place for pharmacy compounding.

In addition, compounding large volumes of standardized drugs and copying FDA-approved drugs circumvents important public health requirements. These practices undermine the drug approval process, which is the evidence-based system of drug review that consumers and health professionals rely on for safe and effective drugs.

My written statement that you have describes FDA's statutory and regulatory authority over compounded drugs. FDA has regulated compounded drugs consistent with its Compliance Policy Guide on pharmacy compounding, or CPG.

This CPG explains that FDA generally exercises enforcement discretion toward traditional compounding. But when a pharmacy's activities raise concerns normally associated with the drug's manufacture and result in significant violations of the Food, Drug and Cosmetic Act, FDA considers enforcement action. The CPG identifies some of the factors that FDA evaluates in deciding when and how to act.

FDA is aware that a growing number of pharmacists compound hormone products for treatment of symptoms of menopause. These pharmacists often promote their products as so-called bioidentical to the hormones produced by a woman's body. The phrase "bioidentical hormone replacement therapy," or BHRT, has been used to describe these products.

Compounded BHRT products typically contain various forms of estrogen and progesterone and, in some cases, testosterone and dehydroepiandosterone.

Some compounding pharmacists claim that their BHRT products are a "natural alternative" to FDA-approved drugs because the compounded hormones are identical to the hormones produced in the body. These pharmacists may also claim that their natural compounded products are safer and more effective than FDA-approved hormone replacement drugs.

FDA is not aware of any credible scientific evidence supporting these claims. Nor is FDA aware of sound evidence showing that the side effects or risks of compounded BHRT products are different than those of FDA-approved hormone replacement drugs.

Because many claims regarding the safety, efficacy and superiority of compounded BHRT products have not been substantiated, FDA is concerned that they mislead patients and practitioners.

In 2003, FDA began a focused public awareness campaign about the risks and benefits of hormone therapy for indications including the symptoms of menopause. This outreach campaign has two parts.

Part one included the development of partnerships and educational materials. In implementing this, FDA's Office of Women's Health formed a working group that included members from NIH, the Agency for Healthcare Research and Quality, and 25 women's health and professional organizations.

The working groups identified a target audience, women aged 40 through 59, and developed core messages, such as "Get informed" and "What can you believe?" The working groups supplemented these messages with campaign materials and strategies for disseminating key information.

Part two was a national media outreach effort. Campaign materials developed in part one were publicized through the media and community outreach, Internet, and print advertising and direct e-mail. The materials developed as part of this campaign continue to be requested and distributed, and are available on our Web site.

FDA has not focused only on compounded BHRT drugs. Hormone replacement therapy products are also marketed as over-the-counter drugs and dietary supplements, often on television and on the Internet.

In the fall of 2005, the FDA worked with FTC to address the marketing of unapproved hormone replacement products. FDA sent warning letters to 16 dietary supplement and hormone cream marketers who were making unproven claims that their "alternative hormone replacement therapy" products were useful in treating or preventing cancer, heart disease, osteoporosis and other serious diseases.

In closing, I assure you that FDA is aware of and attentive to the many concerned voices about hormone replacement therapy

products, including compounded so-called bioidentical drugs. As these products have become increasingly prevalent, so has our attention to them.

I am happy to answer your questions.

[The prepared statement of Dr. Galson follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

STATEMENT BY

STEVEN K. GALSON, M.D., M.P.H.

DIRECTOR

CENTER FOR DRUG EVALUATION AND RESEARCH

U.S. FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SENATE SPECIAL COMMITTEE ON AGING

HEARING ON

BIO-IDENTICAL HORMONES: SOUND SCIENCE OR BAD MEDICINE?

APRIL 19, 2007

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Rear Admiral Steven K. Galson, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to discuss FDA's role with regard to pharmacy compounding and compounded bio-identical hormone replacement therapies.

In my testimony, I will provide background information on pharmacy compounding, explain FDA's current statutory and regulatory authority in this area, and describe FDA's approach to address the public health issues associated with pharmacy compounding generally and compounded bio-identical hormone products in particular.

BACKGROUND

FDA's Historical Approach to Traditional Pharmacy Compounding

FDA believes that pharmacists engaging in traditional compounding provide a valuable medical service that is an important component of our pharmaceutical armamentarium. FDA regards traditional pharmacy compounding as the combining or altering of ingredients by a pharmacist in response to a licensed practitioner's prescription, which produces a medication tailored to an individual patient's special medical needs. In its simplest form, traditional compounding may involve reformulating a drug, for example by removing a dye or preservative in response to a patient allergy. Or it may involve making a suspension or suppository dosage form for a child or elderly patient who has difficulty swallowing a tablet.

It is FDA's view that compounded drugs are "new drugs" within the meaning of the Federal Food, Drug, and Cosmetic (FD&C) Act and that, like all new drugs, compounded drugs may not be introduced into interstate commerce without FDA approval. The drugs that pharmacists compound are rarely FDA-approved and they lack an FDA finding of

safety and efficacy. However, as a matter of policy, FDA historically has not brought enforcement actions against pharmacists engaged in traditional compounding, recognizing the important public health function that compounded drugs play for certain patients with specialized medical needs. Instead, FDA directs its enforcement resources against establishments whose activities raise the kinds of concerns normally associated with a drug manufacturer and whose compounding practices result in significant violations of the new drug, adulteration, or misbranding provisions of the FD&C Act.

FDA's Cooperation with States

FDA recognizes the important role of state authorities in overseeing the practice of pharmacy and generally defers to these authorities regarding the regulation of traditional pharmacy compounding. FDA often refers complaints to state authorities, provides them with support upon request, and cooperates with them in investigations and follow-on actions. However, state resources may be limited and states have varying standards and regulatory requirements that affect their oversight of pharmacy compounding. For example, it may be difficult for state regulators to respond to drugs that are compounded and shipped from across the country (or even from nearby states). Or state regulators may lack the resources or authority to respond to poor compounding practices in their own states. In cases like these, to protect the public health, FDA may need to act independently of state regulators.

FDA's Public Health Concerns Regarding Compounding

The public health threat posed by inappropriate drug compounding is the object of FDA concern and enforcement. Improper compounding has caused patient harm and death. Although many pharmacists are well-trained and well-equipped to compound certain medications safely, not all pharmacists have the same level of skills and equipment, and some products may be inappropriate for compounding. In some cases, compounders may lack sufficient controls (equipment, training, testing, or facilities) to ensure product quality or to compound complex products such as sterile or modified release drugs. The quality of the drugs that these pharmacists compound is uncertain and these drugs pose potential risks to the patients who take them.

Moreover, when compounding occurs on a large scale and it is not performed properly, compounders can expose many patients to health risks associated with unsafe or ineffective drugs. This is especially the case when patients take these compounded drugs in lieu of FDA-approved products.

FDA is also troubled by pharmacists that compound large volumes of drugs that are copies of FDA-approved drugs. This practice circumvents important public health requirements, including the FD&C Act's drug approval provisions. By definition, pharmacy compounding involves making a new drug whose safety and efficacy have not been demonstrated with the kind of data that FDA requires to approve a new drug. Consumers and health professionals rely on this evidence-based drug approval process to ensure that drugs are safe and effective.

FDA'S LEGAL AUTHORITY OVER COMPOUNDED DRUGS

The Federal Food, Drug, and Cosmetic Act

The FD&C Act's comprehensive scheme for the regulation of drugs includes provisions applicable to compounded drugs. Under the FD&C Act, it is unlawful to introduce or deliver for introduction into interstate commerce any new drug intended for human use without FDA approval. Title 21, United States Code (U.S.C.) §§331(d), 355(a). The FD&C Act defines a "new drug" as "*[a]ny* drug . . . that . . . is not generally recognized . . . as safe and effective for use under the conditions prescribed, recommended, or suggested in [its] labeling." *Id.* at §321(p). FDA has consistently interpreted the FD&C Act's broad new drug definition to embrace compounded drugs.

The FD&C Act also imposes requirements on drugs to ensure that they are not "adulterated," 21 U.S.C. §351, and it requires the labeling of drugs to provide consumers, physicians, and pharmacists with necessary information about drug contents, uses, and effects; drugs that are not properly labeled are "misbranded." *Id.* §352. The

adulteration and misbranding provisions of the FD&C Act do not contain exemptions for compounded drugs.

To facilitate enforcement of the approval, adulteration, misbranding, and other FD&C Act provisions, Congress has authorized FDA to enter "any . . . establishment" where drugs are "manufactured, processed, packed, or held" and to inspect such establishments and "all pertinent equipment, finished and unfinished materials, containers, and labeling therein." *Id.* §374(a)(1). This authority extends to "all things" in these establishments, including records relating to prescription drugs. *Id.* The statute provides an exemption from records inspection for pharmacies that comply with local pharmacy law and that satisfy other criteria. But there is no specific exemption from inspection for compounding pharmacies or compounded drugs.

The 1992 Compliance Policy Guide on Compounding

FDA has long interpreted the FD&C Act to apply to compounded drugs, including the provisions addressing new drug approval requirements, adulteration, and misbranding. However, FDA has historically exercised its discretion to exempt from enforcement pharmacists engaged in traditional compounding.

In March 1992, responding to a significant increase in pharmacy compounding, FDA issued a compliance policy guide (CPG), section 7132.16 (later renumbered as 460.200) to delineate FDA's enforcement policy on pharmacy compounding. This CPG relied on enforcement discretion, rather than legal exemptions from the FD&C Act's new drug approval and other requirements, to guide FDA's regulatory approach. After Congress enacted the Food and Drug Administration Modernization Act of 1997 to specifically address FDA's role in the regulation of pharmacy compounding, the 1992 CPG was rescinded.

Food and Drug Administration Modernization Act of 1997

The Food and Drug Administration Modernization Act added section 503A to the FD&C Act to clarify the status of pharmacy compounding and compounded drugs under Federal

law. Under section 503A, compounded drugs that satisfied certain requirements were exempted from three key provisions of the FD&C Act: (1) the adulteration provision of section 501(a)(2)(B) (concerning good manufacturing practice requirements for drugs); (2) the misbranding provision of section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and (3) the new drug approval provision of section 505.

Thompson v. Western States Medical Center

Section 503A included prohibitions on the solicitation of prescriptions for, and the advertising of, compounded drugs. In November 1998, these solicitation and advertising provisions were challenged by seven compounding pharmacies as an impermissible regulation of commercial speech. A federal district court ruled in the pharmacies' favor and held that the solicitation and advertising restrictions violated the First Amendment. On appeal, the Ninth Circuit Court of Appeals affirmed the District Court's holding that the solicitation and advertising provisions unconstitutionally restricted commercial speech. The Court also declared section 503A to be invalid in its entirety, meaning that the unconstitutional speech provisions could not be severed from the rest of 503A. *Western States Medical Center v. Shalala*, 238 F.3rd 1090 (9th Cir. 2001)). The Supreme Court affirmed the Ninth Circuit's decision that the advertising and soliciting restrictions were unconstitutional, but it did not consider whether these restrictions could be severed from the rest of section 503A. *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002). FDA shares the Ninth Circuit's view that section 503A is now void.

Compliance Policy Guide of May 2002

In order to fill the regulatory vacuum created by the Supreme Court's decision in *Thompson v. Western States Medical Center*, FDA issued Compliance Policy Guide section 460.200 ["Pharmacy Compounding"] in May 2002. FDA issued this CPG in final form, and requested and received numerous comments on it. FDA stated that it would review these comments and revise the CPG, if appropriate. That process is underway, and FDA plans to issue a revised CPG, in draft, for public comment.

The 2002 CPG reflects FDA's current enforcement policy with respect to human drug compounding. It recognizes that pharmacists traditionally have extemporaneously compounded reasonable quantities of drugs upon receipt of a valid prescription for an individually identified patient. This traditional compounding is not the subject of the guidance. Instead, the CPG provides that, when the scope and nature of a pharmacy's activity raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the FD&C Act, FDA will consider enforcement action. The CPG identifies factors that FDA evaluates in deciding whether to take action; these factors are not intended to be exhaustive.

Medical Center Pharmacy v. Gonzales

In 2004, ten pharmacies specializing in compounding brought suit in the United States District Court for the Western District of Texas, challenging FDA's authority to regulate compounded drugs. In August 2006, the court ruled, among other things, that compounded drugs are "implicitly exempt" from the FD&C Act's new drug approval provisions. *Medical Center Pharmacy v. Gonzales*, 451 F. Supp. 2d 854 (W.D. Tex. 2006). The government has filed an appeal with the U.S. Court of Appeals for the Fifth Circuit. Pending resolution of this appeal, the district court's decision applies in the Western District of Texas. Elsewhere, FDA continues to be guided by the 2002 CPG when considering enforcement actions regarding compounded drugs.

COMPOUNDED BIO-IDENTICAL HORMONE REPLACEMENT THERAPY PRODUCTS

FDA is aware that an increasing number of pharmacists compound hormone products for use by postmenopausal women. These pharmacies often promote their products as "bio-identical" to the hormones produced by a woman's body, and the phrase "bio-identical hormone replacement therapy" (BHRT) has been used to describe these products. Compounded BHRT products typically contain various forms of estrogen and progesterone and, in some cases, testosterone and dehydroepiandrosterone. BHRT drugs

are compounded for oral, topical, transdermal, suppository, and other routes of administration.

FDA's regulatory approach toward compounded BHRT products is framed by its general approach to compounded drugs: FDA recognizes the legitimacy of traditional pharmacy compounding of BHRT products, *i.e.*, when a pharmacist compounds a BHRT product in response to a licensed practitioner's decision that a patient's specific medical need cannot be met by an FDA-approved drug. FDA will generally continue to defer to state regulators regarding this practice.

Claims Regarding Compounded BHRT Products

FDA is concerned, however, that a number of pharmacies make claims about compounded BHRT products that are false and that may mislead patients and practitioners as they decide whether these products are appropriate. Drugs that make false and misleading claims are misbranded under the FD&C Act.

FDA believes that some promotional materials for compounded BHRT products contain inaccurate information and do not adequately advise patients and practitioners of the risks associated with compounded hormone products (risks that appear to be the same as the hazards related to FDA-approved hormone products). These promotional materials may also contain unsubstantiated claims about the safety and efficacy of compounded BHRT products.

Moreover, some compounding pharmacists claim that their BHRT products are a "natural" alternative to FDA-approved drugs, because the compounded hormones are identical to the hormones produced in the body. These pharmacists may further claim that their "natural" compounded BHRT products are a safe alternative to FDA-approved drugs because they lack the risks and side effects associated with those drugs. FDA is unaware of any credible scientific evidence supporting the assertions that these bio-identical compounded products are a safe or effective alternative to FDA-approved drugs containing hormones.

Equally concerning are claims by compounding pharmacists that compounded BHRT products can be used to prevent serious illnesses, including breast and colon cancers, cardiovascular disease, and Alzheimer's disease. These claims are not substantiated by scientific evidence for these compounded BHRT products, and they risk misleading consumers into using compounded BHRT products to prevent these illnesses in the absence of any evidence supporting there effectiveness.

FDA is also not aware of sound evidence showing the superiority of compounded BHRT products over FDA-approved drugs. Likewise, FDA has no information indicating that the side effects and risks of compounded BHRT products are dissimilar to those of FDA-approved drugs. Thus, claims regarding the safety, efficacy, and superiority of compounded BHRT products have not been substantiated by FDA and may mislead patients and practitioners.

Lack of Warnings and Information: Compounded BHRT Products

FDA regulations require prescription drugs containing estrogen to be dispensed with a patient package insert explaining the drug's benefits and risks. 21 CFR §310.515. Compounded BHRT products are often dispensed without this information. Thus, patients are not explicitly advised of the risks associated with the use of these compounded products. The absence of warnings and risk information may be viewed by patients as implicit evidence that compounded BHRT products are safer than FDA-approved drugs, when there is no data to support this conclusion.

FDA's Shared Concerns with Medical Professional Organizations

FDA is not alone in its concerns regarding compounded BHRT products. A number of medical professional organizations, including the American Medical Association (AMA), the Endocrine Society, and the American College of Obstetricians and Gynecologists have published formal statements regarding compounded BHRT products.[1] On the

[1] *See* American Medical Association House of Delegates Resolution 706, "FDA Oversight of Bio-identical Hormone (BH) Preparations," September 27, 2006; Endocrine Society Position Statement, "Bio-identical Hormones," October 2006; American College of Obstetricians and Gynecologists, Committee on Gynecologic Practice Opinion on Compounded Bio-identical Hormones, November 2005.

whole, these medical organizations believe that there is inadequate scientific evidence to support the claims made regarding the safety and efficacy of compounded BHRT products. Furthermore, two of these organizations, the AMA and the Endocrine Society, expressed concerns about the spread of false and misleading information in conjunction with the promotion of compounded BHRT products.

The Wyeth Citizen Petition

Currently, FDA is considering a Citizen Petition filed by Wyeth on October 6, 2005, concerning compounded bio-identical hormone replacement therapy drugs. FDA Docket No. 2005P-0411. The petition requests that FDA take a number of actions regarding compounded BHRT drugs, including enforcement action, investigations, requiring certain labeling and promotional disclosures, and engaging in educational initiatives. On April 4, 2006, Wyeth submitted a Supplemental Filing (Supplement) to the petition to address issues raised in comments submitted to the docket by the International Academy of Compounding Pharmacists and the National Community Pharmacists Association.

FDA has received more than 68,000 comments concerning this petition, and continues to receive comments. These include at least 13,000 form letters and comments from individual consumers, pharmacists, pharmacy groups, and health care practitioners. FDA also has received comments from consumer health care and professional organizations, including the National Women's Health Network, the National Black Women's Health Project, the National Association of Nurse Practitioners in Women's Health, the American Medical Women's Association, the North American Menopause Society, American Society for Reproductive Medicine, the Society for Women's Health Research, the Jacobs Institute of Women's Health, and the American College of Obstetricians and Gynecologists, among others.

The majority of the comments – submitted by individual consumers, health-care practitioners, pharmacists, alternative-medicine advocacy groups, and compounding pharmacy associations – ask that we deny Wyeth's petition. It is noteworthy, however, that we received some comments from pharmacists and health-care practitioners who are

concerned about the use and marketing of compounded BHRT products. The comments received from consumer health organizations generally support Wyeth's petition.

The petition and comments raise complicated scientific issues of safety and efficacy, as well as regulatory and policy questions. FDA is currently evaluating these complex questions. When its analysis is complete, FDA will provide a written response to the petitioner, which will be available from FDA's Dockets Management Branch and will be posted on FDA's website.

Other Unapproved Hormone Replacement Products

FDA is concerned about the distribution of other unapproved hormone replacement products, including products marketed as over-the-counter drugs and dietary supplements.

In the fall of 2005, FDA worked with the Federal Trade Commission (FTC) on a joint effort to address the marketing of unapproved hormone replacement products. In November 2005, FDA sent warning letters to 16 dietary supplement and hormone cream marketers who were making unproven claims that their "alternative hormone replacement therapy" products were useful in treating or preventing cancer, heart disease, osteoporosis, and other serious diseases. All of the products were available for purchase directly from these firms' websites without a prescription. FDA advised the firms that their products were "new drugs" because they claimed that the products were useful in treating or preventing disease. The products were not approved by FDA for these uses, and thus violated the FD&C Act's new drug approval requirements. In addition, the firms violated an FDA regulation, 21 CFR §310.530, which prohibits the marketing of over-the-counter topically applied hormone-containing products without an FDA-approved application.

CDER issued three of the warning letters to these firms. Two of the three firms that received these letters no longer sell the hormone products. The third firm initially complied, but a recent review of the firm's website indicates that it is once again

promoting hormone creams, albeit for different, less serious diseases. We are actively reviewing this matter to determine the best course of action.

The Center for Food Safety and Applied Nutrition (CFSAN) issued thirteen of the warning letters to firms marketing oral preparations as dietary supplements. Eleven of the thirteen firms that received these letters promised corrections that included removing the offending claims cited in the warning letters, discontinuing marketing the non-compliant products, or taking down the websites on which the products were marketed. CFSAN confirmed these corrections, but a recent review of the firms' websites showed that two firms are now marketing new products with similar claims. CFSAN is considering the steps that it will take to respond to this information.

FTC, in a joint effort with FDA, also sent notices to thirty-four websites promoting hormone replacement products with unsubstantiated claims. FTC stated in its "Notice of Potentially Illegal Marketing of Menopausal/Hormonal Products" that the FTC Act, 15 U.S.C. §41 *et seq.*, prohibits unfair or deceptive acts and practices, including false and unsubstantiated advertising claims.

FDA's Office of Women's Health (OWH) Menopause and Hormones Campaign

In FY 2003, OWH was mandated by Congress to spearhead an "Agency outreach campaign to provide concise information to women and health professionals about hormone replacement therapy" as a result of the findings of increased risk of heart attack, stroke and breast cancer in the National Institutes of Health (NIH) Women's Health Initiative (WHI) combination hormone therapy study in 2002. In this directive, FDA was to "work collaboratively with physicians, women's health groups, and federal agencies to conduct a public awareness campaign about the use of hormone therapy, including the treatment of menopausal symptoms."

The menopausal hormone therapy outreach campaign had two parts. Part I included the development of materials and partnerships (2003-2004) and Part II included nationwide media outreach (2004-2005).

Part I: Materials and Partnership development

OWH formed a working group that included members from CDER, HHS Office on Women's Health, NIH, Agency for Healthcare Research and Quality (AHRQ), and 25 women's health and health professional organizations. The group was tasked with identifying the target audience, developing key messages, campaign materials, and strategies for dissemination.

Rollout of the campaign materials was held on September 9, 2003. Materials included a fact sheet and a purse guide (discussed below). The targeted audiences were women ages 40-59, with a dissemination of materials to geographic areas across the U.S. with the greatest density of women in these age groups. The key messages, which were confirmed through focus group research, were:

- Menopause and Hormones: "What Can You Believe?"
- Get informed
- Talk to your health care professional and decide if hormone therapy is right for you.
- If you choose to use hormones, use them at the lowest effective dose for the shortest amount of time needed.

The "Menopause and Hormones" fact sheet defines menopause and symptoms, as well as hormone therapy for menopause. It also describes known benefits and risks of hormone therapy as well as advises:

- who should not take hormone therapy;
- that the risks and benefits may be the same for all hormone products; and
- that the risks and benefits of "herbs or other natural products" are not currently known.

The "Menopause and Hormone" purse guide contains questions to facilitate discussion between the woman and her health care professional on whether use of hormone therapy is appropriate. It also provides an area for taking notes, suggests other beneficial health tests or screening that could be discussed during the visit and provides federal resources to find more information on hormone therapy for menopause.

Part II: National media outreach

Campaign materials developed in Part I were publicized using several different approaches and elements to involve partners. These included FDA Public Affairs Specialists; media outreach in both print and radio; Internet advertising; print advertising; outreach to community based organizations; and direct e-mail.

Campaign Conclusions

Based on the combined circulation totals for all media activities used, projections of membership in the community organizations contacted, and volume of materials ordered, the campaign can account for nearly 100 million times that the menopause message was delivered to peri-menopausal and postmenopausal women. In addition, the materials developed as part of this Congressional mandate continue to be requested and distributed. These materials are free and can be accessed via FDA's Office of Women's Health website (*http://www.fda.gov/womens/menopause/mht-FS.html*) and the Federal Clearinghouse at Pueblo (*www.pueblo.gsa.gov*), and are available in both English and Spanish. An extension of this campaign involves the development of a brochure on FDA-approved medications for menopausal symptoms – which has become available in the past month. This document was created in response to requests from women for an FDA guide that provides basic information about menopausal hormone therapy and describes all prescription products currently approved by the Agency for this indication. The booklet is not intended to be used in place of the labeling, but to help women talk to their doctor, nurse, or pharmacist about what they should know about risks and side effects, and general safe use for each of these medications.

CONCLUSION

FDA intends to continue to address pharmacy compounding, including compounding of BHRT products, in a manner that respects traditional pharmacy compounding. FDA will pursue enforcement action against compounded drugs, including compounded BHRT

drugs, when the compounding of these drugs raises concerns normally associated with drug manufacturing and results in significant violations of the new drug, adulteration, or misbranding provisions of the FD&C Act.

This concludes my testimony, Mr. Chairman. I will be glad to answer any questions you may have.

Senator SMITH. Thank you very much.
Dr. GALSON. Thank you.
Senator SMITH. Eileen Harrington.

STATEMENT OF EILEEN HARRINGTON, DEPUTY DIRECTOR, BUREAU OF CONSUMER PROTECTION, FEDERAL TRADE COMMISSION, WASHINGTON, DC

Ms. HARRINGTON. Good morning, Ranking Member Smith. I am Eileen Harrington, the deputy director of the FTC's Bureau of Consumer Protection.

The commission's written testimony has been submitted for the record. My oral statement and answers to any questions you may have represent my views.

You have asked us to discuss the FTC's efforts to address the misleading online advertising of alternatives to hormone replacement therapy, as well as our work to combat all types of Internet fraud.

Among its many benefits, the Internet provides consumers with access to a vast array of information and products, including health-related items. Unfortunately, it also provides an opportunity for irresponsible marketers to prey on consumers, making false or misleading claims, causing economic injury, and posing potentially serious consequences for consumers' health.

For over a decade, the FTC has been on the forefront of efforts to protect consumers from online fraud. In doing this, we use a three-pronged strategy.

First, we take law enforcement action to stop deceptive practices and obtain redress for victims of fraudulent schemes.

Second, we conduct consumer education campaigns, often in partnership with colleagues like the FDA, to help consumers spot and avoid online scams in the first instance.

Third, we educate businesses to help them comply with the law and avoid engaging in deceptive practices.

The FTC's work to address deceptive online health and safety claims exemplifies our use of this strategy. We have aggressively enforced the law, bringing 229 enforcement actions challenging online false and misleading health and safety claims for products ranging from weight-loss pills to cancer cures.

For example, last November, following a fierce trial, the FTC won a Federal court order requiring the sellers of the Q-Ray Bracelet to refund up to $87 million to consumers who had purchased the product based on false claims that the bracelets would significantly reduce their pain.

On the consumer education front, the FTC provides consumers with useful, creative and timely information to help them avoid falling victim to false claims for everything from cure-alls to diet and fitness products. We provide all of these materials on our Web site. We spread the word offline, as well, often partnering with private- and public-sector organizations to distribute publications and our messages.

Our efforts involving alternative HRT products are a good example of our use of the third prong of our strategy: educating business about their legal responsibilities.

Our staff identified 34 Web sites with claims that alternative natural progesterone creams and sprays were safe or would prevent, treat or cure serious cancer, heart disease or osteoporosis. We sent a warning e-mail to each of those site operators; the e-mails putting them on notice that they must have substantiation for any health claims that they make about their products and urging them to review their product claims to make sure they complied with the law.

Our staff recently conducted a follow-up review of those Web sites and has continued working with companies to clean up their claims. Fifteen of the 34 Web sites have either removed the claims or no longer sell the products.

As I said, we are continuing to follow up directly with the remaining sites, and our staff will be making appropriate enforcement recommendations about those that do not comply with the law.

The FTC's efforts to halt deceptive health-related claims online are part of its larger program to combat Internet fraud. Since 1994, the FTC has launched 538 law enforcement actions, garnering nearly $1 billion in judgments against those who have used the Internet to prey upon American consumers.

Online deception generally falls into two categories: old-fashioned schemes that have simply migrated online and new high-tech schemes that are unique to the computer age.

Spam presents a hybrid of the two. Spammers use low-cost new technology e-mails to carpet consumers with old-fashioned deceptive claims about everything from miracle cures to bogus investment opportunities.

The FTC has pounded the pavement on the spam beat for over a decade. Since 1994, we have litigated 89 actions against 241 defendants in which spam was an integral element of the scheme, and 26 of those cases use the relatively new Can Spam Act.

As technology and scams change over time, the FTC continues to shift its resources and adjust its priorities, targeting those frauds that cause the most harm to consumers.

False and misleading claims that affect consumers' health and safety are prime targets, and they will remain prime targets, of the FTC's enforcement efforts. We will continue our efforts to ensure the truthfulness and accuracy of advertising for health-related products, regardless of the medium in which those ads appear.

Thank you, again, for inviting us. I am happy to answer your questions.

[The prepared statement of Ms. Harrington follows:]

PREPARED STATEMENT OF

THE FEDERAL TRADE COMMISSION

on

ALTERNATIVE HORMONE REPLACEMENT THERAPY PRODUCTS

Before the

SENATE SPECIAL COMMITTEE ON AGING

Washington, DC

April 19, 2007

I. Introduction

Chairman Kohl, Ranking Member Smith, and Members of the Committee, I am Eileen Harrington, Deputy Director of the Bureau of Consumer Protection of the Federal Trade Commission ("FTC" or "Commission").[1] I appreciate the opportunity to discuss the Commission's efforts to address the misleading online advertising of "alternatives" to hormone replacement therapy as well as its work to combat all types of Internet fraud.

Among its many benefits, the Internet provides consumers with access to a vast array of information and products, including health-related items. Unfortunately, the online medium also provides an opportunity for irresponsible marketers to prey on consumers with false or misleading claims that can cause economic injury and have potentially serious consequences for consumers' health. Therefore, pursuant to its broad authority to prevent "unfair or deceptive acts or practices,"[2] the FTC has a longstanding and active program to protect consumers in the online environment.

This testimony provides an overview of the FTC's efforts with respect to health-related fraud, including an explanation of its jurisdiction over health products and a discussion of the FTC/FDA project to address the misleading marketing of hormone replacement therapy alternatives. Pursuant to the Committee's request, the testimony then discusses the FTC's broader program to combat online scams in general.

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[1] This written statement presents the views of the Commission. My oral testimony and responses to questions reflect my views and do not necessarily represent the views of the Commission or any individual Commissioner.

[2] Section 5 of the Federal Trade Commission Act, 15 U.S.C. § 45(a). In addition, Section 12 of the Federal Trade Commission Act prohibits the false advertisement of "food, drugs, devices, services, and cosmetics." 15 U.S.C. § 52.

II. Health-Related Fraud

A. Overview

The Commission employs a three-pronged strategy to protect consumers from deceptive claims for health-related products: (1) law enforcement; (2) consumer education; and (3) business outreach. In each of these areas, the FTC works closely with its state, federal, and international partners, including state attorneys general, the Food and Drug Administration ("FDA"), and members of the Mexico, United States, and Canada Health Fraud Working Group.

On the law enforcement front, over the past decade the FTC has initiated 229 enforcement actions challenging false and misleading health and safety claims for products ranging from weight-loss pills to cancer cures. Of particular note, the Commission successfully challenged deceptive "fountain of youth" claims used to advertise purported human growth hormone ("HGH") products in a number of cases.[3] Additionally, in November the FTC obtained a federal court order requiring the purveyors of the Q-Ray bracelet to refund up to $87 million to consumers who had purchased the product based on the defendants' false representation that the bracelets significantly alleviated pain.[4]

On the consumer education front, the Commission has released a host of materials on how to avoid being victimized by false claims for everything from cure-alls, to indoor tanning, to

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[3] *E.g.*, *FTC v. Pacific Herbal Servs.*, No. CV05-7247 (C.D. Cal.) (Prelim. Inj. Oct. 19, 2005), www.ftc.gov/os/caselist/pacificherbal/pacificherbal.shtm; *FTC v. Global Web Promotions*, No.04C3022 (N.D. Ill.) (Final Order June 16, 2005); www.ftc.gov/os/caselist/0423086/0423086.shtm; *FTC v. Great American Prods.*, No. 3:05CV170 (N.D. Fla.) (Final Order May 20, 2005), www.ftc.gov/os/caselist/0323247/0323247.shtm; *FTC v. Creaghan Harry*, No. 04C4790 (N.D. Ill.) (Final Order May 5, 2005), www.ftc.gov/os/caselist/0423085/0423085.shtm.

[4] *FTC v. QT Inc.*, No. 03C 3578 (N.D. Ill.) (Final Order Nov. 13, 2006), www.ftc.gov/opa/2006/09/qray.htm.

diet and fitness products.[5] For example, the FTC issued a Consumer Alert on HGH pills and sprays.[6] Most recently, the Commission released its "Glucobate" teaser website advertising a phony miracle product to help consumers avoid deceptive diabetes claims.[7]

On the business outreach front, the Commission has created numerous materials geared toward helping businesses avoid making deceptive claims. For example, the FTC's publication "Dietary Supplements: An Advertising Guide for Industry," provides easy-to-understand explanations of advertising standards for the marketing of health products, along with many useful examples.[8] Additionally, the Commission conducts advertising "surfs" looking for potentially violative claims, and then follows up with warning letters, which can ultimately lead to law enforcement action. For example, the FTC sent warning letters to more than 90 Internet marketers promoting purported HGH products for "anti-aging" benefits.[9] Finally, the Commission has worked with industry trade associations to implement effective self-regulation procedures.

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[5] *See*, respectively, www.ftc.gov/bcp/conline/edcams/cureall/coninfo.htm; www.ftc.gov/bcp/conline/pubs/health/indootan.htm; and www.ftc.gov/bcp/conline/edcams/fitness/index.html.

[6] www.ftc.gov/bcp/conline/pubs/alerts/hghalrt.pdf.

[7] Teaser sites mimic real web pages, using common buzz words and making exaggerated claims like those found on many deceptive websites. At first glance, the teaser site appears to advertise a miracle cure. When consumers click for more information, they learn the ad is actually a consumer education piece posted by the FTC to warn consumers about rip-offs. *See* www.wemarket4u.net/glucobate.

[8] www.ftc.gov/bcp/conline/pubs/buspubs/dietsupp.htm. This publication was accessed over 25,000 times last year.

[9] www.ftc.gov/opa/2005/06/greatamerican.shtm.

On all three fronts, the FTC frequently collaborates with the FDA on health issues. Although the FTC and the FDA both have jurisdiction over health-related products, the agencies coordinate closely pursuant to a longstanding agreement.[10] Under this agreement, the FTC has primary responsibility to regulate the advertising of over-the-counter drugs, food, cosmetics, and devices, while the FDA regulates the labeling of these products. The FDA also has primary responsibility to regulate claims made in both the advertising and labeling of prescription drugs. In many cases, however, the agencies work together to leverage resources and have a greater effect on the marketplace. The agencies' project to address misleading claims for alternative hormone replacement therapy products sold on the Internet is a good example of these joint efforts.

B. Targeting Deceptive Claims for Hormone Replacement Therapy Alternatives

Hormone replacement therapy is medication containing female hormones that doctors prescribe to treat symptoms of menopause as well as other conditions. In 2002, the Women's Health Initiative (sponsored by the National Institutes of Health) terminated a clinical trial of hormone replacement therapy because the overall health risks (e.g., of heart disease and breast cancer) outweighed the benefits of the therapy.[11] This stunning news fueled the growth of a market promoting "natural alternatives" to hormone replacement therapy. These products

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[10] Working Agreement Between the FTC and FDA, 3 Trade Reg. Rep. (CCH) ¶ 9,859.01 (1971).

[11] National Institutes of Health News Release, July 9, 2002, www.nhlbi.nih.gov/new/ press/02-07-09.htm. Since that time, researchers further analyzed the trial data and one recent review suggests that the heart risks may have been overstated. Jacques E. Rossouw, MD, *Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause*, 297 JAMA 1465-1477 (2007).

include "natural" progesterone creams and sprays.[12] Some of the marketers claim that their "natural" progesterone products are safe and effectively prevent, treat, or cure serious diseases, such as cancer, heart disease, and osteoporosis. However, the FTC is not aware of competent and reliable scientific evidence to substantiate these claims.[13]

Therefore, working in conjunction with the FDA, FTC staff surfed the Internet for websites claiming that their progesterone products were safe or could prevent, treat, or cure serious diseases. The staff used search engines to identify relevant websites and then examined the sites to determine whether they made potentially deceptive claims. The FDA staff conducted its own surf to identify websites. The FTC and FDA staff coordinated efforts and compared surf results so that each agency would send letters to different targets and therefore have a greater impact. The FTC found 34 websites making questionable safety and disease prevention claims and sent warning letters to each. The FDA staff sent letters to an additional 16 websites.

The FTC staff's emails explained that the marketers must have competent and reliable scientific evidence to substantiate any health claim they make about their products. The emails urged the marketers to review their product claims to make sure they complied with the law. In addition, the FTC's emails provided information about FDA law, as well as links to resources the

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[12] In addition, some online pharmacies offer compounded hormones which they claim are customized to an individual's needs based on an analysis of a saliva sample.

[13] FTC law requires that marketers possess competent and reliable scientific evidence to substantiate claims about the safety and efficacy of health-related products, including dietary supplements. FTC Policy Statement Regarding Advertising Substantiation, *appended to Thompson Med. Co.*, 104 F.T.C. 648, 839 (1984), www.ftc.gov/bcp/guides/ ad3subst.htm.

marketers could consult for guidance.[14] Likewise, FDA warning letters provided information about FTC law.

The FTC staff recently conducted a follow-up review of the websites to determine if the sites removed or modified the safety or disease prevention claims. Although many sites revised their claims, unfortunately, slightly more than half of the websites, 19 of 34, continue to sell "natural" progesterone creams and sprays by making unsubstantiated claims that they are safe or can treat or prevent cancer, heart disease, or osteoporosis. The FTC staff now is following up with the companies and will make enforcement recommendations.

III. Internet Fraud

The Commission's efforts to halt deceptive, online, health-related claims are part of a larger, aggressive program to combat Internet fraud. For over a decade, the FTC has employed the same three-pronged strategy discussed above – law enforcement, consumer education, and business outreach – to address a wide array of online consumer protection problems, including data security, pretexting, identity theft, children's online privacy, spam, and spyware.

Online fraud generally falls into two categories: (1) old-fashioned schemes that have simply moved online, such as pyramid schemes, deceptive work-at-home opportunities, and false product claims;[15] and (2) Internet trickery and other scams that exploit new technology and are

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[14] *See* FTC Press Release and Sample Warning Letter, www.ftc.gov/opa/2005/11/hormone.htm.

[15] *See, e.g.*, *FTC v. SkyBiz.com, Inc.*, No. 01-CV-396-EA (N.D. Okla.) (Stipulated Final Order Jan. 28, 2003), www.ftc.gov/opa/2003/03/skybiz.htm (pyramid); *FTC v. Stuffingforcash.com*, No. 02C 5022 (N.D. Ill.) (Stipulated Final Order Jan. 30, 2003), www.ftc.gov/opa/2003/07/spammers.htm (work at home); *FTC v. Phoenix Avatar, LLC*, No. 04C 2897 (N.D. Ill.) (Stipulated Final Order Mar. 29, 2005), www.ftc.gov/opa/2005/03/phoenix.htm (diet patches).

unique to the computer age, such as pagejacking, phishing, and modem hijacking.[16] Since 1994, the FTC has filed 538 actions against individuals and corporations that have used the Internet to unleash a wide variety of deceptive and unfair practices on American consumers. The Commission's efforts to address deceptive spam and spyware illustrate this broader Internet fraud program and the tools the FTC employs to combat online scams.

Since 1997, the Commission has filed 89 actions against 241 defendants in which spam was an integral element of a scheme that harmed consumers.[17] Twenty-six of these cases were filed after Congress enacted the CAN-SPAM Act,[18] which, among other things, prohibits email senders from using deceptive message headers and subject lines. In many instances, scam artists use unsolicited commercial email to put a new twist on schemes that previously could be conducted in the offline world. For example, last year the FTC alleged that Internet marketer Jumpstart Technologies disguised commercial email messages to appear as personal messages from friends and misled consumers as to the terms and conditions of its "free" movie ticket promotions. To resolve those allegations, the company paid $900,000, the largest civil penalty obtained under the CAN-SPAM Act.[19] Deceptive spam also can be part of a scheme that is

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[16] *See, e.g.*, *FTC v. Carlos Pereira*, No. 99 Civ. 562 (E.D.N.Y.) (Final Order Jan. 24, 2005), www.ftc.gov/opa/1999/09/atariz.htm (pagejacking); *FTC v. Hill*, No. H 03-5537 (S.D. Tex.) (Stipulated Final Order May 24, 2004), www.ftc.gov/opa/2004/03/ phishinghilljoint.htm (phishing); and *FTC v. Sheinkin,* No. 2-00-3636-18 (D.S.C.) (Stipulated Final Order Aug. 15, 2001), www.ftc.gov/opa/2001/08/ sheinkin.htm (modem hijacking).

[17] Two of these cases addressed the deceptive sale of human growth hormone. *Supra* note 3.

[18] Controlling the Assault of Non-Solicited Pornography and Marketing Act, 15 U.S.C §§ 7701-7713.

[19] *United States v. Jumpstart Techs., LLC*, No. C-06-2079 (N.D. Cal.) (Stipulated Final Order Mar. 22, 2006), www.ftc.gov/opa/2006/03/freeflixtix.htm.

unique to the Internet. For example, in one case the FTC alleged that a defendant's email messages claimed that consumers won a Sony PlayStation in order to lure consumers to an adult website and surreptitiously redirect their Internet connections through a 900-number that charged them up to $3.99 a minute for the new connection.[20]

The FTC also has taken law enforcement actions against distributors of spyware – another technology-driven scheme that provides digital data thieves with a back door into consumers' online lives. Spyware is downloaded without authorization and may be used to send high volumes of pop-up ads, redirect computers to unwanted websites, monitor Internet surfing, or record consumers' keystrokes, which, in turn, could lead to identity theft. In the past three years, the Commission has filed 11 cases against purveyors of spyware, disgorging over $12.9 million of their alleged ill-gotten gains. In the Commission's most recent spyware case, the FTC alleged that Direct Revenue, LLC surreptitiously installed advertising software programs, which monitored Internet use to display targeted pop-up ads on consumers' computers, and deliberately made the programs difficult for consumers to identify and remove. To settle these charges, Direct Revenue agreed to disgorge $1.5 million and to abide by injunctive provisions that will protect consumers from these practices in the future.[21]

The FTC employs a number of tools to develop its cases targeting online fraud. For example, the Commission identifies potentially violative commercial email through its spam database. Each day, the FTC receives approximately 300,000 pieces of spam – forwarded by

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[20] *FTC v. BTV Industries*, CV S-03-1306 (D. Nev.) (Stipulated Final Order Nov. 25, 2003), www.ftc.gov/opa/2004/02/playstation2.htm.

[21] *In re DirectRevenue, LLC*, FTC File No. 052-3131 (Consent Agreement Feb. 16, 2007), www.ftc.gov/opa/2007/02/directrevenue.htm.

computer users to spam@uce.gov – and stores it in a large database, which currently houses more than 400 million pieces of unsolicited commercial email, including emails regarding apparently bogus health claims.

The FTC's Consumer Sentinel database also plays a central role in the agency's law enforcement efforts. The Consumer Sentinel database contains over 3.7 million consumer fraud and identity theft complaints filed with the FTC; other federal, state, and local law enforcement agencies; and private organizations. The FTC, as well as more than 1,600 law enforcement entities worldwide, use the database to identify scams, specific companies generating high levels of complaints, and individual consumers who may have been harmed by illegal activity.[22]

In addition, the recently-enacted US SAFE WEB Act[23] provides the Commission with important new tools to fight online fraud that crosses international borders. The Commission's efforts to combat illegal spam, deceptive health-related advertising, and spyware illustrate the need for these tools. Spam is often routed through servers and proxies located overseas and contains links to websites hosted by foreign companies. In addition, sellers of bogus health-related products may be located in foreign countries, but can promote their products to U.S. consumers using the Internet and satellite TV. Spyware distributors also can be located overseas or use foreign ISPs to host their websites. Therefore, in each of these situations, scammers, consumer witnesses, and money derived from scams are located in foreign countries. To help

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[22] A number of the law enforcement entities that have access to the Consumer Sentinel database investigate health-related matters, including the FDA, state attorneys general, the California Department of Consumer Protection, the Connecticut Department of Consumer Protection, the Montana Department of Administration's Office of Consumer Protection, and the Texas Department of Health.

[23] Undertaking Spam, Spyware, and Fraud Enforcement With Enforcers Beyond Borders Act of 2006, Pub. L. No. 109-455, 120 Stat. 3372 (2006).

overcome the challenges of investigating and prosecuting these types of international fraud, the US SAFE WEB Act strengthens the FTC's ability to cooperate with its foreign counterparts, gather information from international sources, and follow the money trail without tipping off the fraud's perpetrators.

As with health-related fraud, the FTC combines its law enforcement efforts against all types of Internet fraud with consumer education and business outreach campaigns. The FTC has produced a wide array of materials to educate consumers on how to spot and avoid online scams and to increase business awareness on how to comply with the law. For example, the award-winning website, OnGuardOnline.gov, contains tips, articles, videos, and interactive materials to educate consumers on guarding against Internet fraud, filter spam, secure their computers, and protect their personal information. The FTC developed OnGuardOnline in conjunction with industry partners and other agencies, and since its launch in late 2005, the site has attracted more than 3.5 million visits. The FTC also disseminates a variety of business education materials, including materials to inform businesses about complying with the CAN-SPAM Act,[24] and publications providing advice on making clear disclosures in online ads.[25]

IV. Conclusion

The FTC has been involved in policing the Internet for more than a decade and will continue to protect consumers from the various types of online fraud. As technology and scams change, the Commission continues to shift its resources to target those frauds that cause the most harm to consumers. In addition, the FTC will continue its efforts to ensure the truthfulness and

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[24] *See* www.ftc.gov/bcp/conline/pubs/buspubs/canspam.htm.

[25] *See* www.ftc.gov/bcp/conline/pubs/buspubs/dotcom/index.pdf.

accuracy of advertising for health-related products, regardless of the medium in which the ads appear. This includes efforts against deceptive advertising targeted toward older Americans, who are among our most vulnerable populations. Thank you for providing the Commission an opportunity to appear before the Committee.

Senator SMITH. Thank you very much, Eileen.

Ladies and gentlemen, I am holding in my hand a jar called Products of Nature Natural Woman Progesterone Cream.

Dr. Rossouw, my staff purchased this on the Internet just a few days ago. It comes with certain claims, specifically that, if applied topically, it will greatly decrease a woman's risk of breast cancer; that women who have previously had breast cancer will have little or no reoccurrence if using natural progesterone cream.

In your scientific opinion, are there any studies that would support such claims?

Dr. ROSSOUW. No. There are no studies that support such a claim. I would make two further points.

First, that, you know, the dichotomy between natural and synthetic—which this kind of product plays on—appeals to an idea amongst the public that natural is somehow better than synthetic.

From the scientific standpoint, there are either drugs that work and are safe or drugs that don't work or are not safe. Their origin is quite irrelevant, firstly.

Second, if you look at the risk factors for breast cancer epidemiologically, they are all related to the levels and duration of exposure to the natural human hormones estradiol and progesterone, such as the earlier the onset of the menarche or the later the delay in the menopause; with longer exposure the greater the risk of breast cancer.

So I think the evidence would be, though inferential, to the contrary. There is no evidence that progesterone prevents breast cancer. I suspect that, in combination with estrogen, it probably increases the risk.

Senator SMITH. It increases the risk.

Dr. ROSSOUW. From what we know, the likelihood is that it increases the risk.

Senator SMITH. Topically applied, I mean, does that—there is no value——

Dr. ROSSOUW. Well, there is a question of how much is absorbed. My colleague from the FDA can address that. But if it is absorbed, and a woman has circulating estradiol, then I would not regard this as a favorable scenario.

Senator SMITH. You know, on the Western frontier, they had a lot of snake oil salesmen. Do we have that in the 21st century, if those claims are being made?

Dr. ROSSOUW. Well, I would just go so far as to say that these claims are unsubstantiated.

Senator SMITH. Ms. Harrington, I am wondering why my staff was able to purchase this on the Internet off a Web site that was one of 34 companies that you sent warnings to in November of 2005.

Two weeks ago, this company was still in business. As far as I know, they still are. As far as I know, this is still—I could get it today, or a woman could get it today if she sought it.

Of the 34 companies that received warnings from the FTC in 2005, 32 of them still had Web sites up and running as of 2 weeks ago.

Now, you have identified in your testimony that 19 of these sites are still selling hormone products that make unsubstantiated health-related claims.

I guess what I am asking is, what revisions is the FTC going to be making to enforce its policies to ensure that this type of egregious enforcement lapse does not reoccur?

Ms. HARRINGTON. Senator, we, as I said, will be receiving enforcement recommendations on companies that are not in compliance. I can't say, in a public setting, precisely when and what the nature of those will be.

I think we could have moved faster here, and we should have.

Senator SMITH. Well, I don't mean any personal embarrassment to you. But, I mean, I am just saying that, in this senator's opinion, the American people are owed better by the FTC than what the evidence shows by my staff's being able to buy this with these kind of claims on the Internet; something that may be harmless, it may be dangerous, but it is unproven and ought not to be out there as modern-day snake oil.

Ms. HARRINGTON. Point well-taken, Senator.

Senator SMITH. After the early termination of the Women's Health Initiative study, the FDA issued a black box warning indicating that estrogens with or without progestin should be prescribed at the lowest effective doses for the shortest duration.

However, it is my understanding that when the FDA issued the guidance, there were no studies indicating at what dose women faced the lowest risk of serious side effects. It seems to me that the Federal Government is playing a guessing game with women's health, and I think they deserve better.

So, Dr. Rossouw and Dr. Galson, without studies indicating at precisely what dose women will see less risk of serious side effects, why did the FDA take such an extreme position?

Dr. GALSON. Well, let me make a few points.

The first is that, with any area where there is a lot of scientific information, the data available to physicians and patients changes month by month with more publications by Dr. Rossouw's group and others around the country. The challenge we have at FDA is interpreting this information, deciding which of that information warrants changing the instructions to patients and physicians.

At any one moment, when we are convening, when we get together at advisory committees, and we meet internally and we make a decision about how to change a label and change the instructions, we base it on the best information that we have available at that moment.

We are aware, as we were when we most recently changed the labeling, that there are many ongoing studies on hormone products. So we anticipate continuing to make changes in these instructions. But at the point which we put on those warnings, that was the best information we had.

We do know that the news is not all bad. There are some women, at some times in their life, depending on their symptoms, who may benefit from short courses of these hormones. It wouldn't be right for us to completely shut the door and say they are never indicated, never appropriate.

Senator SMITH. So that brings me to the obvious question: Should the FDA then require black box warnings for compounded products containing hormones?

Dr. GALSON. The issue there and, you know——

Senator SMITH. There are none now.

Dr. GALSON. We really share your concern about this. One of our major problems with compounded products, be they prescription compounded products or over-the-counter hormone products, is that they don't contain the same sort of comprehensive labeling that FDA-approved products have.

For example, the information available on the Web site for the product you mentioned—although I haven't looked at it personally, I can see it up there—and other products just doesn't match what we think the state of the science indicates patients and physicians should have.

So we share your concern about that.

Senator SMITH. Well, it needs to match.

It is my understanding that when asked by my staff for a full written accounting and summary of enforcement actions taken against compounding pharmacies in general, and bioidentical products in particular, the FDA proffered a mere three examples of enforcement activity.

Specifically, (1) was a 2001 limited survey of compounded drugs; (2) 16 warning letters issued in 2005; and (3) an assertion that the FDA may inspect a pharmacy on a for-cause basis.

Given that, by your own policy, compounded pharmaceutical products are unapproved new drugs subject to enforcement under the Food Drug and Cosmetic Act, why has the agency done so little to regulate this industry and to protect consumers from bad actors?

Dr. GALSON. As you know, there are tens of thousands of these pharmacies, and we have a lot of other compliance activities that are going on throughout the agency not related to compounded drugs. So, at any one moment, we have to balance the resources that we have available with the largest risks to public health.

We have taken regular action against compounded pharmacies. Sure, you can argue that we should do more. We have to, at any moment, balance what we can do with the information out there.

We do think it is important to continue to take these compliance actions, and we are going to do that.

Senator SMITH. Well, I know you are under a lot of pressure from a lot of different angles. I am just simply aware in the press and best-selling books out there now, a lot of things are being pushed right now that really do demand, I believe, a more vigorous response from the FDA.

I am very troubled by the thousands of Web sites touting bioidentical products as natural and safe, in light of the fact that there is no regulation regarding the term "bioidentical." What precisely that term means, I don't know. I don't know that there is a definition out there. I think there needs to be one. Medical doctors have one definition, yet marketers use the term in a myriad of ways.

The FDA has indicated to my staff that, "The term 'bioidentical' has no defined meaning in any medical or conventional dictionary and is not accepted by the agency as a substantiated labeling

claim." Therefore, since the term "bioidentical" has become commonplace in the industry, shouldn't the FDA develop guidance with respect to the term that could be used both on over-the-counter and prescription products? Is there any effort to do that, to define this?

Dr. GALSON. The term, you are correct, does not mean anything to us.

I was just talking to Dr. Rossouw before the hearing got started about the fact that in my remarks I was very careful to say "so-called bioidentical" hormones. Dr. Rossouw didn't mention the term at all.

We hate this term. We don't think it means anything. We are not sure that it should mean anything.

It implies, by the very words "identical" and "bio," that it is something that patients should like and should use. We just don't think—we think these are drugs, and they deserve warning labels like the drugs that we approve.

Senator SMITH. So you have a problem with all the Web sites out there using this term that holds out medical promise and hope?

Dr. GALSON. I certainly do.

Senator SMITH. I certainly hope that the FDA will define the term "bioidentical" or at least repudiate it; and that then the FTC will do its part in getting these Web sites down. It just shouldn't be happening in this day and age.

Do you have any comment about the term "bioidentical," Dr. Rossouw?

Dr. ROSSOUW. Except to agree with my colleague. It is not a medical term. It is a marketing term.

Senator SMITH. Yes. That is the same kind of marketing they used to do in the 19th century.

Let me thank you all. This is, I am sure, not pleasant for you, but it is important to the American people that we highlight what is out there and that they not just be told, "Buyer beware," because we are dealing with people's health here.

So, please regard this hearing as done in the spirit of trying to get information out there so that people aren't just told to beware, that they actually have the opportunity to buy products that have health benefits to them and are not scammed by things that may actually be harmful to their health.

So, with that, I thank you for your attendance.

We will call up our next panel.

On our second panel, we are pleased to welcome medical experts and industry representatives to further outline these issues.

Our first witness will be Dr. JoAnn Manson, who is the Chief of preventive medicine at Brigham and Women's Hospital in Boston. She is also the Elizabeth F. Brigham professor of Women's Health and professor of Medicine at Harvard Medical School. Dr. Manson is a recognized medical expert in hormone therapy and has published a substantial body of work on the topic; and has recently served as a medical consultant for the "Today" show.

That is why I recognize you.

She will be followed by Dr. Leonard Wartofsky, who is the chairman of the Washington Hospital Center's Department of Medicine and is the president of the Endocrine Society, an internationally recognized association of 11,000 members from over 80 countries.

He will be followed by Dr. Loyd Allen. He is here representing the International Academy of Compounding Pharmacists. Dr. Allen also serves as the editor-in-chief of the International Journal of Pharmaceutical Compounding, among several other pharmacy-related posts.

Our final witness will be T.S. Wiley, who is a researcher, published author, creator of the Wiley Protocol, a bioidentical hormone regimen that she has developed for women seeking an alternative to conventional hormone therapy.

Dr. Manson, we will start with you.

STATEMENT OF JOANN MANSON, CHIEF OF PREVENTIVE MEDICINE, BRIGHAM AND WOMEN'S HOSPITAL, PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MA

Dr. MANSON. Thank you.

Ranking Member Senator Smith, thank you for the opportunity to speak to you today about bioidentical and custom-compounded hormones.

Because of the risks of conventional hormone therapy that you have heard about, identified by the Women's Health Initiative, including stroke, venous blood clots, breast cancer, and other health problems, there has been a growing interest in bioidentical and custom-compounded hormones as potentially safer alternatives.

The key question is: Are these products indeed safer or more effective than conventional hormone therapy, as proponents of these treatments claim?

Unfortunately, there is little evidence, as you have heard, to support this assertion. Moreover, women are not getting accurate and unbiased information to help them make an informed choice about the use of these hormones.

In addition, what is the rationale for a different policy about FDA regulation of bioidentical hormones when they are manufactured en masse and sold by retail pharmacies, where there is full FDA regulation, and not for bioidentical products that are custom-compounded by pharmacists? There is no clear rationale for a difference in regulation.

Advocates of bioidentical hormones, particularly custom-compounded ones, assert that these products are more effective at relieving menopause symptoms, have fewer side effects, and offer a better balance of long-term health benefits and risks than other hormone options.

However, the truth is, we simply don't know that these claims are valid. Large-scale, scientifically rigorous studies of bioidentical hormones have not been conducted.

Until we have solid data to indicate otherwise, virtually all medical authorities and professional societies agree that a conservative and prudent approach is to assume that all hormone formulations confer a similar balance of benefits and risks.

The following are specific concerns about custom-compounded hormones due to their lack of FDA oversight.

As you have heard, quality control is problematic. Preparation methods can differ from one pharmacy or pharmacist to another, so patients may not receive consistent amounts of hormones. In addition, inactive ingredients vary, and contaminants may be present.

Such quality control problems have been demonstrated by a government study in 2001. The government purchased and tested 29 products, including hormone preparations from 12 compounding pharmacies, and found that 34 percent of the samples failed one or more standard quality tests. Ninety percent of the failing samples contained less of the active ingredient than advertised.

In contrast to this 34 percent failure rate, the failure rate for FDA-approved drug therapies was less than 2 percent.

Another problem is that the value of saliva or blood testing of hormone levels to guide dose adjustments for these hormones is unsubstantiated.

Before custom-compounded hormones are prescribed, a saliva or blood test is often performed to measure a woman's natural hormone levels. The belief is that the test can guide the dose of hormones to prescribe.

However, the value of these tests is highly questionable and not supported by scientific evidence. Hormone levels fluctuate throughout the day, as well as from day to day, and these levels are not clearly linked to severity of menopausal symptoms or to the dose of hormones needed to control symptoms.

Expense and cost are also important issues. Many custom-compounded hormone products, as well as the associated blood or saliva testing, which must be done every few weeks or months until hormones are "balanced," are expensive and not covered by health insurance.

Some women's out-of-pocket costs, which can add up to thousands of dollars per year, tend to be higher with custom-compounded hormones than with bioidentical hormones or other hormones that are covered by health insurance—the traditional hormone therapy.

Consumers lack reliable product information and can fall prey to misleading advertising claims. Unlike retail pharmacy prescriptions, compounded products are not required to have a warning package insert with information about benefits and risks, and as you have heard, do not have a black-box warning and are subject to fewer checks on their advertising claims.

Some women may request bioidentical or custom-compounded hormones because they are misled by the following claims often made by their proponents.

One claim is that bioidenticals are not drugs. This is false. Bioidentical products are indeed drugs that provide hormone doses that are not usually experienced by women after menopause. As a result, they cannot be considered natural. These are not natural levels that women experience during the post-menopause.

It is important to consider that even a woman's natural estrogen can confer some health risks, as Dr. Rossouw mentioned. For example, women with higher natural estrogen levels after menopause, as seen with obesity, have a higher risk of breast cancer. Also, women's natural estrogen levels climb during pregnancy. This rise is linked to a higher risk of blood clots in the legs and lungs.

So the assertion that bioidentical estrogen has no risks because it is natural is untrue. The assertion that bioidentical estrogen confers less risk than synthetic forms of estrogen is unproven.

How can we determine whether bioidentical hormones are safe and effective? By conducting well-designed clinical trials which are scientifically rigorous to gauge the safety and effectiveness of these medications.

Unfortunately, for many bioidenticals, and for custom-compounded bioidenticals specifically, such trials have not been done. Without clinical trials, we simply don't know how safe or effective these drugs are.

Trials of a relatively small size and short duration could prove or disprove whether such hormones are effective in treating hot flashes, night sweats or other symptoms of menopause. These trials would have to be placebo-controlled.

However, larger-scale trials, even more than 25,000 women—the scale of the Women's Health Initiative, the both hormone trials—would be needed to substantiate or refute the claim that bioidentical or custom-compounded products are safer than conventional hormone therapy in terms of clinical outcomes such as heart attack, stroke, or venous blood clots, or breast cancer.

Mid-size studies can be done to look at intermediate end-points such as blood markers of clotting or inflammation and also non-invasive imaging of atherosclerosis. Some trials, such as the Kronos Early Estrogen Prevention Study and the ELITE Trial, are in progress looking at those issues. But they cannot address whether there is a difference in clinical outcomes such as cardiovascular events or breast cancer.

In summary, the prudent policy, in the absence of scientific evidence to the contrary, is to assume that all post-menopausal hormone formulations confer similar risks and benefits. However, many proponents of custom-compounded bioidentical hormones are making unsubstantiated claims of superiority that run directly counter to this policy.

Given this pervasive and misleading marketing, I have a deep concern that women, and even some of their doctors, are not getting the objective information necessary to make well-informed choices about hormone therapy.

There is an urgent need for increased regulatory oversight of custom-compounded bioidentical hormones as is done for traditional hormone therapy, including assessment of purity and dosage consistency, the inclusion of uniform patient information about risks and benefits in the packaging of these products, mandatory reporting by drug manufacturers and compounding pharmacies of adverse events related to these hormones, and clinical trials testing the safety and efficacy of these products.

Thank you very much. I would be happy to answer any questions.

[The prepared statement of Dr. Manson follows:]

Statement Before the U.S. Senate Special Committee on Aging, Washington, D.C., April 19, 2007

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Mr. Chairman, ranking member Senator Smith, and members of the Committee, thank you for the opportunity to comment on bioidentical and custom-compounded hormones. Due to the risks of conventional hormone therapy identified by the Women's Health Initiative and other studies, there has been growing interest in bioidentical and custom-compounded hormones as potentially safer alternatives. The key question is: are these products indeed safer or more effective than conventional hormone therapy, as many proponents of these treatments claim? Unfortunately, there is little evidence to support this assertion. Moreover, women are not receiving accurate and unbiased information to help them make an informed choice about the use of these hormones and there are concerns about the relative lack of regulation and oversight of this industry. I am grateful that the Committee is considering efforts to address these issues that are so important to women's health.

The landscape of hormone therapy in the post-Women's Health Initiative (WHI) era

The hormone therapy component of the WHI consisted of two randomized clinical trials in postmenopausal women who were aged 50-79 years (average age, 63 years) and generally healthy at baseline. The trials were designed to test the effect of estrogen plus progestin (for women with a uterus) or estrogen alone (for women with hysterectomy) on coronary heart disease (CHD), stroke, hip fracture, breast and colorectal cancer, and other health outcomes, and whether the possible benefits would outweigh possible risks. Taken in aggregate, data from observational studies had suggested benefits for osteoporotic fractures, heart disease, and colorectal cancer and risks for breast cancer, stroke, and blood clots in the legs or lungs[1]. Until the WHI, however, no large-scale clinical trial in healthy women had been conducted to confirm or refute these observational findings.

The WHI results not only disprove the theory that supplemental estrogen confers heart protection in women who are on average more than a decade past menopause onset but also indicate that this hormone, when taken in combination with a progestin, may actually increase the risk of coronary heart disease in such women.[2-4] Moreover, the findings suggest that the overall health risks associated with hormone therapy tend to outweigh the benefits in women distant from the onset of menopause.[2, 5] However, because few participants were within 5 years of menopause, the WHI trials could not conclusively determine the balance of benefits and risks in recently menopausal women. Nonetheless, the WHI results are critically important because the study halted what was becoming an increasingly common clinical practice of initiating hormone therapy in older women and those at elevated risk of CHD.

The WHI results have led to revisions of clinical guidelines for hormone therapy use. The U.S. Preventive Services Task Force,[6] American College of Obstetricians and Gynecologists,[7] American Heart Association,[8] Canadian Task Force on Preventive Health Care,[9] and the North American Menopause Society[10] now recommend against the use of estrogen with or without a progestogen to prevent CHD and other chronic diseases. Hot flashes and night sweats that are severe or frequent enough to disrupt sleep or quality of life are currently the only compelling indications for hormone therapy. The WHI results suggest that key factors to consider in deciding whether to initiate hormone therapy in a woman with these symptoms (assuming she has a personal preference for such therapy) are where she is in the menopausal transition and whether she is in good cardiovascular health. A younger, recently postmenopausal woman—one whose final menstrual period was 5 or fewer years ago—at low baseline risk of CHD, stroke, or blood clots is a reasonable candidate for hormone therapy. Conversely, an older woman many years past menopause, who is at higher risk of these conditions, is not. Use of hormone therapy is best limited to 2 to 3 years and generally no more than 5 years, as breast cancer risk increases the longer hormones, particularly estrogen plus progestin, are used.

The WHI trials will undoubtedly remain the "gold standard" of evidence on the health effects of hormone therapy for years to come, but their limitations must be acknowledged. Although the WHI provided clear data on the benefits and risks of hormone therapy in women aged 60 and older and ended the increasingly common practice of starting hormones in these women for the express purpose of preventing CHD, the overall findings likely overstate the risks for healthy women aged 40 to 59 who begin hormone therapy closer to menopause onset. Moreover, only one type and dose of oral estrogen and progestogen was tested, so the results may not apply to other formulations, doses, and routes of administration. There are few or no trials on alternative hormone medications, particularly custom-compounded "bioidentical" hormones. The lack of data on these agents, however, should not be construed to mean that they are safer or more effective at preventing chronic disease; more research is needed to answer these questions. Until such data are available, the prudent strategy—and one endorsed by all major medical organizations in the U.S.—is to assume all formulations have a similar safety and risk profile.

Follow-up studies that have been conducted to help clear up confusion after the WHI

The divergence between earlier observational studies, which suggested that hormone therapy might protect against heart disease, and the WHI trials, which did not, raised concern that the coronary benefit seen in observational studies might simply reflect the fact that women who choose to use hormone therapy tend to be healthier, have greater access to medical care, and embrace health-promoting habits (e.g., eating a nutritious diet and exercising regularly) more readily than women who do not choose to use hormones. Nevertheless, the concordance between observational studies and the WHI for other endpoints, particularly stroke, which have lifestyle determinants similar to those for CHD, suggest that these biases are not the primary explanation for the discrepant CHD results.[11, 12] Instead, a closer examination of available data suggests that the timing of initiation of hormone therapy in relation to menopause onset may affect the association between such therapy and risk of CHD. Hormone users in observational studies typically start therapy within 2-3 years after menopause onset, which occurs on average at age 51

in the U.S., whereas WHI participants were assigned to hormones more than a decade later. These older women likely had less healthy arteries than their younger counterparts.

Small trials conducted prior to the WHI had shown that estrogen therapy has both beneficial and harmful effects on blood and other markers of cardiovascular health. In light of findings from the WHI, as well as findings from clinical trials of hormone therapy among women with preexisting heart disease (e.g., the Heart and Estrogen/progestin Study [HERS][13, 14]), scientists have hypothesized that the clot- and inflammation-promoting effects of supplemental estrogen may be more problematic among women with advanced atherosclerosis who initiate hormone therapy well after the menopausal transition, whereas women with less arterial damage who start hormone therapy early in menopause may benefit most from estrogen's favorable effect on cholesterol levels and blood vessel elasticity.[11, 15]

Animal experiments support the idea that the coronary effect of hormone therapy depends on the initial health of the arteries. In one series of studies, investigators induced menopause in monkeys by surgically removing their ovaries and then attempted to induce atherosclerosis by feeding them an "imprudent" diet high in fats.[16] Some of the monkeys were given hormone therapy immediately upon ovary removal and initiation of the imprudent diet. The remaining monkeys were given hormones only after a 2-year lag (the equivalent of 6 years in a woman) or were not given hormones at all. Compared with the monkeys that didn't get hormones, the monkeys that received the hormones early—and, presumably, before their arteries had advanced fatty deposits—had 70% less atherosclerosis, while the monkeys that didn't get hormones right away had no reduction in atherosclerosis.

The WHI findings have prompted reanalyses of data from existing observational studies and randomized clinical trials to examine whether timing of initiation of hormone therapy affects coronary and other outcomes. Investigators with the Nurses' Health Study, the largest and longest-running observational study of hormone therapy and CHD in the United States, who earlier reported that current use of hormone therapy was associated with an approximate 40% reduction in risk of CHD in the cohort as a whole,[17] recently found that the coronary benefit was largely limited to women who started hormone therapy within 4 years of menopause onset.[18] A 2006 analysis that pooled data from 22 smaller randomized trials with data from the WHI found that hormone therapy was associated with a 30 to 40% reduction in CHD risk in trials that enrolled predominantly younger participants (women under age 60 or within 10 years of menopause) but not in trials with predominantly older participants.[19]

The ongoing Early versus Late Intervention Trial with Estrogen (ELITE) is testing whether there are differential effects of hormone therapy on the development and progression of atherosclerosis according to the age at which therapy is initiated.[20]

It should be noted that the evidence for differential health effects of hormone therapy by age or time since menopause, though strong, is not yet conclusive. Nonetheless, even if differential health effects do not exist, the much lower absolute baseline risks of coronary and other events in younger or recently postmenopausal women means that these women experience much lower absolute excess risks associated with hormone therapy use as compared with their counterparts who are older or further past menopause.

Recent WHI findings assessing the role of a woman's age and time since menopause: what it means for the current approach to hormone therapy

To test the hypothesis that timing of initiation of hormone therapy may influence its benefit-risk profile, WHI investigators[21] recently conducted a combined analysis of the two hormone therapy trials of the WHI. We found that women who begin hormone therapy closer to the onset of menopause tend to have more favorable outcomes, in terms of cardiovascular disease and mortality, than women who begin treatment at older ages and when more distant from menopause. Specifically, women who were less than 10 years since menopause when randomized to hormone therapy had a 24% *reduced* risk of heart disease compared with those randomized to placebo, while women 10-19 years past menopause had a 10% *increased* risk and women 20 years or more past menopause had a 28% *increased* risk (p-value for trend=0.02). When examined by age group, hormone therapy had a neutral effect on risk of heart disease in women aged 50-59 and 60-69, but caused a 28% *increase* in risk among women aged 70-79. We also found that total mortality rates with hormone therapy appeared to be more favorable in younger women (a statistically significant 30% reduction in death rates), while older women had slightly higher mortality rates with hormone therapy than placebo. Overall, the findings suggest that timing of initiation does influence the benefit-to-risk profile of hormone therapy and provide some reassurance for recently menopausal women considering hormone therapy for treatment of menopausal symptoms. However, stroke risks were elevated with hormone therapy among women in all age groups. The results do not change the recommendation that hormone therapy should not be used for the express purpose of preventing cardiovascular disease in women, regardless of age.

Bioidentical or custom-compounded hormone therapy and the new "alternative" protocols

There is very limited research on the efficacy and safety of bioidentical hormone therapies overall and custom-compounded bioidentical hormone preparations in particular. Women may be misled into believing that various "protocols" or regimens are safer or more effective than they may actually be, and they may not be getting objective information and a balanced overview about side effects, long-term risks, and benefits. There is no rigorous scientific research on most, if not all, of these protocols with respect to safety and efficacy—i.e., they have not been tested in large-scale clinical trials with large numbers of women followed for long durations. The data that do exist are primarily anecdotal.

As mentioned above, due to the risks of conventional hormone therapy identified by recent randomized clinical trials, including stroke, venous blood clots, and breast cancer, there has been growing interest in bioidentical and custom-compounded hormones as potentially safer alternatives. The key question is: are these products indeed safer or more effective than conventional hormone therapy? Unfortunately, there is little evidence to support this notion. Moreover, women aren't getting accurate, unbiased information to help them make an informed choice about whether to use such hormones or not. Some consumer books have blurred the line

between science and hearsay and promulgatd protocols that may expose women to serious health dangers[22].

It is important to define and clarify the terminology, which has caused enormous confusion. Scientists and mainstream healthcare providers use the term "**bioidentical hormones**" to refer to medications that contain hormones that are an exact chemical match to those made naturally by our bodies. Women make three types of estrogen—estradiol, estrone, and estriol—as well as progesterone and other hormones. Thus, bioidentical hormones are medications that provide one or more of these hormones as the active ingredient. Bioidentical hormones are available with a doctor's prescription at commercial retail pharmacies in a range of standard doses. Commercially available bioidentical estradiol comes in several forms, including pills (Estrace & various generics), skin patches (Alora, Climara, Esclim, Vivelle, Estraderm), skin creams (EstroGel & Estrasorb), and various vaginal preparations (Estrace vaginal cream & Estring vaginal ring). Commercially available bioidentical progesterone can be purchased as a capsule (Prometrium, which has a peanut oil base) or a vaginal gel (Prochieve vaginal gel). Because they are manufactured en masse and sold by retail pharmacies, these bioidentical products are regulated by the FDA.

Many consumers and naturopaths use the term "bioidentical hormones" to refer exclusively to custom-mixed cocktails of these hormones, prepared according to an individualized prescription from a doctor by compounding pharmacies. A more precise term for these preparations is **"custom-compounded"** bioidentical hormones. Although hormone compounding has been popular in Europe for years, interest in the U.S. surged only after the WHI results shifted the pendulum away from traditional hormone therapy. There are no reliable estimates of how much of the U.S. prescription hormone market is serviced by compounders, but some compounding pharmacies have claimed that as many as 2 million U.S. women rely on customized hormone products.[23]

Advocates of bioidentical hormones—particularly custom-compounded ones—assert that these products are more effective at relieving menopause symptoms, have fewer side effects, and offer a better balance of long-term health benefits and risks than other hormone options. However, we simply don't know whether these claims are valid, because large-scale, scientifically rigorous studies of bioidentical hormones have not been conducted. Until we have solid data that indicate otherwise, virtually all medical authorities (e.g., the North American Menopause Society, the Endocrine Society, the American College of Obstetricians and Gynecologists, and others) agree that a conservative and prudent approach is to assume that all hormone formulations confer a roughly similar balance of benefits and risks.

It is true that custom-compounded hormones benefit women who for some reason cannot use a commercially available preparation. For example, a patient may be allergic to an ingredient, such as the peanut oil in Prometrium, or may require a specific dose or product mixture not produced by a pharmaceutical company, although this is uncommon given the large and increasing number of options offered by commercial manufacturers. However, there are also unique risks associated with custom-compounded products, as they are not under the oversight of the FDA:

Quality control is problematic. Preparation methods differ from one pharmacy (and pharmacist) to another, so patients may not receive consistent amounts of hormone. In addition, inactive ingredients vary, and contaminants may be present. In 2001, the government purchased and tested 29 products, including hormone preparations, from 12 compounding pharmacies and found that 34% of the samples failed one or more standard quality tests.[24] Additionally, 90% of the failing samples contained less of the active ingredient than advertised. In contrast [to the 34%], the testing failure rate for FDA-approved drug therapies is less than 2%.[25]

The value of saliva and blood testing is unproven. Before custom-compounded hormones are prescribed, a saliva or blood test is typically performed to measure a woman's natural hormone levels. The belief is that the test can determine whether a woman has the "right amount" or "right balance" of hormones and guide adjustment of hormone doses. However, the value of these saliva and blood tests is highly questionable, and there are little scientific data to support their use. Optimal estrogen and progesterone levels in blood or saliva have not been established for postmenopausal women. Hormone levels fluctuate throughout the day as well as from day to day, and these levels are not clearly linked to the presence or severity of menopausal symptoms, short-term side effects of hormone therapy (e.g., headaches), or, in most instances long-term health outcomes (e.g., heart attack).

Expense is an issue. Many custom-compounded hormone products, as well as the associated blood and saliva testing—which must be done every few weeks or months until hormones are "balanced"—are expensive and are not covered by health insurance. Lab tests cost roughly $100 to $400 per visit, while hormones cost approximately $30 to $100 per month.

Consumers lack reliable product information and can fall prey to misleading advertising claims. Unlike retail pharmacy prescriptions, compounded products are not required to have a package insert that contains information about their benefits and risks, do not have a "black box" warning about side effects, and are subject to fewer checks on advertising claims. Testimonials by patients—including books by celebrities—are commonly used to endorse custom-compounded products, with little or no mention of the known risks of supplemental hormones. Some women may request bioidentical or custom-compounded hormones because they are misled by the following claims often made by their proponents:

- ***"Bioidenticals are not drugs."*** This is false—bioidentical products are indeed drugs that provide hormone doses that are not usually experienced by women after menopause.
- ***"Bioidenticals are 'natural' and are therefore safe."*** In reality, bioidentical products produce hormone levels that are not "natural" for women to experience after menopause. Moreover, "natural" is not necessarily safe. Bioidentical estrogen has the same chemical structure as a woman's natural estrogen, but even a woman's natural estrogen confers some health risks. For example, women with higher natural estrogen levels after menopause have a higher risk of breast cancer. Also, women's natural estrogen levels climb during pregnancy and this rise is linked to a higher risk of blood clots in the legs and lungs. The assertion that bioidentical estrogen has no risks is patently untrue, and the assertion that bioidentical estrogen confers less risk than synthetic forms of estrogen is unproven.

How can we determine whether bioidentical hormones are safe and effective or not? By conducting well-designed clinical trials, which are the scientifically rigorous way to gauge the safety and effectiveness of medications. Unfortunately, for many bioidenticals and for custom-compounded bioidenticals specifically, such trials have not been done. Without clinical trials, the best and most truthful thing we can say is that we simply don't know how safe or effective these drugs are.

As mentioned above, trials of relatively small size and short duration should suffice to prove or disprove whether such hormones are effective at treating hot flashes, night sweats, or other symptoms of menopause. However, a research effort on the scale of the WHI—which followed 27,000 women for 5 to 7 years to determine the risks and benefits of conventional hormones—will be needed to substantiate or refute the claim that bioidentical—and custom-compounded—products are safer than conventional hormone therapy or that they offer an acceptable balance of long-term health benefits and risks (in terms of clinical outcomes such as heart attacks, strokes, venous blood clots, breast cancer, and fractures).

Available evidence does suggest that patch estrogen may have an advantage over pill estrogen in that it may be less likely to cause blood clots. There are also data to suggest that bioidentical progesterone may have an advantage over synthetic progesterone in that it may be less likely to interfere with the ability of supplemental estrogen to boost HDL (good) cholesterol levels and to dilate arteries (improve blood flow). But no large-scale trials have been undertaken to provide head-to-head comparisons of bioidentical versus traditional hormones in terms of their effects on hard clinical outcomes such as those mentioned above.

Studies that are needed to shed light on bioidenticals and their potential place in menopause management

To shed light on bioidenticals, we need to conduct well-designed randomized clinical trials, which are the scientifically rigorous way to gauge the safety and effectiveness of medications. As noted above, for many bioidenticals and for all custom-compounded bioidenticals, such trials have not been done. Without clinical trials, we simply don't know how safe or effective these drugs are.

Trials of relatively small size and short duration should suffice to prove or disprove whether such hormones are effective at treating hot flashes, night sweats, or other symptoms of menopause. However, a research effort on the scale of the WHI—which followed 27,000 women for 5 to 7 years to determine the risks and benefits of conventional hormones—will be needed to substantiate or refute the claim that bioidentical—and custom-compounded—products are safe (i.e., offer an acceptable balance of long-term health benefits and risks).

There is evidence suggesting that patch estrogen (available only in bioidentical form) may have an advantage over pill estrogen (available in both bioidentical and conventional forms) in that it may be less likely to cause blood clots.[26] There are also data to suggest that bioidentical progesterone may have an advantage over synthetic progesterone in that it may be less likely to interfere with the ability of supplemental estrogen to boost HDL (good) cholesterol levels and to

dilate arteries and improve blood flow.[27] The ongoing Kronos Early Estrogen Prevention Study (KEEPS) is a clinical trial comparing the effect of conventional vs. bioidentical hormones (oral vs transdermal) on the development and progression of atherosclerosis, cognitive function, and quality-of-life outcomes in recently menopausal women.[28] But no large-scale trials have been undertaken—or are currently planned—to provide a head-to-head comparison of bioidentical versus traditional hormones in terms of their effects on hard clinical outcomes such as heart attack, stroke, or breast cancer.

Dangers with over-the-counter products

Over-the-counter products that contain bioidentical hormones may carry real health risks and should not be used without supervision by a qualified clinician. Among such products are skin creams that contain bioidentical progesterone. Doctors routinely prescribe progesterone for women who take estrogen to protect against possible overstimulation of the uterine lining, which could lead to uterine cancer. Existing data on progesterone skin creams are not consistent as to how much progesterone is absorbed; moreover, such preparations are often not standardized. Thus, it's hard to know exactly how much progesterone one may be getting. Progesterone skin creams may not adequately protect the uterine lining and should not be used for this purpose.

Some naturopaths and medical authors (most notably the late Dr. John Lee, whose hormone books have been recent best-sellers) advocate using progesterone cream alone, without estrogen, to relieve hot flashes and other menopausal symptoms. However, there has been little research on whether it's effective in doing so, and, more importantly, no research on potential long-term risks of this approach. I, along with the majority of doctors, don't recommend it. Of concern, such products are widely available without a doctor's prescription over the Internet. Although classified as a cosmetic by the FDA, progesterone skin creams may produce similar exposure levels in the body as prescription oral progesterone (research is limited and contradictory on this point) and may confer similar long-term health risks, although no rigorous research has been conducted on this subject. It's a dangerous practice to use this product, or any hormone product, without a doctor's supervision

An over-the-counter product marketed as "wild yam cream" contains an inactive precursor of progesterone that cannot be metabolized by the human body. Given that it contains no active hormones, wild yam cream is not likely to cause harm—but it won't help with menopause symptoms and it can be expensive.

Summary

The prudent policy recommended by all major medical organizations is, in the absence of scientific evidence from well-designed studies comparing various forms of hormone therapy, is to operate on the assumption that all postmenopausal hormone formulations confer similar risks and benefits. However, many proponents of custom-compounded bioidentical hormones are making unsubstantiated claims of superiority that run directly counter to this policy. Given this pervasive and misleading marketing, I have a deep concern that women—and even some of their

doctors—are not getting the objective information necessary to make well-informed choices about hormone therapy. There is an urgent need for (a) increased regulatory oversight of custom-compounded bioidentical hormones, as provided for traditional hormone therapy, including assessment of purity and dosage consistency; (b) inclusion of uniform patient information about risks and benefits in the packaging of these products; (c) mandatory reporting by drug manufacturers and compounding pharmacies of adverse events related to these hormones; and (d) clinical trials testing the safety and efficacy of these products. Thank you very much for your consideration of these issues and I'd be pleased to answer any questions.

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Senator SMITH. Dr. Manson, I wonder if you would agree with the conclusion of some on the first panel that "bioidentical" is a marketing term and it has no medical definition?

Dr. MANSON. I would agree. I think that there is a great difference between the way the term "bioidentical" is used by scientists and the way it is being used by alternative medicine practitioners and in the mass media.

The scientists use it for hormones that are chemically identical to those produced naturally by the body.

There are three types of natural estrogen that women make. In addition, there is progesterone, as well as testosterone, and other hormones. Many of these hormones, as we have discussed, these bioidentical hormones, are available through FDA-regulated medications that are produced en masse and available in retail pharmacies.

These custom-compounded hormones, often we don't even know what is in them. They do not have any clear advantage over the bioidentical hormones that include the estradiol or progesterone that are available through a retail pharmacy.

Senator SMITH. Do you know of any head-to-head studies between traditional hormone therapy versus bioidentical hormone therapy?

Dr. MANSON. That is an interesting question. The only current trial is the Kronos Early Estrogen Prevention Study, and it is ongoing. The results are not yet available. It is a head-to-head comparison of oral conjugated equine estrogens, which were tested in the Women's Health Initiative, but a lower dose is being tested in the Kronos trial, and a transdermal estradiol patch.

Senator SMITH. Who is doing that test?

Dr. MANSON. It is being done by the Kronos Longevity Research Institute, a private foundation. It is not a drug company-sponsored trial.

Senator SMITH. Do you think the Federal Government ought to take the lead in it, or participate in it, or——

Dr. MANSON. I think it would be helpful for the Federal Government to get involved in providing some support so that women can get answers to these questions. So it will be comparing the oral conjugated estrogens in low dose with the transdermal bioidentical form of estradiol.

Senator SMITH. You spoke in your testimony about the role of the physician in prescribing bioidentical hormones. Do they have enough information to prescribe them? Are they doing that?

Dr. MANSON. Yes. Some of them are.

I do not think that, with how busy physicians are these days and all of the other issues that they have to attend to, that most have really gotten the information that they need about what bioidentical hormones are, what custom-compounded hormones are—all of these issues and concerns that we have been discussing this morning—and that they really have a full understanding of what they are prescribing for their patients because of just a lack of available information.

Senator SMITH. I mean, the obvious conclusion is some of them may unwittingly be practicing some form of quackery by getting into this area.

Dr. MANSON. Well, I think that more information is necessary. I think that some physicians consider that they have adequate information.

But given the paucity of information out there, it is hard to understand how a rationale can be given for prescribing these hormones over the retail pharmacy-available hormones, unless there is a specific reason, such as a patient is allergic to peanuts and there is peanut oil in the natural micronized progesterone that is available in retail pharmacies.

Senator SMITH. Maybe a message of this hearing ought to be "Doctors beware."

Dr. MANSON. Absolutely.

Senator SMITH. Thank you, Dr. Manson.

Dr. Wartofsky, please.

STATEMENT OF LEONARD WARTOFSKY, PRESIDENT, THE ENDOCRINE SOCIETY, CHEVY CHASE, MD

Dr. WARTOFSKY. Senator Smith, thank you for the opportunity to testify today. My name is Leonard Wartofsky. I am chairman, Department of Medicine at the Washington Hospital Center, and Professor of Medicine at Georgetown University.

But today I am here as President of the Endocrine Society, the world's largest professional organization of endocrinologists, representing over 14,000 members.

The Society is deeply concerned about the safety of these so-called bioidentical hormones and believes the Federal Government should increase regulatory oversight of these compounds.

As you mentioned in your opening comments, Senator, bioidentical hormones have been touted inaccurately, by high-profile individuals with no medical training, as being safer and more effective than traditional hormone therapies.

You have raised the question of the definition of "bioidentical." As Dr. Manson said, scientists describe compounds as bioidentical that are identical to similar compounds produced naturally in the body.

We do not oppose the use or prescribing of FDA-approved bioidentical hormones, which have been available to the public for years. Rather, our concern is with custom-compounded bioidentical hormones.

The WHI study uncovered risks to women taking hormone replacement, as we heard this morning. We caution physicians and patients alike against the unfounded presumption that bioidenticals would be any safer.

In fact, no study as comprehensive as the WHI has assessed bioidentical hormones. Until authoritative clinical trials of bioidentical hormones are conducted, patient safety is best assured by assuming these hormones carry the same benefits and the same risks as those studied in the WHI.

Claims about safety and efficacy come from the belief that compounded hormones are precisely and individually custom-formulated. While theoretically appealing, such customization is difficult, if not impossible, to achieve.

Perhaps most alarming, compounded preparations, as you again mentioned this morning, are not required to have the black-box ad-

visory warning, as required for FDA-approved hormones. This is a serious concern for women and their doctors.

Compounding pharmacies are not required to adhere to the strict manufacturing processes governing FDA-monitored facilities, raising concerns about purity, potency and quality.

In one FDA-conducted post-market survey, 4 out of 11 compounded hormones failed tests for potency and/or uniformity.

Our concerns are shared by the broader medical community, including multiple other professional medical organizations. The AMA recently adopted a policy in support of our society's positions.

In conclusion, the society supports legislative action to standardize regulation of compounded hormones to include requirements for: (1) surveys for purity and potency; (2) mandatory reporting of adverse events; (3) a registry of these events; (4) inclusion of uniform patient information in the packaging; and finally and (5) limits on the use of this term, "bioidentical hormones." The fact is that scientific evidence is lacking at this time to either negate or support claims that bioidentical hormones are safer and more effective than other commonly prescribed hormones. Until conclusions are based on science, the Federal Government must ensure patients receive safe and effective drugs with accurate information.

That concludes my personal remarks, Senator. I would be happy to answer any questions.

[The prepared statement of Dr. Wartofsky follows:]

Statement of Leonard Wartofsky, M.D.
On Behalf of The Endocrine Society
Before the Senate Special Committee on Aging

April 19, 2007

Mr. Chairman, I would like to thank you, as well as the distinguished Ranking Member, Senator Smith, and the members of the committee, for the opportunity to testify today. My name is Leonard Wartofsky. I am the Chairman of the Department of Medicine at the Washington Hospital Center. I previously served as Director of the Endocrinology Division and the Endocrinology Fellowship Training Program, and Chief of the Department of Medicine and Program Director of the Internal Medicine Residency at Walter Reed Army Medical Center. I am an elected a Master of the American College of Physicians, Professor of Medicine at Georgetown University School of Medicine and Professor of Medicine and Physiology at the Uniformed Services University of Health Sciences. In my professional capacity as a physician, I treat patients suffering from a variety of endocrine disorders, such as thyroid disease, pituitary disease, diabetes, and obesity.

I am here today, however, as President of The Endocrine Society, the world's largest and most active professional organization of endocrinologists representing more than 14,000 members worldwide. Our organization is dedicated to promoting excellence in research, education, and clinical practice in the field of endocrinology. Appropriate clinical use of hormone therapy of all kinds falls under the purview of endocrinology and the Endocrine Society. My testimony will address The Endocrine Society's concerns regarding the compounding of what are commonly known as "bioidentical hormones." Specifically, The Endocrine Society believes it is critical that the federal government increase the regulatory oversight of bioidentical hormones, which have been inaccurately touted as safer and more effective than traditional hormone therapies.

Claims such as these, which are propagated by the popular media, are leading women to request bioidentical hormones from their doctors. As the leading experts in hormone treatments, endocrinologists are constantly approached by patients who are convinced that bioidentical

hormone therapy will cure their ills without risk of side effects such as those reported in the Womens Health Initiative (WHI). Despite their expertise, our doctors often find it extremely difficult to reverse the misinformation held by their patients who hope to find relief of their symptoms without the adverse effects reported in the WHI Study.

Initial analysis of The Women's Health Initiative—a large, long-term, prospective study of menopausal and post-menopausal women taking traditional hormone therapy for a period of several years—has raised concerns among some patients and physicians regarding long-term use of hormone replacement therapy. The study was cut short due to evidence of increased risk of cardiovascular disease in women taking estrogen or a combination hormone replacement therapy, and increased risk of breast cancer in women taking combination hormone therapy. Although further analysis of this study shows that the risks vary by age cohort and at what age hormone therapy began, the recent reports of these findings appeared too late to stop women from searching for alternative methods to treat the symptoms of menopause. This has created an environment for the proliferation in the lay media of the scientifically unproven idea that "bioidentical hormones" are somehow safer and more effective than traditional hormone therapies.

It is important at this point to identify some confusing aspects of this topic and to clarify definitions. Much of the public demand for "bioidentical hormone" therapy has arisen as a result of coverage in the media and popular press that encourages women to aggressively seek out and utilize "bioidentical hormones" that are supposedly customized or individualized for a particular woman's needs. This is misleading in a number of ways. First, women are led to believe that the terms "bioidentical" and "customized" are interchangeable. In fact, the word "bioidentical" simply describes a compound that has exactly the same structure as one produced in the body.

Under this appropriate and precise definition, there are bioidentical hormones that exist as FDA-approved drugs that have been available to the public for years. While we do not oppose the use or prescribing of FDA-approved bioidentical hormones, we caution physicians and patients alike against the presumption that they are safer or more effective than those hormones studied

in the WHI. In fact, no study as comprehensive as the WHI has been performed to assess FDA-approved bioidentical hormones. Therefore, it is impossible to directly compare the safety and efficacy of bioidentical hormones with that of the drugs used in the WHI. In order to ensure patient safety, then, we must begin with the assumption that "bioidentical hormones" would perform similarly to their counterparts if tested in a similar study.

Second, women are led to believe that compounded hormones are all bioidentical and are provided in a dose and form that is precisely formulated for their bodies. In reality, compounding does not by default make a hormone bioidentical; non-bioidentical hormones can also be manipulated by compounding pharmacies. The purported customization, while perhaps theoretically logical, is very difficult, if not impossible, to achieve.

Some compounding pharmacies are taking things even further by directly marketing their products to the public. Clearly, such activities are outside the scope of compounding pharmacies, which are intended to serve the special needs of patients on an individual basis.

The overall result of the activities I've just described has been one of confusion regarding the definition of "bioidentical hormones."

A further effect of this confusion is that women have been led to believe that bioidentical hormones are more natural than those studied in the Women's Health Initiative. Given this perception, it is easy to understand why women are drawn to these medications. In truth, bioidentical hormones are produced in labs, just as many other drugs are. Furthermore, compounded hormone preparations are not required to include any black box warning that reflects the findings of the Women's Health Initiative, as is required for FDA-approved estrogens and progesterones, which may also be bioidentical. The lack of patient information in these formulations highlights the reason that the Society is here testifying before your committee today. We are concerned that patients are not receiving accurate information regarding the safety and efficacy of compounded hormones.

Because compounding pharmacies are regulated by state boards of pharmacy, they are not required to adhere to the strict manufacturing processes that govern FDA-monitored facilities. Nor are they required to follow the same rigorous testing process for either safety or efficacy that FDA requires for FDA-approved drugs. This raises questions regarding the purity, potency, and quality of compounded drugs, that reflects in turn upon their safety and efficacy. In fact, the FDA performed a post-market analysis of 29 product samples from 12 compounding pharmacies in 2001. This revealed that 34 percent failed one or more standard quality tests. In contrast, the testing failure rate for FDA-approved drugs is less than 2 percent. Nine of the ten failing products, four of which were compounded hormones, failed assays for potency, in that they contained less of the active ingredient than expected. These results raise great concern about the inconsistencies and unknown risks of compounded bioidentical hormones. Without proper oversight and control of these products, the public has no way of knowing precisely what they are getting or what effect the drugs will have.

These concerns, as well as the Endocrine Society's call for greater oversight of bioidentical hormones, are outlined in the Society's 2006 position statement on the topic. This policy is supported by many organizations that represent the interests of female patients, including the American College of Obstetricians and Gynecologists, which issued their own Committee Opinion in November 2005 on the use of bioidentical hormones, and by the North American Menopause Society, which endorses The Endocrine Society's 2006 position statement.

The broader medical community also shares the Society's views, as the position statement was the basis for an overwhelmingly supported new policy of the American Medical Association. This new policy calls for greater oversight of compounded bioidentical hormones, tracking of adverse events, and inclusion of uniform patient information with each prescription.

In summary, the Endocrine Society is concerned that patients are receiving potentially misleading information about the risks and benefits associated with "bioidentical hormones." The Society supports FDA regulation and oversight of all hormone therapies—including both traditional and bioidentical hormones—regardless of chemical structure or method of manufacture. However, legislative action must be taken in order to give the FDA the authority to regulate these hormone therapies. Regulations should include requirements for:

1. Surveys for purity and dosage accuracy;
2. Mandatory reporting by drug manufacturers or compounding pharmacies of all adverse events;
3. A registry of adverse events related to the use of hormone preparations, including those that come from compounding pharmacies;
4. Inclusion of uniform information for patients, such as warnings and precautions, in packaging of all hormone products, compounded or commercial; and
5. According to the AMA's policy, use of the term "bioidentical hormones" should be prohibited unless the preparation is approved by the FDA.

Scientific evidence is lacking at this time that either negates or supports the claims that bioidentical hormones are safer and more effective than those hormones commonly prescribed. This would require controlled studies directly comparing bioidentical hormones to other hormone treatments. Even though the WHI was halted more than four years ago, its results have not been adequately analyzed to draw conclusions for all treatment groups. It is likely to take years for the scientific community to definitively determine whether bioidentical hormones are indeed safer than hormones that are not naturally produced in the human body. Until such time as these conclusions are reached, the federal government must ensure that patients receive safe and effective drugs, and accurate information about drugs they are taking. We believe that a regulatory mechanism is the only way to ensure patient safety.

This concludes my prepared remarks. Thank you again, Mr. Chairman, for the opportunity to testify before you today. I would be pleased to answer any questions that you or other members of the committee may have.

Senator SMITH. Thank you, Doctor.

I am going to let Dr. Allen testify, and then I have a question for the both of you.

STATEMENT OF LOYD ALLEN, EDITOR-IN-CHIEF, INTERNATIONAL JOURNAL OF PHARMACEUTICAL COMPOUNDING, SUGAR LAND, TX

Dr. ALLEN. Thank you, Senator Smith. I appreciate and share your dedication to improving the health of Americans. I thank you for the opportunity to speak to you about my profession, pharmacy compounding, and the role that we play in preparing compounded hormone treatments.

In the way they are prescribed, prepared and regulated, compounded hormones are just like all other compounded medicines, so I will first address pharmacy compounding overall briefly.

Most of the time, when patients need pharmaceutical treatment, doctors prescribe mass-produced, off-the-shelf drugs. But for some patients, those drugs are inappropriate. When they are, doctors may prescribe compounded medications, which are then custom-compounded by licensed and trained compounding pharmacists.

Compounded medicines are most commonly prescribed for a number of reasons. Sometimes patients are allergic to the inactive ingredients that are in off-the-shelf products. Other patients require personalized dosage strengths or delivery forms. Also, many times pharmaceutical manufacturers discontinue drugs because they aren't profitable but patients still rely on them and can have doctors prescribe compounded versions of them.

Hospice care patients, cancer patients, dental patients, especially pediatric patients, HIV and AIDS patients, ophthalmology patients all tend to have individual medical needs and, thus, tend to rely on compounded medicines.

State boards of pharmacy, State medical boards, the Food and Drug Administration, the Federal Trade Commission, the Drug Enforcement Agency, and other Federal and State agencies each have some degree of oversight over pharmacy compounding. The United States Pharmacopeia and the Pharmacy Compounding Accreditation Board all play critical roles. Together, they have constructed a web of regulations and standards that protect patients.

State boards of pharmacy license pharmacists and pharmacies and enforce laws that cover the processes and equipment pharmacists use to prepare these medicines, including sterile medicines, recordkeeping, and labeling, among other aspects of pharmacy practice.

Since 1820, the United States Pharmacopeia has been the national standard-setting body for pharmaceuticals and pharmaceutical ingredients, and recognized by Congress as such. It, too, has strong enforceable standards for pharmacy compounding of both sterile and non-sterile medications. States are increasingly codifying USP standards.

The profession is also taking action. Most notably, the United States Pharmacopeia, American Pharmacists Association, National Community Pharmacists Association, National Boards of Pharmacy, and other associations have launched the Pharmacy Compounding Accreditation Board.

The FDA also regulates aspects of compounding, including the suppliers of the ingredients that pharmacists use to compound. FDA also has authority to inspect any pharmacy's facility, equipment and ingredients. Federal laws also prohibit the making of unsubstantiated claims of safety and efficacy.

A fundamental question is, what is the difference between compounded and manufactured medicines?

First, compounded medications are always prepared pursuant to a doctor's prescription. Second, compounded medicines are retail only, sold directly to the patient.

Third, they are not copies of commercially available drugs. They are significantly different, as determined by the prescriber, whereas manufactured medicines are produced well in advance of any prescription and distributed at wholesale.

So how does this relate to hormone therapy? As I said, like compounded medications overall, by definition compounded hormones are always prescribed by doctors, prepared pursuant to those prescriptions, and dispensed directly to patients at retail.

Compounded hormones meet the needs of patients that are otherwise unmet by manufactured hormone products. For many patients, these products are effective, but for some, they are not. That may be because the manufactured drugs simply don't relieve the symptoms of menopause. It may also be because doctors determine that their patients need a lower dose than what is available commercially. The Women's Health Initiative recommended that women in search of relief from menopause symptoms take the lowest effective dose.

Doctors may find that some patients respond better to different delivery forms or drug combinations. Also, some drugs are made with peanut oil, and patients allergic to peanut oil may need the active ingredient to be compounded without it.

Each and every time, though, that doctors prescribe compounded hormones, they do it because they determine that their patients have needs for medications that are significantly different from what is manufactured.

Compounded hormones, like compounded medicines overall, are regulated by State boards of pharmacy. The U.S. Pharmacopeia and Pharmacy Compounding Accreditation Board set standards for their preparation. FDA regulates the suppliers of the ingredients that pharmacists use to compound these medicines. the FDA and the Federal Trade Commission regulate the marketing practices of pharmacies.

In conclusion, millions of women have been prescribed manufactured hormone products. Many of them have found relief from the torturous symptoms of menopause. Some have not and, instead, have been prescribed compounded hormones by their physicians, and they have found relief.

I would respectfully urge the members of this committee, and Congress overall, to consider the impact of any new policies that they would have on them.

Thank you.

[The prepared statement of Dr. Allen follows:]

Statement of Loyd V. Allen, Jr., Ph.D., R.Ph.
Editor-in-Chief, *International Journal of Pharmaceutical Compounding*
Before the U.S. Senate Special Committee on Aging
Washington, DC
April 19, 2007

Pharmacy compounding is the preparation of a customized medicine that has been prescribed by a doctor and is prepared by a state-licensed pharmacist. It has been recognized by the Food and Drug Administration (FDA), the U.S. Supreme Court, Congress and virtually every major health professional organization as a vital part of healthcare.

Millions of Americans have unique health needs that off-the-shelf prescription medicines cannot meet. For many of them a customized, compounded medication prescribed by licensed physicians or veterinarians and mixed by trained, licensed compounding pharmacists are the only way to better health. If customized medicines were not available, some of our most at-risk patients would needlessly suffer and some would die.

Compounded medicines can only be prescribed by physicians, veterinarians and other licensed health professionals as allowed under state law. They alone can assess their patients' conditions and determine when a compounded medicine is the most effective treatment. The basis of the profession of pharmacy has always been the triad – the patient-physician-pharmacist relationship. Through this relationship, patient needs are determined by a physician, who chooses an appropriate treatment regimen. Because every patient is different and has different needs, customized, compounded medications are a vital part of quality medical care.

Patients Who Rely on Compounded Medicines

Examples of those who rely on compounded medicines include:

- Infants and children: Compounding pharmacists can transform medicines from hard-to-swallow pills intended for adults into syrups, elixirs, suspensions, and emulsions for children, at the request of physicians. Flavors offered by compounding pharmacists can make drugs more palatable to children. In addition, premature infants often rely on lifesaving and life-sustaining drugs made only in compounding pharmacies.

- Hospital patients: Many, if not most, of the lifesaving intravenous drugs given in hospitals and clinics are compounded. Because hospital patients are often on multiple medications, compounding them into one treatment saves the hospital personnel time and the patient multiple injections or administrations.

- Cancer patients: Cancer treatment often involves special mixtures of cancer drugs that are compounded pursuant to a doctor's prescription. Pharmacists can combine multiple drugs into one treatment, leading to shorter administration times for cancer patients.

- Senior citizens: Elderly patients often have difficulty with traditional dosage forms, such as pills taken orally. Compounding pharmacists create alternate methods of delivery, like transdermal gels, to make it easier for the elderly to take their medicine.

- Pets: Animals come in all shapes and sizes, so one-size-fits-all pharmaceuticals do not always meet their needs. In many cases, a compounded medication may be necessary for a non-food animal to be satisfactorily treated.

- Patients with allergies: Patients who are allergic to a preservative, dye, flavor or other ingredient in commercial products can have their doctor write a prescription for a compounding pharmacist to customize the same medication without the offending ingredient.

- Menopausal women: Many women experience significant pain and discomfort as their bodies' progress through menopause. Doctors prescribe bioidentical hormones for patients for whom synthetic hormone treatments may be ineffective or produce undesired side effects. Several bioidentical hormone products are available in FDA-approved, one-size-fits-all formulations from pharmaceutical companies. However, physicians may determine that their patients have unique needs that warrant prescribing a different compounded hormone treatment. This often allows patients to take the smallest amount of a given hormone preparation to treat their symptoms, in conjunction with the recommendation provided by the Women's Health Initiative study.

- Patients who require non-traditional dosage forms: Many patients are unable to take medications orally or as injections – the traditional dosage forms for manufactured drugs. Compounding pharmacists can create alternate methods of delivery, like ointments, solutions or suppositories, to fit these patients' unique health needs. The pharmaceutical industry supplies only limited strengths of drugs, which some patients cannot tolerate. It is often necessary for a doctor to request a different strength of a drug for a patient through compounding.

- Patients who rely on discontinued drugs: Pharmaceutical manufacturers have discontinued thousands of drug products over the years, due to low profitability. For certain groups of patients, these were very effective, important, and sometimes life-saving medications. Such medications are now only available if a doctor prescribes them to be compounded.

- Hospice patients: End-of-life therapy involves the compounding of many different and unique dosage forms to allow patients to live out their lives free of pain and discomfort. Many combinations of drugs are prescribed by doctors and used for these patients who cannot swallow medications and who don't have the muscle mass that is required to receive multiple injections each day. Compounding pharmacists can provide alternate delivery methods such as oral inhalation, nasal administration, topical, transdermal or rectal use.

Statement of Loyd V. Allen, Jr., Ph.D., R.Ph.
Before the U.S. Senate Special Committee on Aging
April 19, 2007

State and Federal Regulation of Pharmacy Compounding

State boards of pharmacy, state medical boards, the Food and Drug Administration, the Federal Trade Commission, the Drug Enforcement Agency, and other federal and state agencies each have some degree of oversight over compounding practice. The U.S. Pharmacopeia and the Pharmacy Compounding Accreditation Board also play critical roles. Together, they have constructed a web of regulations and standards that protect patients.

States boards of pharmacy license pharmacists and pharmacies. State pharmacy laws, enforced by state pharmacy boards, govern the processes and equipment pharmacists use to prepare those medicines. States also have requirements that mandate record keeping, labeling, and proper procedures for sterile compounding, among other aspects of pharmacy practice.

The FDA, which primarily regulates manufacturers, still has an important role to play in regulating compounding. Compounded medicines, including compounded hormones, are prepared using ingredients that must come from FDA-registered facilities – ultimately, the same facilities that supply manufacturers. The FDA also has authority to inspect any pharmacy's facilities, equipment, and ingredients. In addition, the FDA and the Federal Trade Commission have authority over false and misleading marketing practices by pharmacies.

In addition to state boards and federal agencies, compounding pharmacists follow national standards and guidelines set by the U.S. Pharmacopeia (USP). Since 1820, USP has been the official national standards-setter for pharmaceutical ingredients, recognized by Congress as such. It has strong standards for compounding of both sterile and non-sterile medications. USP's compounding committee, of which I am a member, is continually improving and strengthening its standards.

The increase in activity of the USP since the 1980s and 1990s has resulted in revision of chapters related to compounding, both nonsterile and sterile. The revisions resulted in USP Chapter <795> Nonsterile Compounding and USP Chapter <797> Sterile Compounding, both of which have many new and rigorous standards. Since 1995, most state boards of pharmacy have developed comprehensive regulations for pharmacy compounding and now many are beginning to adopt the USP standards as well. In fact, this May at their annual meeting, the National Association of Boards of Pharmacy is conducting special training for state board inspectors with regards to the USP standards for pharmacy compounding.

As an example, for sterile compounding, the process must be done in an ISO Class 5 environment using specialized equipment and documented procedures. By incorporating standards that adopt or mirror USP standards, state boards require much more detail regarding the environment in which both nonsterile and sterile compounding must be done and the documentation that is required. Also, standard operating procedures are required as well as additional continuing education, testing of compounded preparations, record-keeping, quality assurance and patient education.

In 2004, the pharmacy profession joined together to form the Pharmacy Compounding Accreditation Board (PCAB), a voluntary accreditation body whose mission is to assure the quality of compounded medications that patients are prescribed. PCAB's founders include the American Pharmacists Association, the National Association of Boards of Pharmacy, USP, and five other organizations.

To become PCAB-accredited, compounding pharmacies are tested against ten stringent standards, most with detailed sub-standards. These standards encompass regulatory compliance; personnel; facilities and equipment for both sterile and non-sterile compounding; chemicals and the compounding process; beyond-use dating and stability; packaging, labeling, delivery for administration and dispensing; practitioner and patient education; quality assurance and self-assessment.

PCAB-accredited pharmacies must adhere to the following set of principles:

- **Compounding is the preparation of components into a drug product** either as the result of a practitioner's prescription drug order based on a valid **practitioner/patient/pharmacist relationship** in the course of professional practice, or for the purpose of, or as an incident to, research, teaching, or chemical analysis that are not for sale or dispensing. Compounding is a part of the practice of pharmacy subject to regulation and oversight from the state boards of pharmacy.

- **Compounded medication may be dispensed to prescribers for office use,** where applicable state law permits. Office use does not include prescribers reselling compounded medications.

- **Compounding may be conducted in anticipation** of receiving prescription orders when based on routine, regularly observed prescribing patterns. Anticipatory compounding is limited to reasonable quantities, based on such patterns.

- **Compounding does not include** the preparation of copies of commercially available drug products. Compounded preparations that produce, for the patient, a **significant difference** between the compounded drug and the comparable commercially available drug product or are determined, by the prescriber, as necessary for the medical best interest of the patient are not copies of commercially available products. "Significant" differences may include, for example, the removal of a dye for a medical reason (such as an allergic reaction), changes in strength, and changes in dosage form or delivery mechanism. Price differences are not a "significant" difference to justify compounding.

- **Both the prescriber** (via the prescription) **and the patient** (via the label) should be aware that a compounded preparation is dispensed.

- **The pharmacy may advertise** or otherwise promote that it provides prescription drug compounding services. Such advertising should include only those claims, assertions, or inference of professional superiority in the compounding of drug products that can be independently and scientifically substantiated.

An extensive Accreditation Summary is publicly available for every accredited pharmacy, and contains information on compounding pharmacy, the pharmacy's scope of compounding at the time the pharmacy was last inspected; the date of the last and next Review and Survey (inspection), and the results of the inspection.

With 13 pharmacies already accredited, and nearly 100 others pending, PCAB is already giving patients and prescribers a way to select a pharmacy that meets high quality standards.

Additionally, the association representing compounding pharmacists – the International Academy of Compounding Pharmacists (IACP) – has issued guidelines for the labeling of compounded medications. These are designed to help pharmacists communicate to their patients that the compounded medications they've been prescribed are different from off-the-shelf, one-size-fits-all pharmaceuticals and offer a unique value – a medication customized to meet the individual patient's unique needs.

Pharmacists and physicians communicate much of this information to patients already, but the labeling guidelines provide an extra measure to ensure patients understand (1) that their medicine was compounded in a pharmacy, (2) how to use and care for the medication, and (3) that their doctor or pharmacist can provide additional information.

IACP's guidelines are meant to encourage pharmacists to go beyond what the laws require to ensure patients understand the unique value of compounded medicines. For the first time, the guidelines will provide a standardized labeling model for compounded medicines across all 50 states.

Compounded Medicines are not Subject to the FDA New Drug Approval Process

Despite the fact that state boards of pharmacy primarily oversee pharmacy compounding, the FDA has stated: "A new drug -- including a compounded new drug -- may not be legally manufactured or sold in the United States unless it has been pre-approved by FDA as safe and effective for its intended uses. ... In virtually every instance, the drugs that pharmacists compound have not been so approved." *(emphasis added)*

While the FDA approval process is well suited for mass-produced pharmaceuticals, inserting the FDA into the approval process for each of the individual compounded medications, which number in the millions, is simply unworkable. Patients' access to these needed medications would be cut off. Already, many practitioners are discouraged from prescribing and administering the most appropriate medications to patients because of the misconception that compounding is illegal.

There is legal precedent for exempting compounded medicines from the FDA new drug approval process. As federal district court Judge Robert Junell ruled in *Medical Center Pharmacy v. Gonzales* in 2006, "Public policy supports exempting compounded drugs from the new drug definitions. If compounded drugs were required to undergo the new drug approval process, the result would be that patients needing individually tailored prescriptions would not be able to receive the necessary medication due to the cost and time associated with obtaining approval. When a licensed practitioner writes a prescription for a compounded drug for a patient, the medication is normally needed soon thereafter. It is not feasible, economically or time-wise for the needed medications to be subjected to the FDA approval process. It is in the best interest of public health to recognize an exemption for compounded drugs that are created based on a prescription written for an individual patient by a licensed practitioner. [...] Compounded drugs, when created for an individual patient pursuant to a prescription from a licensed practitioner, are implicitly exempt from the new drug definitions."

In *Tommy G. Thompson, Secretary of Health and Human Services, et al., Petitioners v. Western States Medical Center et al.* in 2002, the United States Supreme Court ruled that "The Government argues that eliminating the practice of compounding drugs for individuals would be undesirable because compounding is sometimes critical to the care of patients with drug allergies, patients who cannot tolerate particular drug delivery systems, and patients requiring special drug dosages. Preserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible to be subject to that approval process. The Government also has an important interest, however, in permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs. And it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process. Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so requiring such testing would force pharmacists to stop providing compounded drugs."

Bioidentical Hormone Replacement Therapy (BHRT)

All medications, including all compounded medications containing any form of estrogen, require a valid prescription from a licensed prescriber. Physicians work with their patients to determine when bioidentical hormones are appropriate and, if they are, they work with pharmacists to design individualized treatments to meet their patients' individual needs – needs that are unmet by off-the-shelf, one-size-fits-all, mass-produced pharmaceuticals. Doctors often prescribe manufactured synthetic hormone products such as Premarin and Prempro. When they determine those products are inappropriate, doctors sometimes prescribe bioidentical hormones tailored to meet each patient's unique needs. Also, there are manufactured bioidentical hormones on the market – Prometrium and Estragel are two examples.

For many patients, manufactured synthetic products are effective, but for some they are not.

- That may be because the manufactured drugs simply don't relieve the symptoms of menopause. It may also be because doctors determine that their patients need a lower dose than what is available commercially.
- Some patients experience adverse side effects from the manufactured synthetic products. In those cases a compounded medication may be prescribed in the attempt to lessen the bad effects while achieving intended therapeutic effect.
- Other times, doctors find that changing combinations of hormones – progesterone, estradiol, estriol and estrone – in ways that are not commercially available alleviate their patients' symptoms.
- Or doctors find that different delivery forms – creams, liquids, capsules, troches – are more effective for an individual patient.
- One manufactured bioidentical medication, Prometrium is made with peanut oil, a common allergen. Many patients are allergic to peanut oil and need progesterone – the active ingredient in Prometrium – to be compounded without it.
- When compounded hormones are prescribed, it is because doctors determine that their patients have needs for medications that are significantly different from what is manufactured.

Existing laws enforced by the FDA and the Federal Trade Commission prohibit the making of unsubstantiated claims of safety and efficacy in pharmacists marketing practices. It is important to remember that compounded hormones are prescribed by doctors and no amount of marketing is going to allow a patient to obtain compounded hormones without a doctor's prescription. Also, compounded hormones are always prepared pursuant to a doctor's prescription and dispensed directly to patients at retail.

Because compounded medications are regulated by state pharmacy boards and are not subject to federal laws designed to regulate mass-produced drugs, bioidentical hormones are not subject to FDA approval. While the pharmacy profession supports and is funding studies to determine the risk profile of BHRT, there are risks with all pharmaceuticals. It is up to a physician to weigh the risks and rewards of any prescription drug.

Millions of women have been prescribed manufactured hormone products. Many of them have found relief from torturous symptoms of menopause. Some have not and, instead, have been prescribed compounded hormones by their physicians. They have found relief and I would respectfully urge the Members of this Committee and Congress overall to consider the impact any new policies would have on these patients.

Senator SMITH. Dr. Allen, as I have listened to your testimony, it seems to me that you are saying the doctor just recommends a certain compound and sends that to the pharmacy, and then that is a kit made just for that particular patient.

What guidance do they have? I mean, is it just based on their training as a physician, or is there something deeper that they know that traditional therapies don't have?

Dr. ALLEN. Pharmacists will only fill a prescription from a licensed physician or a health-care practitioner. It is the responsibility of the health-care practitioner to care for the patient and to prescribe appropriate medications.

So, yes, you are correct. When the physician determines that a specific patient needs a compounded medication, then it is originated at the physician's office.

Now, in some cases——

Senator SMITH. Well, I assume, because they are doctors, they are very well-trained, but I don't know if their training goes this deeply into how all these things interact.

I am not a physician. I was trained in law. But I would think, based on my training in law, they are out there on their own, if they are doing this, if there is some ill effect from it.

Dr. ALLEN. That is correct. They are trained.

Basically the physician will prescribe, first of all, the drug, the dose, the dosage form, the frequency of administration, and the quantity. That would all go on the prescription. Then they work with the pharmacist in order to compound the medication specifically for that patient.

Senator SMITH. Is there any ever very ill effects from this pioneering method that each physician would take?

Dr. ALLEN. Well, there are obviously ill effects from almost any medication that may be prescribed across the board. But with clinical experience, the physicians, you know, continue to prescribe medications for these specific patients.

Senator SMITH. So it is sort of an ad hoc building block. What has worked in the past? Let's try this and do that?

Dr. ALLEN. Yes. It is very similar to just the standard practice of medicine. Not everything works for everybody, and so the physicians will try a drug product until they find something that that specific patient will respond to.

Senator SMITH. I appreciate the education you are giving me.

Dr. Wartofsky and Dr. Allen, your two organizations have two very different positions as to who ought to regulate bioidentical hormones made by compounding pharmacies. The International Academy says States are best to regulate it. The Endocrine Society believes that the FDA, the Federal Government, is best to regulate it.

I wonder if you can each tell the committee how your groups have reached their very different positions, including what evidence or information you found to support the conclusion of your academy or society.

Specifically, did you consider mortality and morbidity rates, consumer complaints, State statutory and regulatory provisions regarding compounding? How did you come to such different places on that?

Dr. WARTOFSKY. In the case of the Endocrine Society, I mentioned our professional organization of endocrinologists, the specialty of medicine that deals with hormone therapies. Our members brought to our attention that they were getting questions from their women patients about these bioidentical hormones. They were lacking information. They were concerned about the claims that were being made about these bioidentical hormones—custom-compounded hormones.

Although Dr. Allen is correct that pharmacists should not prescribe anything without a prescription written by a physician, our information is that there are large pharmacy chains that sell these products on the Web; that one can get these mail-order; that they, in fact, will provide the names of physicians who will write prescriptions for these compounds.

We believe these physicians are acting without a basis in science, as you alluded to, that they are perhaps on the fringe of medicine and do not represent our mainstream endocrinologists.

Senator SMITH. These pharmacies—we call it "forum shopping" in the law—do they doctor-shop to find physicians who——

Dr. WARTOFSKY. I am sure that is the case, yes.

Our concern about the need for a Federal regulation is because the degree of regulation by the States is highly varied. From State to State, there is no consistency.

The National Association of State Boards of Pharmacy has issued guidelines for compounding which, as of recently, were adopted and codified by less than a quarter of the States in the U.S. So these guidelines are not uniform.

We have heard this morning how difficult it is for the FDA, given everything that is on their plate, to do the kind of enforcement and regulation that Dr. Allen indicates that they do do, because this is not happening. It just is not feasible, given the broad practice of the dispensing of these bioidentical hormones.

So we believe there should be some greater oversight at the Federal level with more formal guidelines for regulation under which the State boards of pharmacy would operate; that there would be consistency throughout the country; and importantly, that there would be more teeth put into the regulations with enforcement.

Senator SMITH. Dr. Allen, obviously, if these products are being sold on the Web and somebody in Oregon can get it from a doctor in Arkansas on a Web site, that is clearly an interstate commerce issue. That is where the Federal Government comes into play. So I wonder how you reach a conclusion that the States ought to do it.

Dr. ALLEN. Well, basically the individual States recognize professions—medicine, pharmacy, nursing, et cetera—in their State professional acts. In addition to that, they establish certain laws governing that profession and State boards to regulate those and enforce those.

The State boards, then, enact regulations to govern the practice of pharmacy. So the practice of pharmacy and medicine is something that should be regulated at a State level.

Now, from the pharmacy standpoint, if a pharmacy sends a compounded preparation into another State, they are required to be registered with the State board of pharmacy in that State.

Now, when you are talking about the other aspects of it—the physician's prescription—that is getting into marketing, and that is a different story. Probably should be under the FTC or whatever. But the pharmacies—any State that a pharmacy sends a compounded prescription to, they must be registered in that State.

Senator SMITH. Well, the lack of concrete evidence on the whole issue of bioidenticals is what has led me and my staff to conclude that we need some more information. That is why I have asked the Congressional Research Service to prepare a report on the status of laws across all 50 States.

It seems to me that before we can assess who is in the best position to regulate this industry, we need to know more than we now know.

I guess a further question is, does each State track adverse related events in pharmacy-compounded products? In other words, does the Oregonian who gets the prescription out of Ohio—how do they track it, what it has done to them?

Dr. ALLEN. Currently, there is no requirement for pharmacists to report any adverse reactions for either a commercial manufactured product or a compounded preparation.

Now, the USP in our chapter—it is either 795 or 1075—there is a statement that adverse reactions should be reported to the USP MedMarks reporting system. That is something, I think, that can very easily be adapted to this so that it becomes a standard of practice.

Senator SMITH. Without the information, though, how do we know that people aren't being harmed? Shouldn't the States or the FDA track the information?

I mean, it does seem to me that this is an area where the Federal Government really ought to get involved and play a role.

Dr. ALLEN. Currently, the success of therapy or any adverse responses to therapy should be picked up by the physicians and changes in therapy made. I would think that a physician would—it would be incumbent upon them, if the patient is not responding or is responding adversely, that there would be a change in the therapy of that patient.

Senator SMITH. Do you feel like there are some physicians out there that will prescribe anything for a fee? That this may not be being done at the highest standards of science?

Dr. ALLEN. I can't really answer that question.

Senator SMITH. Dr. Allen, you are going to feel like I am picking on you, and I am not trying to. I am asking these questions for the record of the U.S. Senate and for my own understanding of this issue, because there is reason to be concerned.

It leads me to my next question.

Some of the biggest criticisms against compounded products that I have heard are their variability in composition, the fact that physicians and patients may not know exactly what is in the final medication, and the lack of warning labels and patient information.

So, as to the labeling issue, I understand the International Academy of Compounding Pharmacists has developed a suggested label. That label, however, as has been suggested, does not mention the potential risks, any side effects, any contraindications of medications that may be present.

If so, why not? It seems to me like the most basic kinds of labeling that consumers ought to have.

Dr. ALLEN. You are exactly right.

Now, to address that issue, the USP standards for compounding are currently looking at incorporating additional labeling standards for all compounded preparations to at least incorporate the level of information that you just mentioned.

In addition to that, you have referred to black box warnings and things like that previously. The U.S. Pharmacopeia has had a set of reference books called the "USP Drug Information." There have been three volumes: Volume One, Drug Information for the Health Care Practitioner; Volume Two, Drug Information for the Patient; and then Volume Three, which is basically the FDA orange book, et cetera.

What is feasible is to take the information, the data, from Volume Two and put that in a data base in the pharmacy compounding computer system software, so that as prescriptions are filled for specific drugs, like progesterone or whatever, it will automatically print out the information for the specific patient, just like the commercial products is being done today. So that is something that we are looking at.

Senator SMITH. Well, thank you. I think it is very important.

I think the most vital consumer information is what customers ought to be given, and it ought to include the risks, the side effects and what kind of consequences there may be for using these products. So, I don't think we have that yet.

But thank you, Dr. Allen.

Dr. ALLEN. You are welcome.

Senator SMITH. Ms. Wiley, your testimony, please.

STATEMENT OF T.S. WILEY, WRITER/RESEARCHER, CREATOR OF THE WILEY PROTOCOL, SANTA BARBARA, CA

Ms. WILEY. Mr. Chairman, members of the committee, I am T.S. Wiley, and I thank you for inviting me to address you on the subject——

Senator SMITH. Can you hit your microphone button? There you go.

Ms. WILEY. I thank you for inviting me to address you on a subject to which I have devoted over a decade of my life.

I have no formal training or indoctrination in the world of medicine. I am a writer and a researcher in the areas of endocrinology and women's health.

Over 47 million women in menopause in our country are facing the same dilemma we are in this room today: what to do.

At the turn of the century, women died on average by 47. But life expectancy is now well over 80. That means a great many of us must go on perhaps 30 years or more without the hormones that our minds and bodies have always had.

The Women's Health Initiative, now the gold standard regarding hormone replacement therapy, interestingly enough never looked at hormones at all; only drugs with hormone-like effects that were dosed in a regimen that in no way resembled replacement in human beings.

The only thing the WHI proved was that static doses of synthetic hormone-like drugs caused cardiovascular harm in women over 65. This information was not pertinent to women 40 to 60 looking for answers. Thirteen years ago, I was one of those women.

To me, the answer seemed simple. Since women's hormones are rhythmic with ups and downs across the 28-day cycle, I decided to copy nature precisely with a bioidentical regimen based on a model of hormone replacement seen in Type 1 diabetics who use bioidentical insulin—you may argue with the term—biomimetic insulin—taken through the skin and fat in doses their bodies would have produced it.

That is all there is to the Wiley Protocol. It is a simple, logical model using bioidentical compounded estrogen and progesterone in variable dosing.

I arranged for the reporting of adverse events. We use a patient insert with contraindications and warnings, and we test for purity and potency quarterly in the pharmacies I work with.

I have standardized the production, the methods and materials, of the compound so it could merit study on a large scale in clinical trials, of which there are none right now, except, I believe, the one we are planning at the University of Texas.

Menopausal women are orphans in the health-care system in this country. There is no one to take care of us. Doctors prescribing the standard of care, HRT, or even bioidentical hormones have little support or education in the matter.

Big pharmaceutical companies and the compounders are now at war over who gets to make a fortune on us women.

Instead of modeling hormone replacement like diabetes care, women were given a once-a-day-dose pill of synthetic drugs, instead of hormones, because that was easier for the pharmaceutical company and the doctors to monitor.

The last pronouncement from the NIH was just that quite simply the drugs—and they weren't hormones—studied by the WHI don't work. They are, in fact, dangerous, now that you have bothered to look 20 years later.

So now women just can't have any hormones because big pharma couldn't get it right in the first place. That is unacceptable.

The majority of Western medicine has been on a wild goose chase for the elusive proof that being completely hormoneless will save our lives in the face of massive evidence with all of our estrogen blocked at every turn we still keep dying of cancer. Logically, if high circulating estrogen caused cancer, all young women would be dead; all pregnant women would be dead.

Now, the most recent move to keep us hormoneless is the debate over the value of compounded bioidentical hormones.

The National Institute of Neurological Diseases and Strokes sees the value in compounded hormones.

A national clinical trial designed to see if high doses of compounded progesterone can protect the brain from destruction is planned for military use and because 78 million voters are in their peak years for stroke and degenerative brain disease.

Each year, 700,000 Americans suffer strokes and 500,000 more are diagnosed with neurodegenerative disease.

Dr. David Wright at Emory University Medical School in Atlanta has been testing compounded progesterone for head injury. In a 3-year trial of 100 such patients, 80 received high-dose progesterone over 72 hours after trauma and 20 did not.

The study on young men—not women—found that those receiving compounded progesterone were 50 percent less likely to die. There was less disability at the 1-month mark than would normally be expected considering the severity of their head injuries.

Marcus Baskett of Commerce, GA, was one of those patients in a head-on automobile collision just 3 weeks shy of his high school graduation. Early tests of his brain function suggested massive and disabling head injury.

He spent almost 3 weeks in a coma. Then, 4 weeks later, Baskett was released with lingering physical injuries but little evidence of the severe head trauma. Three years later, a 21-year-old Baskett is back 100 percent.

There are uses for compounded bioidentical hormones that none of us have ever even imagined. To consider eliminating them is to limit the researchers' imagination everywhere.

[The prepared statement of Ms. Wiley follows:]

Testimony
Of
T.S. Wiley
before the
Special Committee on Aging
United States Senate
April 19, 2007

Mr. Chairman, Members of the Committee, I am T.S. Wiley and I would like to thank you for inviting me here today to share my expertise and experience with menopause and, of course bio-identical hormone replacement therapy and compounding pharmacy. I am a medical theorist in the field of Darwinian Medicine and writer/researcher on the use of hormones, particularly in postmenopausal women.

I have devised and developed a new method of hormone replacement therapy (HRT) called the Wiley Protocol for women to use as a more accurate form of replacement for lost endocrine function. The remedies available to women suffering from hormone deficiency are woefully inadequate. The commercial pharmaceutical offerings are either bio-identical and too low in dosage to have efficacy, or synthetic drugs, far too dangerous to take. Here in the United States, there are over 40 million women between the ages of 40 and 60.

Worldwide, about 25 million women enter menopause annually. It is estimated that by the year 2030, that number will increase to 47 million women per year. Since 1900, in the developed countries, the life expectancy of women has increase from age 47 to well over age 80, however, the average onset of menopause has remained at 50 as recorded for the last 150 years. That means, overall, women are living at least thirty years longer than they did at the turn of the century.

Our society has never felt the impact of the majority of women living 30 or more years in a hormone deficient state. It won't be pretty. Right now, modern medicine keeps us propped up with antibiotics and surgery, thanks to blood transfusion and anesthesia. But just being alive does not assure "quality of life." Without it, extended lifespan is far less than a gift. It's estimated that eighty percent of women experience a variety of

transiently debilitating symptoms in menopause and 30% of those are classified as severe.

About ten years before women ever have a hot flash or a migraine, we have odd, too-short menstrual periods, we're up half of every night and we start to *look* old. And almost as soon as we start to look old, we start to *feel* old. Exhaustion coupled with plummeting sex hormones creates a life in tatters and a mind like Swiss cheese. Sex would be a memory, if we could remember anything. Our joints twinge and, worst of all, we can't fall asleep or stay asleep. It is anecdotal common knowledge that older people wander around all night limping and bumping into things when they should be out like a light.

Given the evidence that these symptoms of menopause, which can begin for women as early as their late thirties, are the same as the daily challenges the elderly face -- that we become, in fact, "old" when our hormones start to plummet -- we can probably assume we're going to be sick, too, if we aren't already.

Because it is, again, anecdotal common knowledge that old really equals sick in the preponderance of cases -- and sick and old in our culture means usually means cancer, diabetes, heart disease, glaucoma, depression, even Alzheimer's, and since we've established that menopausal symptoms are the same symptoms "old" people experience, then, ***menopause must really equal sick,*** and since all those outcomes above of "sick" can be life-threatening, menopause, itself, must really be *life-threatening.*

If menopause might really equal cancer, diabetes, heart disease, glaucoma, depression, and Alzheimer's, why is it, then, that in those ads for "menopause products", and in the health advice from the North American Menopause Society (NAMS), the Women's Health Intiative (WHI), the Food and Drug Administration (FDA), the American College of Obstetricians and Gynecologists (ACOG), no one ever mentions any of the life-threatening disabilities associated with hormonal decline and urges women to accurately replace those hormones that have gone missing?

Confusion and Media Hype

Instead, women are told that the FDA sanctioned hormones from Big Pharma are really way too dangerous to take (WHI) and biodentical compounded hormones have never been studied (AMA). The most twisted take on the current predicament women face when trying to decide on a mode of relief is the one taken by Barbara Kantrowitiz and Pat Wingert, columnists for *Newsweek* magazine, who have written their own book called, "*Is it Hot in Here or Is It Me? , The Complete Guide to Menopause.*" Wingert and Kantrowitz, ostensibly women themselves, oddly have written an article blaming women for not being resilient enough to tough it out without HRT. They portray menopause as a transitional state that anybody with enough planning can live though. After all, they report that you should not consider yourself "a lost cause," you're just passing through "menopause milestones". As if, on the other side of this *change,* your life and health will suddenly just fall back into place. It doesn't. It's never the same again.

Generations of women (and men) before us knew forty was almost "old" and fifty was as close to sixty as it was to forty. Most of our parents had children in their twenties when they were our age. We knew *they* were old. How do we continue to deny how old we really are?

Baby Boomer women have certainly had help sustaining this mass hallucination. The feminists of our youth, like Betty Friedan and Germaine Greer, have written books exalting this new "undiscovered country" and all of Gyneculture has a whole cable channel called *Lifetime Network* to celebrate it. The trend was to embrace our reproductive denouement -- sort of. "Medicated" conventional menopause was becoming more and more acceptable until the WHI report. Doctors handed out PremPro like Pez and no one questioned it.

Every gynecologist with word processing software has told us the sum total of their knowledge on the subject and has been interviewed by every morning show on every network. So, we all really understood "menopause" and we were OK with it. Those were the good old days. Women knew it was something they couldn't avoid, unless they lived fast, died young and left a beautiful corpse. We all know that unless you go out young, the only certainties in life are *death*, *taxes* and ***menopause.***

In that list only taxes aren't natural, right?

The Inevitable is Acceptable Because it's Natural

Not even. Menopause is certainly not "natural." *There is no menopause in nature.* They never mention that on Lifetime. You'll get more accurate scientific reporting on Animal Planet. The animals always die when they're no longer reproductive.

Otherwise, we would hang around and compete for the food supply with the offspring of the reproductive (young) animals. That scenario benefits no one. That's why there's a fail-safe in nature. When a female runs out of eggs and her hormone levels bottom out, its *game over*. Her judgment flags, her spirits plummet, her immune system freaks out, homeostasis goes out the window and she goes not so gentle into that goodnight, unless someone does the right thing and pushes her out to sea on an ice floe for the good of the "group".

The elderly experience auto-immune conditions like arthritis or Lupus or Parkinson's disease and the more obvious degenerative states like Alzheimer's or cataracts and macular degeneration. But, what if real hormone replacement could really mimic youthful hormone levels, not just mask a few obvious symptoms, and therefore; was a cure for those diseases? It does make logical sense. After all, *young* women don't have those diseases and the difference between young women and old women is reproductive capacity and the attendant hormones. Therefore, it's logical that the majority of women *with normal hormones* don't have those diseases.

Menopause, and andropause in men, are states of hormone depletion akin to the failure of Type I diabetics to produce insulin from their own pancreas. ***Type I diabetics take a bio-identical molecule of insulin, using a short needle, through their skin, dosing it as their bodies would have produced it—after a meal, depending on what the meal consisted of,*** and they live long, pretty comfortable, healthy, productive lives. One of the shining moments in medicine in the last century was the synthesis of insulin for replacement in Type I's, and yet medicine refuses to acknowledge the obvious -- that the replacement of sex hormones in the same manner might put a serious dent in the diseases of old age.

Instead, the *Today Show* offers health advice like "herbs, acupuncture, aromatherapy and massage" for menopausal "discomfort." *Aromatherapy*?? We'd like to

see a doctor tell a diabetic near coma to go get a massage instead of taking insulin. That would be tantamount to murder, but that's what women in 2003 got from the WHI historic report on synthetic drugs with hormone-like effects, PremPro and Premarin.

These substances were donated by the pharmaceutical company that had sold them since 1942 because the assumption was the drugs would be found safe and effective. Nothing could have been further from the truth. After nearly 800 million taxpayer dollars and 14 years later, the overly emphasized negative results of the Women's Health Initiative were released in May 2002. This study was poorly designed, strangely monitored and incompetently analyzed.

The Study that Still Needs to be Studied

The WHI is now the "gold standard" regarding hormone therapy. Interestingly, the WHI never looked at *hormones*, only drugs with "hormone-like" effects that were dosed in a regimen far from that of human replacement. This study has led us to believe that conjugated equine estrogens (from pregnant mare urine) and a synthetic progestin (Prempro) dosed on a daily basis in static doses is clearly very harmful to women after only a few years, and yet, in contradictory reports from the same agency, PremPro seemed to have had positive effects as well. The other drug studied, daily Premarin, seemed to show substantially less harmful effects. Even though the death rate for all arms of this study was equal, the study was dramatically halted early in a very public effort to "save lives."

This confusing and frightening media spin caused millions of women to immediately stop taking their Premarin or Prempro, or any other product deemed a hormone. Physicians also threatened by the negative media reports stopped prescribing them, thus leaving millions of symptomatic women without any reasonable clinical guidance, except the ludicrous exception to the bad news, that lower doses of Prempro, the killer drug, taken for less years is safer.

This advice has not left women feeling safe.

As was alluded to in the beginning of this testimony, the mortality and morbidity of menopause is substantial, as substantial as it is being elderly. Young people *very, very*

rarely experience heart disease, diabetes and cancer. Old people *very, very often* do. And the difference between "young" and "old" is what happens in the middle or mid-life -- hormonal *fall-off.* The incidence of heart disease for women equilibrates (catches up) with men ten years after menopause. The big clue there could be the sudden absence of estrogen for the first time in their lives.

There is enormous data from two researchers named Grady and Rubin, who looked at 85% of the world's data on estrogen and cardiovascular effects and found that the positive cardiovascular effect of estrogen in decreasing blood pressure and lipid profiles was unparalleled by pharmacological agents. Could the just *lack* of hormones explain why the rate of heart attack among women in this country is ten times less than it is in men *until menopause* or, gasp, the epidemic of breast cancer from forty on in women? Makes us wonder. Everybody "knows" estrogen causes cancer. But do we *know* that, or, have we just been *told* that?

Reasoning vs. Rationalizations about Estrogen

Common sense belies the logic that natural (not synthetic drugs with hormone-like effects) hormone replacement, in and of itself, could ever *cause* cancer. If estrogen and progesterone, or even testosterone, caused cancer, all young women would be dead. They're full of it. So if logic tells us that estrogen doesn't actually cause cancer in and of itself, then there must be more to the story—like what kind and how much estrogen and when to take it.

There are too many pieces of evidence that real estrogen replacement, not PremPro, also negates the need for *bisphosphonates*, the commercial pharmaceutical treatment for osteoporosis. Those drugs in newer data are implicated in actually weakening bone. Because this class of drugs blocks old bone resorption and there's no progesterone to normally build new bone—it turns into a substance akin to petrified wood. Bisphosphonates are now known to cause micro-fractures in bone that must have a normal estrogen/progesterone metabolism to be healthy.

Estrogen also alleviates mild to moderate depression, the most common diagnosis in women ages 40 to 50. However, Dr. Joanne Manson of Harvard, who, too, has written her own book, called "*Hot Flashes, Hormones and Your Health,*" insists hot flashes "are

the only compelling reason to take hormone therapy," (what an understatement) and that "hormones are best used for only two to three years." What are the depressed women aged 40 to 50 to do three years later – live on Prozac, when a natural substance would have put them right instead?

Follow the Money

The importance of understanding the biology of menopause and its morbidity must be a primary medical economic concern to America. Relief of menopausal symptoms such as improved sleep will likely translate into a more productive woman whether in the workforce or as a mother or a spouse. Healthcare dollars can be spent more wisely than in Medicare reimbursements for constant doctor visits and endless prescriptions and procedures. Quality of life will improve for most symptomatic women and hormone replacement is an important choice for women since estrogens are known to be the only effective treatment for estrogen-depleted states.

Although no formal medico-economic analysis is yet available, Dr. Julie Taguchi, oncologist at Sansum Clinic in Santa Barbara, California predicts that there would be a substantial medical savings. In prescription drug costs alone, scientifically proven safe and effective HRT could reduce the use of anti-depressants, blood pressure medications, lipid lowering agents, sleeping aids, gastrointestinal drugs, etc. to such an extend that the estimated annual savings in the 10 to 20 billion dollar range would not be unreasonable. Additional cost savings in office visits, hospital stays, productivity are hard to estimate.

The failure of the WHI trial is partially due to the lack of understanding of the biology of the reproductive and menopausal state as well as, the indiscriminant choice of study subjects without well defined entry criteria, such as on the average enrolling subjects 12 to 15 years into menopause, creates unfathomable noise for the outcome.

A larger issue is the administration of drug molecules that are not natural to women's bodies as compounded versions of plant-derived hormones could be. The choice of the molecule, the dosage, and timing of the onset of therapy are the most important variables in the search for safe and effective HRT and the WHI spent almost a billion dollars and never approached any of the most important questions..

Women, now suspicious of drug companies and their compliant physicians, yet desperate for relief of menopausal symptoms, are turning to other treatments or plant based bio-identical hormones in droves. These plant-based hormones of different sorts seem to be the most widely used and promising alternatives at this point in time in the infancy of the endocrinology of menopause. It is clear that the conjugated horse urine estrogens (Premarin) with progestins (Provera) were the number one drug(s) most likely NOT to be refilled. Studies confirm that women can feel a difference between the kinds of hormones taken, so much so, that women prefer black cohosh and lachesis (homeopathic literal snake oil) to Premarin and PremPro.

Alternative medicine is really making a killing (literally and figuratively) on this one. Women are so distraught and physically miserable that they are looking for any answer that doesn't involve a hysterectomy or chemotherapy. Their disillusionment with Western medicine has driven them to herbal and homeopathic "cures," that may or may not do even more damage. They've placed the same blind faith in alternative medicine that has usually been reserved for their Western doctors.

But Western medicine and science have issued edicts that say women can *only* have a medicated menopause courtesy of the drugs they, themselves, have already deemed dangerous or we can grit our teeth (what we have left of them) and try to survive it without any relief. Estrogen is responsible for: *memory, eyesight*, *bones*, *heart*, *teeth*, *sleep*, *ability to withstand stress*, and *progesterone* since ovulation is impossible without estrogen (even using natural progesterone, at this point the receptors aren't "reading" its action because *progesterone receptors* are created by estrogen) And without progesterone women risk: *cancer, sudden vaso-spasm* (female heart attack), *migraines, psychotic behavior, auto-immune diseases like lupus, arthritis, rashes, rosacea, neuralgia, no bones, no libido, high cholesterol and carbohydrate craving, possibly obesity, Type II diabetes.*

Hormone Replacement from Plants is Not a New Idea

Whether or not women replace their missing hormones is not up for debate. Living without them is far too miserable and dangerous. So then, the question becomes "how"? Replacing missing estrogen, progesterone or testosterone with molecules of the

identical hormones synthesized from plants make the most sense. The original hormone substances, before they were changed in the lab to be patentable, in pharmaceutical HRT came from animals and plants, too.

Human beings, like all animals, have receptors in brain and body cells to receive everything that the planet has to offer, from nicotinic receptors to cannabis receptors. "Natural" hormones are made from molecules called phyto- estrogens that, despite their name, are synthesized into natural progesterone first and then tweaked into testosterone and eventually estrogen. The source of these plant-derived hormones is most likely soy beans or Mexican yams, but unlike *progestins* (the artificial molecules served up by pharmaceutical companies as the real thing), the unpatentable natural version fit perfectly into human receptors.

Hormone replacement therapy from plants was never dangerous. Real, natural hormones synthesized from plants have been known throughout history to be safe and effective birth control and death defiers. Only when drug companies got into the act did our lives get shorter and more painful. Hormone replacement from nature's bounty directly to our receptors was as natural as child spacing through lactation. Women always knew how to take care of themselves and each other. Women have always self-medicated with plants for contraception, beauty products and hormone replacement.

It's All Downhill from Here

While estrogen and testosterone levels slide steadily downward from twenty-six years of age on, when human growth hormone slows, the biggest difference between a woman in her twenties and a woman in her late thirties is in the levels of *progesterone* she can produce.

In a normal twenty-year old, the act of ovulating -- which produces progesterone, once a month for fourteen days -- is dependent on a system of feedback loops between the ovaries and the brain which are regulated by levels of estrogen.

Estrogen production is directly dependent upon the number of eggs a woman has left every month after ovulation, deducted from the finite number we are born with. Ovulation uses up about 150 every month in an effort to produce one "good" one. From conception until puberty, eggs are destroyed by a genetic clock. As fetuses, in utero, we

had about one million eggs, but by the time we were born -- we were down to half a million. At puberty we're down again by half, to a quarter of a million. Every seven years after puberty the number of eggs diminishes by one half of the declining base number, until we reach about thirty-three, when the decline picks-up speed, and the number of eggs are halved every three years.

In the ten to fifteen years before we actually hit the wall sometime in our fifties, and run out of eggs, the declining estrogen falls in step-fashion with the declining egg base. Therefore, ovulating the remaining eggs gets "iffier" as time goes by (since the system is run by estrogen) and fertility is truly at risk by the time we are in our mid-thirties; because we don't have enough estrogen to tell the brain to send the signal to ovulate, at least not on a regular basis.

So, as we're running out of eggs, the estrogen signal from our ovaries to our brain is weak. The weak estrogen signal is ultimately responsible for the loss of progesterone since progesterone seeps from the blister that housed the egg. -- No pop, no progesterone.

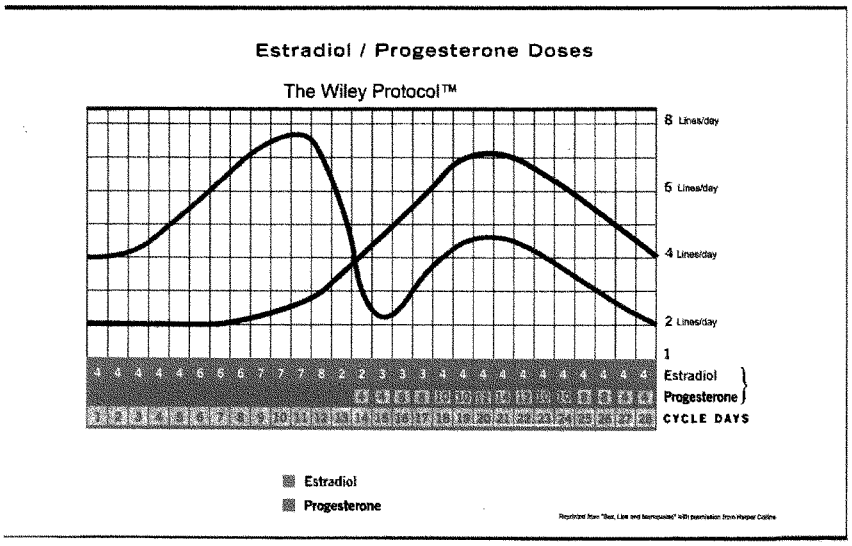
The first hint of estrogen depletion is shorter or longer menstrual periods as I mentioned on page one. The other earliest symptoms are sleeplessness, inability to concentrate or "mind noise," loss of libido and weight gain. And let us not forget the wrinkles. In peri-menopause (age thirty-three to fifty), internal estrogen levels certainly aren't high enough anymore to reliably ovulate, but they are *just high enough **for too long*** to be "normal." Normal levels of progesterone would bring it down. But we don't have normal levels anymore. It's like a game of dominoes.

It's Only Rock and Roll

The problem is one of "priming." The estrogen must create the internal environmental potential for the progesterone to wipe out the growth and start over again. One just doesn't work properly without the other. They are for lack of a better term, "in tandem" rhythmically as long as a woman is young, healthy and fertile. It is impossible to be one out of that list of three without the other two. That's why the menstrual cycle has two peaks that cease to be when one goes missing.

Everything alive has a rhythm.

The world as we know it, from bacteria to blue whales, the whole universe, in fact, is all about timing, within each of us and in relation to everything outside us. The individual rhythms overlap into larger patterns that then weave in and out of each other. Human beings swim in and out of this sea of rhythms. The moon provides more light with its full face and sure enough as the new moon ends, every twenty-eight days females bleed. The circadian clock in every cell of our body measures one spin of the planet, and the moon tracks the repeating 28 of those days 13 times in one revolution around the sun.



To see a graph representation of a menstrual cycle is to see what appear to be two mountains. There's a peak of estrogen and then a peak of progesterone. If one imagines that picture strung together over a year, one month connected to the next, there's a rhythm of unending ups and downs. It's a balancing act. Estrogen's solo in the first half of our cycle sets the stage for pregnancy all over our body. Estrogen *grows*, hence its reputation in cancer research. But estrogen, by way of creating *progesterone receptors,* has sealed its own fate. Progesterone generated by the popping of the egg, steps on stage to end that song of creation.

Cancer

The progesterone that we make naturally, in the second half of our cycle when we're young, protects us from cancer on the molecular level. Natural progesterone is a *genomic effecter for apoptosis.* (In English: natural progesterone latches on to switches on the genes called *promoter regions* for "cell suicide."). Cell suicide is the mechanism that causes the death of the one for the good of the many. *Natural* progesterone in a normal menstrual cycle controls the *destruction phase* which kicks in about half way through your cycle when no conception has occurred.

It's only when the fat lady *never* sings and the opera never ends, when we stop popping eggs and producing progesterone regularly as we head toward menopause -- that estrogen can continue to grow cells unchecked.

And this doesn't just happen in the uterus, either.

These rapidly multiplying estrogen-driven cells exist in our breasts and brain, too, and they have progesterone *receptors* on them. The receptors are waiting for progesterone to signal the final act. The chemical *listening* for that signal from progesterone will go on indefinitely as long as estrogen continues to pour, unless we artificially drop the curtain on the show by replacing from the outside the natural hormones we lack.

Does estrogen cause cancer? No or all young women would be dead.

Can estrogen cause cancer? Yes, but only in the absence of progesterone.

Cells, fed by estrogen and insulin that continue to grow in the absence of progesterone past a programmed growth phase, have all sorts of potential for genetic and immunological mistakes to be made.

We call those mistakes *cancer.*

In reality, the mutational changes that are the hallmark of metastatic cancer are not caused by mistakes during repeated cellular divisions or assaults by toxic pollutants, *rather those changes are caused by the fall-off of regulatory hormones that control the switches on your very DNA for the growth and death of your cells.*
(see abstracts Formby/Wiley)

Knowing that progesterone deprivation is the key to cancer at midlife for women makes the research showing that women who have given birth multiple times, and

thereby experienced long periods of placental progesterone, have much less cancer --it makes those findings make sense in a whole new way. When we examine the statistic that the incidence of breast cancer in our grandmother's day was 1 in 21, and in our mother's generation it was up to 1 in 18, it becomes painfully obvious that our standing at 1 in 8 (in one generation) is self-inflicted.

Our lack of childbearing has prevented the long periods of progesterone exposure necessary to buy time. Repeated pregnancies and bouts of lactation added up to a savings of at least 150 eggs a month or 1350 per birth, and if Grandma nursed for a year or so, another 2100. That means a savings of about 3500 eggs per child. Do the math. Grandma, in her day, would have given birth four to eight times; maybe Mom had three or four. That's 10,000 to 15,000 eggs for Mom and twice that for Grandma. That means Mom and Grandma extended their reproductive lives at least two extra years for every child made viable. Eight children would have extended Grandma's hormonal protection sixteen extra years. Not a bad deal, all in all.

That formula pretty much explains not only the above statistics, but why we experience *peri*-menopause for fifteen years and why they, on the other hand, went from child bearing to menopause at a later age and with fewer physiological repercussions. So the smug assumption that if our mothers and our grandmothers were just fine *without* hormone replacement then we will be too, may be far from a reasonable one. For all time, the only way to beat the reaper was to rack up points by winning at the game of life. For a woman--or any animal, for that matter--that meant to be fruitful and multiply.

Apparently, biology is destiny.

Evidence and logic amply support the theory that random and irregular ovulation due to declining egg stores creates a scenario that features an *over-abundance of estrogen hanging in the balance against a hit-or-miss supply of progesterone* for a good ten to fifteen years. .

What about the Women Who Survive Without HRT?

Grandma's shift to an expanding middle, a little thinner hair on top, and a few chin whiskers was part of her salvation. When estrogen declines and progesterone production stops, all that's left is the testosterone that once upon a time fed our libido. In

the grand scheme of things, old women – aren't women at all past a certain point. If this phase-shift happens quickly -- say after decades of childbearing and breastfeeding --some of us make it through it without getting cancer. But, if it takes too long, we're targeted for transformation, because cancer is an *evolutionary* function in nature. All of the genes active in cancer are active at only one other time in life. They are all switched on in the high estrogen/low progesterone state of the first nine weeks of life in utero when we are neither man nor woman. Since nature abhors a vacuum and is about duality, we must be one or the other -- man or woman.

We can't remain in limbo for more than nine weeks or nature will take over, trying out combinational strategies in an effort to make us become "something". Cancer is no plague on mankind, it is life, it's just the new you. It's a group of cells turned on to rapid unchecked growth by genes that are exactly the same in fetal tissue. That's why they call them *fetal* oncogenes in research.

That's also why cancer isn't something you can kill like a germ with an antibiotic. You can't burn it, poison it or take it away because it is *us* -- or at least what's become of us in the absence of performing a role in nature. Cancer is actually the genetic creativity shown in nature when an organism ceases to fit into The Plan.

Of course, a lot of us die from this evolutionary function, but many of us live with it, too. 93% of elderly men show some degree of prostate cancer on autopsy, but it's not listed as the cause of death. Most of us will likely die *with*, not *of*, some form of cancer.

Cancer is only transformation, unless it kills you first.

I believe there is an alternative. We can turn back the clock with the products nature has to offer. The catch is, how do we prove it? You see only the bio-identical molecules do this. The product from Wyeth does not. The hormone receptors can tell the difference. The bio-identicals need to be compounded from bulk materials and left in their unpatentable form. All that means is that the drug companies won't make as much money as they would by turning it into a drug. That also means there's no money for research because drug companies foot the bills for scientists and those drug companies will never be able to patent a "natural substance" and their already patented drugs don't work the same way on almost any system in a woman's body. Oh, and then there's the impending Kennedy, Burr, Roberts Bill that could literally put an end to it all.

Bio-identical progesterone replacement is a shoe-in as a cancer treatment because cancer was never about cellular *overgrowth*. It has always been about ***not*** enough death--*in the presence of overgrowth*. But cutting edge medicine has never equated menopause with cancer, even though cancer strikes at the time in a woman's life when her hormones are disappearing. The Standard of Care treatment plan is to further remove her estrogen. Taking estrogen away from women, or selectively blocking it without ever considering the synergy between the estrogen and progesterone, *the most selective potent apoptotic factor known in the human body*, is not the way to eradicate cancer.

It's the way to cause heart disease and Alzheimer's.

Are They Bioidentical Hormones Bio-identical or Not?

Even natural bio-identical hormones are not bio-*identical* unless your body can recognize them as hormones. Since natural hormone replacement is possible, the other half of the question is how to take bio-identical hormones? The scientific studies looking at the differences in Oral (by mouth) and Transdermal (using a neutral cream base as a carrier of the hormone) show significantly less side effects when hormones enter the bloodstream through the skin and fat base barrier just like Type Is take insulin. So through the skin is "how". What remains is "when". Replacement is not replacement unless you truly replace what has been lost.

The idea that hormone "replacement" could be affected by a one time a day, same dose every day regimen is illogical. The hallmark of an endocrine system is pulsitilty and amplitude, meaning that hormones pulse every few seconds and their amounts go higher and higher, depending on the time of the month in the case of estrogen and progesterone. So it seemed to me that the way to achieve HRT with least side-effects was to use a bio-identical molecule for both hormones, transdermally, in doses that could increase and decrease over time.

Natural hormones are not bio-identical unless they replace precisely the "natural" rhythmic levels of your own estrogen and progesterone when you were a young woman. Currently, the standard hormone replacement therapy you would receive from a doctor would be PremPro, or Premarin, if you've had a hysterectomy. And doctors who want to

prescribe natural hormones but who aren't familiar with the fact that hormones should mimic your natural hormone rhythms will merely prescribe natural hormones in the same way they prescribe synthetics. The Women's Health Initiative has already found the Standard of Care to be dangerous, what if it's not just the synthetic molecules that are dangerous?

Or, conversely, what if it's really the missing rhythm that matters?

The Wiley Protocol

I decided it was all three, the molecule, the delivery system and the timing. I devised a dosing schedule accomplished in 3cc capped syringes with 30 lines on the each. An average 1 month prescription has nine syringes of estrogen and nine syringes of progesterone. The hormones are dosed in "lines" on the syringes. The dose escalates every three days to address the issue of 72 hour "receptor roll-over". In other words, we wait for the receptors for the hormones to catch-up to the dose before raising it each time. The Basic Wiley Protocol® dosing schedule is the same starting point for all women using this method of BHRT, but it can be individualized by raising or lowering the dose of either hormone by 2 lines in a 28 day period or making more amplitude by raising the dose of the appropriate hormone two more lines on the peak days of Day 12 and Day 21.

The formulation and manner of dosing bio-identical HRT started out as a "thought experiment" in my book, Sex, Lies and Menopause. In the book, I asked the question - "if hormone replacement was made of real bio-identical hormones and dosed to mimic the ups and downs of the hormone blood levels in a normal menstrual cycle in a 20 year-old woman, would all of the symptoms and disease states of aging decline or even, disappear?"

Well, so far we have watched over a thousand women here in Santa Barbara and it looks like the logic holds - because it was the rhythm that was always missing in other regimens. I asked the doctors to prescribe no more than 3 months at a time and require blood tests of estrogen and progesterone at month 3 on the peak days of the cycle to see if we had attained the levels in serum blood work for a woman twenty years-old, or if we

had reached optimum theoretical therapeutic levels. Women intact, or without hysterectomy, have normal menstrual periods, no matter what their symptoms of irregular or absent cycles were previously. We have made every effort among the many doctors and women involved to report adverse events to Dr. Julie Taguchi, in Santa Barbara. The Wiley Protocol is the only HRT or BHRT Protocol developed under the scrutiny of an Oncologist. No other HRT or BHRT can make that claim. Dr. Taguchi has recently reported on 58 cancer patients in her practice, post diagnosis, without active cancers receiving the Wiley Protocol for a median of 2.5 years, 28 of whom had breast cancer. The expected recurrence rate is 1 in 10. We saw only 2.5 recurrences in 58 people and remarkable attenuation of osteoporosis, fibroids and, of course, the garden-variety disabilities of menopause in general. (see slides J. Taguchi, MD)

Any doctor or healthcare practitioner who offers "hormone" replacement that does not result in a 4 to 5 day period of bleeding at the end of 26-30 day cycle in a woman with a uterus has not offered ***hormone*** replacement. Replacing only *some* of our endocrine function does nothing but create *different* disease or, in the case of estrogen without progesterone, sometimes even cancer.

Doctors

Right now, in the wake of the National Institutes of Health (NIH) Women's Health Initiative (WHI), getting hormones, at all, is difficult. Doctors are leery of even the "Standard of Care" approved synthetics in this time and place. Getting legitimate insurance-covered physicians to prescribe even bio-identical hormone molecules of any sort, let alone the Wiley Protocol has, for the last twenty-years or so, been, at best, a roll of the dice.

The majority of Western medicine has been on a wild goose chase for the elusive proof that being completely hormone-less will save our lives, in the face of massive evidence that even with all of our estrogen blocked at every turn, we still keep dying of cancer. In the burst of the Baby Boomers becoming menopausal, doctors from all specialties—ER docs, Internists, Family Practice and GPs along with the usual Ob/Gyns, Naturopaths, Chiropractors, Nurse Practitioners and the occasional Neurologist have clamored to the forefront to be of service. (guesstimates of the incredible revenue stream

are mind-boggling) The problem is, they have no idea how to prescribe hormones for women. Most of them didn't even do a rotation in endocrinology in med school.

They flock to large seminars held on bioidentical prescribing by the larger compounding pharmacies and associations like the American College for the Advancement of Medicine (ACAM) or American Academy of Anti-Aging Medicine (A4M), who can afford the more expensive "talent" (other self-proclaimed physician experts) to draw a crowd. Right now physicians are in serious need of re-education that bears some resemblance to endocrinology. The way women are treated skirts dangerously close to fad. The flavor de jour in BHRT really does change every day.

Doctors who prescribe the Wiley Protocol are in the vanguard of an elite group of forward-thinking physicians and researchers trying to put the scientific method back into medicine. All HRT and bio-identical hormones, particularly, still reside in a no-man's land of uncertainty when it comes to prescribing because of the lack of long-term study and testing. By asking the physicians to use one of the many pharmacies that I've trained with other licensed pharmacists (Dana Nelson, Paul Lofholm R.Ph D.) Registered to dispense the Wiley Protocol® prescriptions, we have eliminated all the guess-work and potential errors in prescribing natural hormones.

Big Pharma is willing to educate the physician, minimally, about synthetic hormones and, of course, all drugs, but, here and now, the only commercial enterprise handing out natural hormone information to any professional group is PCCA (Professional Compounding Centers of America). PCCA aims to educate Compounders on the "hows" and "whys" of preparing bio-identical hormone preparations and, unfortunately, a lot more information that is of questionable value to women. We have a better plan, a plan that keeps the pharmacist from encroaching on the physician's territory.

With the opportunity for our Registered, trained in methods and material, pharmacies to have a Wiley Protocol® Clinical Practice Guidelines Manual, as well as their Wiley Protocol® Methods and Materials Guide, the Doctor and the Pharmacist can be sure that the patients treatment guidelines are consistent, reducing the possible variables for further diagnosis which will make safety and efficacy possible. The doctor

and the patient can be can reassured that the hormones that prescribed are the same compound made with the same raw materials every time.

Compounded Bioidentical Hormones.

As many as two million women in the U.S. use customized hormones for menopause symptoms. Compounding pharmacy can provide a service that industry cannot and will not meet. This service is customizing individualized medications. Put simply, the medications provided by the drug industry do not always come in the dosage forms, strengths, or drugs needed by specific patients. Compounding pharmacies are the only resource that has been able to make and dispense these medications.

The first college of pharmacy in the U.S. was established in 1821 and they had laboratories that taught compounding. The processes of compounding continued to be taught in schools of pharmacy well up until the 1980's. This means each pharmacist was taught standardized methods for compounding. These pharmacy schools were regulated by accrediting bodies. In the 1980's, pharmacy training turned away from its historical roots in compounding and concentrated instead on clinical pharmacy. What this means is that a trained pharmacist became a medicine "cop", whose purpose was to ensure that there were no drug interactions or misuse of medications. Today, there is a much different landscape.

Why did this happen?

Drug companies started to designate dosage forms and drug doses. While they may have been based on scientifically justified conclusions, they certainly left no room for individual variation. The thinking by drug companies was that they would be able to come up with every drug needed by each person at an effective dosage level. With few exceptions, physicians and pharmacists went right along with the drug industry's mandate. However, if we look at reality, compounding never really went away. It continued to exist and be in demand.

Dermatologists realized early on that in order to treat their patients effectively, they would need to combine medications in dosage forms not available from drug companies. Even more prominent, hospital pharmacies continued to compound IV additives and parenteral feedings and specialized medications because there was nothing

available from drug companies that could respond to the individualized need of hospital patients. As pharmacy schools backed off from educating pharmacists in compounding, the art and science of compounding was nearly lost.

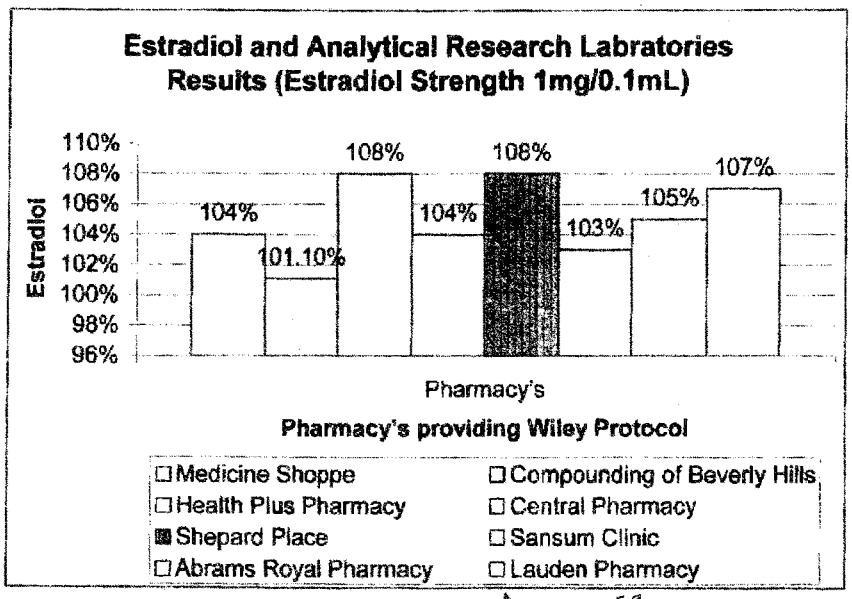
But not surprisingly, the need for specialized drugs with individualized dosing did not go away. Now there is a resurgence of demand for compounding pharmacy, driven by the needs of patients not met by the medications available from the drug industry, patients who cannot be treated with standard dosage forms.

Examples of this include Hospice patients who cannot swallow their medications and need compounded medications in the form of Transdermal creams; patients that are allergic to preservatives and need preservative free medications; patients that are lactose-intolerant and need lactose free medications; neonates and pediatric patients that require drug dosages not available without compounding; and patients that need medications the drug industry has deemed no longer profitable and discontinued.

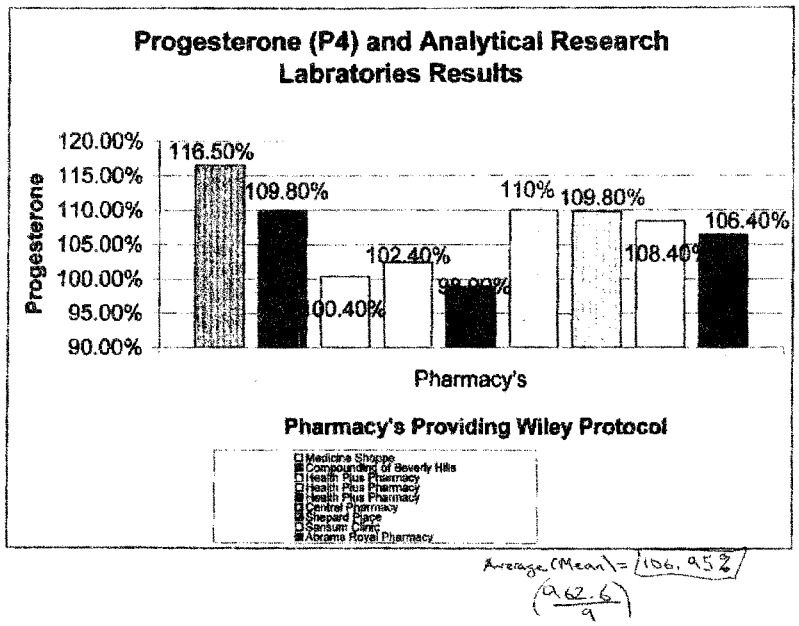
Standards and Over Site on the Wiley Protocol

For the Wiley Protocol the patient doses in a fashion which replicates the reproductive hormonal cycle in serum blood levels. The preparations are not commercially available and are applied to the skin, so, must be compounded by a compounding pharmacist. We have had very significant success in women who can not take other bio-identical or synthetic pharmaceutical medications by mouth, Transdermal route or injection. We will soon publish our accomplished standardization of a Compounded bio-identical hormone results. Contact plofholm@aol.com

Below is just an example of the potency analysis we require of the Registered Pharmacies:



Average (Mean) 105%
Median 104.5%



Average (Mean) = 106.952

$\left(\frac{962.6}{9}\right)$

Who's Watching Women Using the Wiley Protocol?

We are also waiting for our "study number" from the University of Texas at Tyler's Nursing School's IRB Committee. Contact janithwilliams1@msn.com The proposed study is a longitudinal, observational study measuring many of the parameters of the WHI in women currently using the Wiley Protocol.

Though many physicians have been prescribing them for decades, there is a paucity of data in our literature due to the fact that there has not been any pharmaceutical support for plant-based products (considered food and therefore not patentable). They can be compounded by a pharmacist. Another point here is that the same compounded hormone prescription can vary widely from pharmacy to pharmacy, making them virtually "un-studiable."

Thus no standardization exists in this area of hormones for research heretofore.

A controlled systematic pilot clinical study of the most promising few plant based hormone therapy alternatives would quickly yield to a well-organized national multi-centered clinical trial of a large heterogeneous cohort. A short duration observational study with biologically correct endpoints associated with menopause and with periodic measurements of clinically significant biochemical markers should be the next step to jumpstart the WHI-2.

All Wiley "Registered" Pharmacies use ingredients that are all purchased from the same supplier. At the Registered Pharmacies, The Wiley Protocol® is made in small batches (lot# identified) in uniform standardized steps outlined in the Wiley Protocol® Methods and Materials Training Manual and packaged in our unique color-coded identifying system of purple and green for progesterone and estrogen, respectively.

I have recruited these Registered Pharmacies, not only to insure quality control on a very variable treatment - BHRT, but to make sure that in the future a real and legitimate study could be affected on the Wiley Protocol® by requesting 10 pro bono prescriptions per pharmacy for a national study. Also, BHRT has never been studied in any Standard of Care controlled environment because the "study substance" in any legitimate trial has been mandated by the NIH to be donated to the participants. Of course, no small compounder can bear the economic burden of donating 4000 compounded prescriptions, however; the eventual 400 or so Wiley Registered Pharmacies can and will, together. The donations will have been standardized to Good Compounding Practices, so the results of such a study can be taken seriously at any level of scrutiny.

Who's Watching Wiley?

In the spirit of financial disclosure and complete transparency, I trade the Pharmacies the use of my name and list them on the website thewileyprotocol.com in exchange for their commitment to make the bioidentical hormones used in the Wiley Protocol in the standardized method I require and agree to donate a percentage of their volume to a future national study of the Wiley Protocol. They must buy the packaging (purple and green stamped with a 28WP logo) from my company Wiley Systems. The proceeds from the sales of packaging have built the website and paid for the development of the University of Texas study, so far. I take no personal income from Wiley Systems.

It is self-maintaining financially and it's profits are only used to promote the Wiley Protocol to doctors and academic institutions and to develop educational materials like the website.

Our Process for Standardization

In an effort to standardize the compounded preparations of Estrogen and Progesterone we have asked the pharmacists to do several things in order to minimize the potential for variation:

- Drug specifications: we use the bulk drugs estradiol and USP progesterone which are recognized and standardized by the United States Pharmacopoeia. We compare the USP Standards with the Certificate of Analysis which accompanies each bulk drug shipment. We want to assure ourselves of that the Purity and Identification Standards are met.

- Formulation Specifications: We use a detailed formulation so that the prescription conforms from batch to batch. The formulation is spelled out like a recipe (formulary) and the quantities are recorded with the lot numbers, expiration dates, if any, and manufacturer's or supplier's name.

- Method of preparation is detailed and for our preparations we use specific equipment for weighing, measuring, and mixing. i.e. an ointment mill

- In order to assist the patients in measuring the correct dose, we use a special syringe. The objective in using this measuring device is to apply to the skin a specific amount of cream containing a particular content of hormone. The calibrations on the syringe allow for the physician's prescription of the Wiley Protocol to be "individualized" in the spirit of a compounded product to the variation in endocrine physiology from woman to woman. So with the Wiley Protocol we have provided "standardization in customization", something no one has ever done before, except in the case of commercial pharmaceutical products like the Vivelle® and Climera® patches which are offered in a range

of set doses. The Wiley Protocol's delivery system allows for far more individualized, unique, "finger-printing" of a woman's own original menstrual cycle.

- We supply typically a one month supply of medications with a beyond-use date based on literature review, scientific studies, or USP monograph specifications.

- We sample our medications and send them out for independent analysis to validate our work. (see attached evidence)

- We also test our Compounders for the presence or absence of the "drugs" they are compounding for us in their blood stream to assess potential exposure to the hormones that they are working with.

- On the clinical side, we encourage Wiley Protocol prescribing physicians to order blood work for their patients on Days 12 and 21 of the 28 day cycle to assess hormone absorption, compliance and ultimately correlate the findings to the clinical picture so that the patient is best served when adjustments are necessary.

- We support PCCA's invented "physician-pharmacist-patient triad" only in the sense that we stipulate the necessity for Collaborative Agreements between Prescribing Physicians and Wiley Registered Pharmacies allowing the Pharmacist to advise WP patients from the WP Clinical Practice Guidelines Manual only when authorized by a WP prescribing physician, assuring that all patients get the same answers and information to any and all unique questions, creating, again, a standardized mode of follow-up that keeps the physician in the loop and on the same page.

- We support the pharmacy's exemption from the rules which govern manufacturers, while we expect the FDA to enforce standards and principles relating to labeling, purity, content, etc. We believe that the regulation of the healing professions is the purview of the States and should remain there as long as rigid guidelines for methods and materials are maintained by regular State Inspection.

- We support extended education and training for all pharmacists who compound and provide specific training in the above requirement methods for compounding the Wiley Protocol.

The Future of Compounding

While we have a rigorous protocol for the preparations that comprise the Wiley Protocol that our pharmacists compound and we are confident that our preparations contain what they say they contain due to rigorous and frequent testing (evidence attached), should the detractors accuse the profession of custom Compounding to fall short of quality benchmarks in general or in specific cases, more over site of the profession by the States, is long overdue and not an unbearable burden, fiscally. The conundrum is how to regulate compounding pharmacists and pharmacies.

The logical answer is to look back at history. Pharmacy schools need to once again assume the responsibility of training compounding pharmacists. Academic accrediting bodies need to be in charge of credentialing compounding pharmacists. State Boards of Pharmacy need to be in charge of inspecting and monitoring compounding pharmacies. In most states, the State Board of Pharmacy is responsible for licensing sterile compounding; there is no reason why they should not assume to responsibility of licensing non-sterile compounding as well.

If the Federal Government stopped the practice of compounding, all it would achieve is leaving millions of patients without resources to alleviate various conditions. We certainly need the federal government to support Schools of Pharmacy, State Boards of Pharmacy and accrediting agencies, to ensure that compounding pharmacies are meeting the required highest of standards.

I'd advocate for either Accreditation by the Pharmacy Compounding Accreditation Board [PCAB] or equivalent or provide more moneys to the States so that they can hire and train many, many more Compounding Inspectors. A hefty increase in the Licensure Fees for Compounding as was affected for Sterile Compounding would also create a healthy revenue stream to State coffers for recruitment and training of a legion of stringent regular inspectors. As far as models of National, not Federal, regulatory bodies are available for template: the National Association of Insurance Commissioners (NAIC) acts as a forum for the creation of laws and regulations for the insurance industry, with each state's Insurance Commissioners reporting to them.

This model also assumes the registering body would be responsible for the ethics of the profession, but in the UK there has been a move to separate the two roles. Other nations use representation and regulation at the national level such as, the Royal Pharmaceutical Society of Great Britain (RPSGB), the Pharmacy Guild of Australia and we do have our own American Pharmacists Association (APhA) which is a weakly structured organization. A pilot project among interested States could be a good way to start restructuring and remodeling the regulation of compounding pharmacy to Good Compounding Practices (GCP) at a national level.

On the other hand, we have an Accreditation Body who could provide the basis for inspecting to Good Compounding Practices (GCP) as I have mentioned above. For those women relying on the Wiley Protocol for hormone replacement therapy, a compounding pharmacist is essential. I would ask for your support in the potential re-regulation of compounding pharmacy at the States level to achieve Good Compounding Practice (GCP).

While the amount of prescriptions which are compounded is relatively small, compared to the economic Goliath of the big pharmaceutical companies, for those people who need the service, there is no manufacturer who *can or would do it*. The pharmacist plays a vital role in meeting those specific patient needs, if the patient is to be offered a pharmacologic solution.

Furthermore, as I said, compounding is essential in the hospital environment where intravenous prescriptions are compounded daily. In the Los Angeles Times, April 9, 2007, Times Staff Writer, Melissa Healy eloquently investigated three new promising

treatments for stroke, neurogenerative disease and brain trauma. She looked at natural progesterone, creatine and magnesium. In her piece entitled, "*Search for the Brain's First Defense*", she said "When under attack — from ischemic stroke, head trauma or many degenerative diseases — a small cluster of affected brain cells basically commit suicide and, in so doing, release toxins that kill off their neighbors in droves. Neurons tumble like dominoes to their death in a process that can take hours (in a stroke or a head trauma) or years (in Alzheimer's or Parkinson's disease)".

But what if there were a simple way to fortify human neurons against the brain's many disparate enemies? What if some safe, readily available compound, taken before or just after a stroke or injury or even long before a neurodegenerative disease takes hold — could protect the brain against many kinds of insults and injuries in both men and women?

Progestrone's Not Just for Women Anymore

This summer, the National Institute of Neurological Diseases and Stroke is expected to approve and fund a national clinical trial designed to see if high doses of compounded progesterone, a hormone that is present in all human brains — can help disrupt the rapid death of brain cells that frequently follows a trauma to the head. The quest for neuroprotection is driven not only by a deepening understanding of how injury and disease damage the human brain but, by a growing sense of urgency.

In the wars in Afghanistan and Iraq, traumatic brain injury has become widespread, a problem for which the military's medical establishment is poorly prepared. Almost 1,900 U.S. soldiers have been treated for traumatic brain injury, and some Pentagon estimates have suggested that as many as 28% of the 1.4 million troops that have served in Iraq and Afghanistan may have sustained at least mild brain injury from the concussive effects of bomb blast.

As the United States enters its fifth year of war and the U.S. military ponders a world in which its troops will remain vulnerable to improvised explosive devices, the Pentagon has become deeply interested in the science of neuroprotection. In July 2006, the armed services' medical leaders huddled at a military installation outside Washington,

D.C., and established a goal to "develop better neuroprotectants for acute head injuries ranging from severe penetrating injuries to mild traumatic brain injury." Last month, the Pentagon announced it is spending $14 million to conduct more research on blast injuries and to help medics in the field better diagnose mild brain injury. This will include a look into compounded natural USP progesterone. Of course, the big pharmaceutical company trying to steal back its lost market to bio-identicals would have you believe the money they are losing in the interstate commerce of compounded products is the big issue here, but it's not.

Seventy-eight million baby boomers (that's voters, to you) are reaching the peak years for stroke and degenerative brain diseases. Already, in the United States each year, 700,000 Americans suffer a stroke, and as many as 500,000 are diagnosed with a neurodegenerative disease (1.4 million suffer a traumatic brain injury). Such numbers have helped propel the search for an agent that could limit or hold off disability across a range of illnesses.

All of the substances under investigation, like progesterone, have, in some form, long been in safe use in the medical arsenal. And all have shown promise in protecting the brain against other types of injury and disease. Progesterone, for instance, seems to fortify the brain cells against degeneration caused by multiple sclerosis and has shown early promise as a protectant in stroke. "The graveyard of neuroprotectants is absolutely full. It's depressing," says Dr. David Wright, a professor of medicine at Emory University Medical School in Atlanta who has been a leader in testing progesterone for head injury.

But his hopes have been buoyed by early studies suggesting that quickly elevating levels of progesterone, a steroid present in the brains of both men and women, may help save many with traumatic head injury and improve their outcomes. In a three-year trial involving 100 such patients brought to Emory's Grady Memorial Hospital, 80 received a high dose of progesterone over 72 hours and 20 did not, receiving standard care only.

The study suggested that those receiving a rapid infusion of progesterone were 50% less likely to die. And among those who got the progesterone, there was less disability at the one-month mark than would normally be expected, considering the

severity of their head injury. "We think it's just shifting the whole curve," making all but the most severely injured patients better off, Wright says. "It way outdid what we were expecting."

This Could Be Your Son, Brother, Father or Grandson

Marcus Baskett of Commerce, Ga., was one of those patients. A passenger in a head-on automobile collision just three weeks shy of his high school graduation, Baskett was evacuated by helicopter to Emory and received the progesterone infusion upon his arrival. In addition to broken bones, early tests of his brain function suggested massive and disabling head injury, and he spent almost three weeks in a coma.

But seven weeks after his April 2004 injury, Baskett was released from the hospital with lingering physical injuries but little evidence of the severe trauma to his brain. Three years later, a 21-year-old Baskett keeps up a rapid-fire conversation and lives close to his parents' home but independently, keeping track of appointments and birthdays on a cell phone scheduler.

"I wouldn't have believed that a woman's compounded hormone would help my body and brain in a situation like that," Baskett says. "I'm back almost 100%, and I don't think I'd be here if it weren't for progesterone."

Senators Kennedy (D-MA) Burr (R-NC) and Roberts (R-KS), among others are as I write this, considering legislation (Safe Compounding Drug Act of 2007) that would severely restrict and possibly deny access to critical medications. This draft bill is supported not only by Wyeth in an attempt to retrieve their lost revenue stream from Compounders dispensing Bio-identical hormones which out perform Wyeth's PremPro, but by Astra Zeneca, through their funding of Mothers of Asthmatics. Astra Zeneca, by working through this ostensibly public and non-commercial Mothers of Asthmatics has falsely portrayed the *Safe* Compounding Act as a patient-driven. There has been no harm to asthmatics, only to Astra Zeneca's bottom line, because Astra Zeneca believes that Compounders have "knocked-off" one of their inhalant products.

If this legislation passes, federal regulators, not the doctor, will decide what medicines can be taken. I believe that it is fundamentally the right of the consumer to choose and the practitioner to practice.

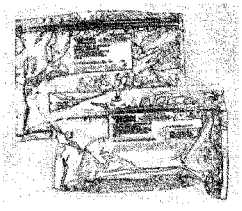
Among other things, the so-called Safe Drug Compounding Act would give the Food and Drug Administration the power to:

- *Broadly eliminate the availability of many critical, commonly compounded medications that many patients rely on* **(most especially bio-identical hormones for women).**
- *Determine when compounded medicines are needed - a decision that has always been and should always be made by doctors.*
- *Restrict the compounded medications the doctor can prescribe even if he or she determines the need for them.*

Among those left with little or no choice will be menopausal women and andropausal men; the Autistic community; individuals living with HIV/AIDS; infants and young children with conditions like gastroesophageal reflux disease (GERD); hospice and nursing home patients; and people who are extremely allergic or sensitive to fillers, dyes, and additives in medicines. And now we can add researchers with imagination like Dr. Wright in Georgia and head trauma victims like the young man, whose life and mind was saved by a Compounded bio-identical hormone. Please don't let this happen.

This is a sample of the patient inserts in every package of the HRT devised by T.S. Wiley:

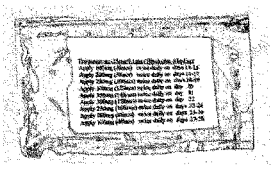
Use Directions for the Wiley Protocol ™



You have received two silver packages.

One has 10 syringes of Estradiol which have Evergreen colored caps and foil labeling. The Estradiol is in a cream base at the concentration of 1mg of Estradiol for each 0.1ml of cream. The syringes hold a total of 3mls's, or 30 "lines" each of 0.1ml.

The other silver package has 9 syringes of Progesterone which have Purple caps and purple foil labeling. The Progesterone is in a cream base and the concentration is 25mg of Progesterone for each 0.1ml of cream. The syringes hold a total of 3ml's, or 30 "lines" each of 0.1ml
This is for the standard Wiley Protocol ™



On the back of each bag you will see **the dosing schedule** for each hormone separately day by day. For the first two weeks of your new cycle and forever after, you will take estrogen only during the first two weeks and progesterone ***and*** estrogen **together** during the second two weeks. The goal of the Wiley Protocol is to re-establish normal rhythmic cycles for estrogen and progesterone in your body by increasing and decreasing (multi-phasic) doses in the undulating rhythm actually documented in young women.

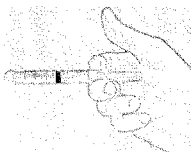
"BID" means twice a day (once in the morning and again in the evening)

The basic Wiley Protocol dose schedule is also shown in the Appendix I on page 219 of the book "Sex, Lies, and Menopause", by T.S. Wiley.

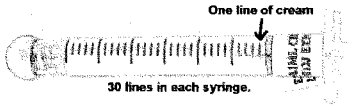
How to Start the Wiley Protocol ™

If you are still having regular periods then DAY ONE is the first day of your period. Take the dose for DAY ONE.

If you have stopped having periods, then DAY ONE for you is shown on the moon or Lunar Calendar which you can find online at the rhythmicliving.com website or maybe included in your hormones packets. The doses are also shown at the bottom of each day of this Lunar Calendar. Most months are not 28 days, so if you are on a Lunar Cycle, you will stop your progesterone on day 28, but continue your Estrogen through the "blank days" until you hit DAY ONE on the next Lunar Cycle.

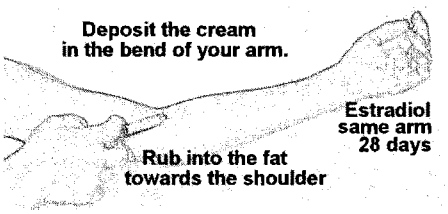


Place the plunger on the palm of your hand and place your



first and second finger on the barrel.

Push plunger carefully. It can be sticky. It takes a few times to develop the skill to measure 1 line at a time.
Measure out 4 lines for your first application of estradiol. Make a dot of cream on your hand or arm for each line of hormone that you measure out to practice controlling the plunger in the syringe.



Deposit the cream in the bend of your arm and use your hand to work the cream into the bend and the fat at the back of your arm towards your shoulder and any fatty arm skin that is not sun damaged.
The larger the application area the better your absorption will be. Rub it in well until it all disappears.
Don't mix or layer over with other creams of any other kind.

You will do this with your estrogen on the ***same*** arm through out your 28 day cycle. Read the bag or book to see how many lines to apply for each application.

On day 14 begin to apply your progesterone to the opposite arm in the same way.

At the start of the next cycle you will switch arms. So you will use the opposite arm for estrogen and the opposite arm for progesterone, switching arms once a month thereafter.

Important Information about the Application of Your Hormone Cream

Do not bathe for 40 minutes to 1 hour after applying the hormones.

Do not exercise for two hours because, although you can't wash off the hormones after an hour, you may sweat them back out of your fat base.

You can also apply the hormones to the back of your knees and inner thighs, but stay consistent. You want to build up a deposit of hormones in the fat base. Either use your arms or your legs.

Expectations during the First Three Months

Changes are going to happen in your body while your hormones and receptors are adapting back to a normal rhythm. You might not or might not feel the minute changes of adaptation. There is an adjustment period as your system "wakes-up". Some side effects of this "wake-up call" that you might experience the first month and even later are: a slight headache during the second progesterone phase, nausea as your blood sugar normalizes, an odd taste in your mouth, dizziness, weight changes (water), hypoglycemia, and breast tenderness.

Your thyroid may have to adjust to having your hormones back so you might feel palpitations or vibrations in the morning or at night when you lie down to go to sleep. Should this occur, spread out the entire day's dose (lines for morning and night added together) throughout the day, for example, 2 lines an hour for five hours. Continue this method for at least three days before returning to BID scheduling. If this thyroid response still continues, you should call your doctor to discuss it and go to the user group to learn about other's experiences with this effect.

These are normal transient effects that are a result of your body making adjustments as your hormones take effect and your receptors return.

If you have a history of heart problems please discuss this with your doctor.

During the first month you may not receive all the estrogen you are applying and probably may not receive much of the progesterone. By month two, the estrogen from the first month's dose will have made enough estrogen receptors in a closed loop to provoke progesterone receptors. By your second cycle the progesterone effect will be more pronounced because it will have progesterone receptors to read to.

By month three a full compliment of receptors should be up and running and then it is time to start adjusting the dose for your individual needs. **Blood testing is in order at this juncture to give your doctor the information to correlate your remaining symptoms with the amounts of hormone you are receiving.** Women who are already cycling when they start the Protocol might need to adjust earlier.

Until your hormones are in synchrony, sleeping patterns may still continue to be broken. To deal with this interval waking, (at 2am and 4am or 1am and 3am) some women use Tylenol PM or sublingual melatonin one hour before bed, but never more than two hours after sunset. This regimen may also be used to "get off" of other common sleep aids. Never use more than 3mg of melatonin in the winter and never more than 1 mg in the summer. Melatonin is a powerful over-the-counter hormone available in the United States.

There is an expanded Frequently Asked Questions on the web site as well as a link to the user group. Questions that are gathered there are submitted to T.S. Wiley. The user group and web page is an educational forum and you are advised to discuss all decisions about your health and dosage changes with your doctor.

Should you have an emergency situation contact your doctor.

About medications, supplements and herbs.

All medications, prescription or otherwise, available to the public work across hormone receptors to be effective, therefore, all medications, supplements, and herbs can have an effect on hormone receptors.

ALL herbs work across hormone receptors. For example, evening primrose oil, Vitex agnus castus Chastetree or berry, Black Cohosh, Estrovan, lignans, red clover and flax have hormonal effects and could interfere with your Wiley Protocol ™. Check the constituents of all "combination" products from healthfood stores and naturopathic and chiropractic practitioners.

Medications that are Contraindicated on the Wiley Protocol™

Arimidex
Anastrazole
Letrezole
Aromasin
Exemestane
Fosamax
Raloxifen
Tamoxifen

Discuss these drugs with your doctor before stopping them.
Down the line you may find you need less of certain conventional medications like anti-depressants, especially SSRIs and Lipitor. *Discuss this with your doctor.*

These products that have been seen to be no problem with the Wiley Protocol™

Magnesium
B-vitamins
Omega 3's and 6's
Lithium
Anti-psychotic drugs
Anti-epilepsy
Common sleep meds like Ambien, Tylenol PM, Melatonin, Resterol, Zantax, Zantac

Bleeding Out of Rhythm

Consult your doctor and the website for information about:
Bleeding before day 21 can be either a sign of too much or too little estrogen. On the basic Protocol™, too much is unlikely. Bleeding on or after day 21: try using 2-4 lines more of progesterone BID for one day only. If the bleeding continues, stop all progesterone and let your period happen. Call the next day DAY ONE. This earlier than normal bleeding indicates the need for 2 more lines of estradiol BID for your entire cycle beginning on this new DAY ONE, so you will make more progesterone receptors and your progesterone can hold the lining past DAY 21.

To see more answers to many frequently asked questions go to the website thewileyprotocol.com
Discuss the educational material with your doctor before you make decisions about your health.

Consultation with your pharmacist

Your pharmacist is only allowed to answer questions *about your order*, to tell you where and how to apply the cream, the production and contents of the cream and hormones, your insurance, compounding information, and business matters pertaining to your order.

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By month 3 and every six months after that you are urged to get your blood tested.

Blood testing is done on day 12 and day 21.
There are cream application issues with regard to blood testing so here are two options for getting blood work done in regard to applying your cream. Stick with one. Morning or afternoon, either before you apply or 3 hr after.

These are abstracts of journal science published in molecular biology on the mechanisms of fetal oncogenes and compounded hormones by T.S. Wiley.

1: Ann Clin Lab Sci. 1998 Nov-Dec;28(6):360-9. Links

Progesterone inhibits growth and induces apoptosis in breast cancer cells: inverse effects on Bcl-2 and p53.

- **Formby B,**
- **Wiley TS.**

Sansum Medical Research Institute, Santa Barbara, CA 93105, USA.

Progesterone inhibits the proliferation of normal breast epithelial cells in vivo, as well as breast cancer cells in vitro. But the biologic mechanism of this inhibition remains to be determined. We explored the possibility that an antiproliferative activity of progesterone in breast cancer cell lines is due to its ability to induce apoptosis. Since p53 and bcl-2 genetically control the apoptotic process, we investigated whether or not these genes could be involved in the progesterone-induced apoptosis. We found a maximal 90 percent inhibition of cell proliferation with T47-D breast cancer cells after exposure to 10 microM progesterone for 72 hours. Control progesterone receptor negative MDA-231 cancer cells were unresponsive to these two concentrations of progesterone. After 24 hours of exposure to 10 microM progesterone, cytofluorometric analysis of T47-D breast cancer cells demonstrated 43 percent had undergone apoptosis without signs of necrosis. After 72 hours of exposure to 10 microM progesterone, 48 percent of the cells had undergone apoptosis and 40 percent demonstrated "leaky" membranes. Untreated cancer cells did not undergo apoptosis. Evidence proving apoptosis was also demonstrated by fragmentation of nuclear DNA into multiples of oligonucleosomal fragments. After 24 hours of exposure to either 1 microM or 10 microM progesterone, the expression by T47-D cancer cells of bcl-2 was down-regulated, and that of p53 was up-regulated as detected by semiquantitative RT-PCR analysis. These results demonstrate that progesterone at a concentration similar to that seen during the third trimester of pregnancy exhibited a strong antiproliferative effect on at least two breast cancer cell lines. Apoptosis was induced in the progesterone receptor expressing T47-D breast cancer cells.

PMID: 9846203 [PubMed - indexed for MEDLINE]

: Mol Cell Biochem. 1999 Dec;202(1-2):53-61. SpringerLink Links

Bcl-2, survivin and variant CD44 v7-v10 are downregulated and p53 is upregulated in breast cancer cells by progesterone: inhibition of cell growth and induction of apoptosis.

- **Formby B,**
- **Wiley TS.**

Sansum Medical Research Institute, Program in Molecular Oncology, Santa Barbara, CA 93105, USA. bent@sansumres.com

Progesterone inhibits the proliferation of normal breast epithelial cells in vivo, as well as breast cancer cells in vitro. But the biologic mechanism of this inhibition remains to be determined. We explored the possibility that an antiproliferative activity of progesterone in breast cancer cell lines is due to its ability to induce apoptosis. Since p53, bcl-2 and survivin genetically control the apoptotic process, we investigated whether or not these genes could be involved in the progesterone-induced apoptosis. We found a maximal 90% inhibition of cell proliferation with T47-D breast cancer cells after exposure to 10 microM progesterone for 72 h. Control progesterone receptor negative MDA-231 cancer cells were unresponsive to 10 microM progesterone. The earliest sign of apoptosis is translocation of phosphatidylserine from the inner to the outer leaflet of the plasma membrane and can be monitored by the calcium-dependent binding of annexin V in conjunction with flow cytometry. After 24 h of exposure to 10 microM progesterone, cytofluorometric analysis of T47-D breast cancer cells indicated 43% were annexin V-positive and had undergone apoptosis and no cells showed signs of cellular necrosis (propidium iodide negative). After 72 h of exposure to 10 microM progesterone, 48% of the cells had undergone apoptosis and 40% were annexin V positive/propidium iodide positive indicating signs of necrosis. Control untreated cancer cells did not undergo apoptosis. Evidence proving apoptosis was also demonstrated by fragmentation of nuclear DNA into multiples of oligonucleosomal fragments. After 24 h of exposure of T47-D cells to either 1 or 10 microM progesterone, we observed a marked down-regulation of protooncogene bcl-2 protein and mRNA levels. mRNA levels of survivin and the metastatic variant CD44 v7-v10 were also downregulated. Progesterone increased p53 mRNA levels. These results demonstrate that progesterone at relative high physiological concentrations, but comparable to those seen in plasma during the third trimester of human pregnancy, exhibited a strong antiproliferative effect on breast cancer cells and induced apoptosis.

PMID: 10705995 [PubMed - indexed for MEDLINE]

Hyaluronidase can modulate expression of CD44.

- **Stern R,**
- **Shuster S,**
- **Wiley TS,**
- **Formby B.**

Department of Pathology, School of Medicine, University of California, San Francisco, California 94143-0506, USA. rstern@itsa.ucsf.edi

CD44 is a family of transmembrane glycoproteins with multiple isoforms generated by alternative exon splicing of a single gene. CD44 and its variants are expressed on a wide variety of cells including cancer cells. The mechanisms by which splice variant exons are selected are unknown. The presence of hyaluronan in the environment of the cell appears to influence that selection process. The expression of particular splice variants of CD44 as well as the simultaneous presence of hyaluronan is important for motility, invasion, and the metastatic spread of some tumors. The influence of hyaluronidase digestion on the expression of CD44 in human cancer cell lines was examined. CD44 isoforms containing alternatively spliced exons were sensitive to hyaluronidase digestion in all lines examined, but differences between cell lines were observed. Expression of CD44s, the standard form, was resistant to digestion in two of three cell lines. A tentative model was formulated proposing that CD44 isoforms containing splice variants are unstable, requiring the continuous presence of ligand for expression. CD44s is relatively more stable, not requiring the continuous presence of hyaluronan. Additionally, a number of new CD44 variant isoforms, not previously observed, were identified. Copyright 2001 Academic Press.

PMID: 11339835 [PubMed - indexed for MEDLINE]

These are experiments by other scientists using compounded progesterone for brain injury:

J Neurosurg. 2000 May;92(5):848-52. Links

Neuroprotective effect of postischemic administration of progesterone in spontaneously hypertensive rats with focal cerebral ischemia.

- **Kumon Y,**
- **Kim SC,**
- **Tompkins P,**
- **Stevens A,**
- **Sakaki S,**
- **Loftus CM.**

Department of Neurosurgery, The University of Oklahoma Health Sciences Center, Oklahoma City, USA. ykumon@m.ehime-u.ac.jp

OBJECT: Exogenous progesterone has been shown to reduce brain edema and ischemia-induced cell damage and to improve physiological and neurological function during the early stage of focal cerebral ischemia. In the present study, the authors assessed the neuroprotective potential of progesterone during the late stage of ischemia in a transient middle cerebral artery (MCA) occlusion model in the rat. METHODS: Forty-eight male spontaneously hypertensive rats were randomly assigned to six groups. Progesterone was dissolved in dimethyl sulfoxide (DMSO). In four groups of rats, the dissolved progesterone (4 mg/kg or 8 mg/kg) was administered for 2 or 7 days after ischemia. In two control groups DMSO was administered for 2 or 7 days after ischemia. Occlusion of the MCA was induced by insertion of an intraluminal suture, and reperfusion was accomplished by withdrawal of the suture. Treatment was initiated on reperfusion, which followed 2 hours of MCA occlusion, and continued once a day. Lesion volume, neurological deficit, and body weight loss were measured 2 or 7 days after ischemia, depending on the animal group. Treatment with a high dose of progesterone (8 mg/kg) resulted in reductions in lesion size, neurological deficits, and body weight, compared with control rats. CONCLUSIONS: Administration of progesterone to male rats 2 hours after MCA occlusion reduces ischemic brain damage and improves neurological deficit even 7 days after ischemia.

PMID: 10794300 [PubMed - indexed for MEDLINE]

1: Pharmacol Biochem Behav. 2003 Sep;76(2):231-42. ELSEVIER FULL TEXT ARTICLE Links

Behavioral effects and anatomic correlates after brain injury: a progesterone dose-response study.

- **Goss CW,**
- **Hoffman SW,**
- **Stein DG.**

Department of Psychology, Emory University, Atlanta, GA 30322, USA.

Evidence suggests that progesterone enhances functional recovery in rats after medial frontal cortical contusions; however, a high dose of progesterone exacerbates tissue loss in a stroke model when administered chronically (7-10 days) prior to injury [Stroke 31 (2000) 1173)]. This study attempts to determine progesterone's dose-response effects on behavioral performance and GABA-A receptor expression following a cortical contusion. Male rats received injections of 0, 8, 16, or 32 mg/kg progesterone in 22.5% 2-hydroxypropyl-beta-cyclodextrin following cortical impact. Lesion 8 mg/kg and lesion 16 mg/kg groups displayed less thigmotaxis in the Morris water maze (MWM) than 0 and 32 mg/kg groups and were not significantly impaired relative to shams on other water maze measures. Increased variability in the 32 mg/kg group during somatosensory neglect testing was the only evidence indicating that a high dose of progesterone was disruptive to a few animals. These results suggest that low and moderate doses of progesterone are optimal for facilitating recovery of select behaviors and that postinjury progesterone treatment permits a wider dose range than preinjury treatment. Progesterone did not affect lesion size, but a strong negative correlation was observed between thalamic GABA-A receptor density and water maze performance. Future studies could explore causes for this relationship.

PMID: 14592674 [PubMed - indexed for MEDLINE]

1: Exp Neurol. 2006 Aug;200(2):378-85. Epub 2006 Jun 22. ELSEVIER FULL TEXT ARTICLE Links

Tapered progesterone withdrawal promotes long-term recovery following brain trauma.

- **Cutler SM,**
- **Vanlandingham JW,**
- **Stein DG.**

Department of Emergency Medicine, Emory University, Atlanta, GA, USA.
scutler@emory.edu

We previously demonstrated that after traumatic brain injury (TBI), acute progesterone withdrawal (AW) causes an increase in anxiety behaviors and

cerebro-cellular inflammation compared to tapered progesterone withdrawal (TW). Our current study investigates the behavioral and cellular effects of AW two weeks after termination of treatments to determine the longer-term influence of withdrawal after injury. Adult, male Sprague-Dawley rats received either bilateral frontal cortex contusion (L) or sham (S) surgery. Rats were injected at 1 and 6 h post-injury, then every 24 h for six days. Vehicle (V)-treated rats were given 9 injections of 22.5% cyclodextrin, whereas AW rats received 9 injections of 16 mg/kg progesterone and TW rats received 7 injections of P at 16 mg/kg, followed by one at 8 mg/kg and one at 4 mg/kg. On day 8, sensory neglect and locomotor activity tests were initiated. Animals were killed 22 days post-TBI and the brains prepared for either molecular or histological analysis. Western blotting revealed increased brain-derived neurotrophic factor (BDNF) and heat shock protein 70 (HSP70) in TW vs. AW animals. P53 was increased in VL animals, whereas all progesterone-treated groups were equivalent to shams. TW animals had markedly decreased sensory neglect compared to AW animals and increased center time in locomotor activity assays. In addition, lesion reconstruction revealed a decreased lesion size for TWL over AWL over VL animals. Glial fibrillary acidic protein (GFAP) immunofluorescent staining followed this pattern as well. In conclusion, after TBI, AW affects select behaviors and molecular markers in the chronic recovery period.

PMID: 16797538 [PubMed - indexed for MEDLINE]

Slides of Recurrence Rates of Cancer Patients on the Wiley Protocol

Clinical Characteristics

•67 women on hormone therapy identified

•54 women Wiley Protocol

–Premenopausal = 2

–Postmenopausal = 52

•Natural = 22

•Surgical = 24

•Chemo induced = 5

•Other = 1

Clinical Characteristics: Age

20 - 29 = 2

30 - 39 = 2

40 - 49 = 12

50 - 59 = 25

60 - 69 = 8

70 - 80 = 5

Years Duration

Years	# women
•>0.5	8
•1+	9
•2+	18
•3+	13
•>4	6

Clinical Characteristics

•Invasive Breast Cancer		28
•Stage I	10	
•Stage II	12	
•Stage III	2	
•Stage IV	4	
•Non-invasive Breast Cancer		5

Receptor Status

•Invasive	
—ER +	24/28
—ER -	4/28
•Non-Invasive	
—ER +	4/5
—ER -	1/5

Clinical Characteristics

•Non-Hodgkin's Lymphoma	4	
•Colorectal	2	
•Ovarian		2
•Post BMT	1	
•Lung	1	
•Leukopenia	3	
•No cancer + FHx, hematological	8	

WP Data

•Average length of use: 2.2 years as on October 2006

–Ranges 6 mo to 4.5 years

•Blood levels and tests

•Dose Adjustments

–28/54

•Compliance

•Drop out

Wiley Protocol AE's

•Pulmonary embolism

–71y.o. after 3 years; cont'd WP

•Breast cancer

–57 y.o. recurrence resected- continued

–59 y.o. new cancer opposite breast after 2 years

•(present at time of initiation)

Adverse Events

60 y.o. breast cancer mass removed- no nodes taken

Started WP 1 year later

Axillary mass 1 years after WP

Restaged- only axilla 2 nodes present at 2nd surgery

Ovarian Cancer IIIc

–49 y.o. 2.5 years on WP

Wiley Protocol Concerns

•Fibroids: for better, stable, or worse-

•Endometrial thickening or cancers - 0

•Cardiac events, stroke, or DVT -0

•Gallbladder disease -3 surgery -2

•Serum levels:

–progesterone levels- accuracy?

–Low day 12 E2

•Hypermetabolism

•Seasonal controlled by light/food/ stress

Benefits

•Bone density

•Lipids

•Perimenopausal symptoms

•Headache

•Mood and psyche

•Deep sleep and dreams

•Incontinence

•Vaginal dryness

•Libido

•Skin

Skin

Lipids

Wiley Protocol Issues

•Labor intense for patient and MD

–Need for patient education and selection

•Not reaching "target" levels

–Absorption / metabolism/ compounding variations

•Early bleeding (day 22 menses)

–Either not enough day 1-21 E2 or P4 sharp fall off

•Symptoms in between doses-

–Raise or change to TID x 3 days

• Dose adjustments- frequent

•Progesterone > estradiol

Wiley Protocol Issues

•Minor:

–Allergic skin reaction

•Base variation

–Thin vs. adipose sufficient

–Denser Breast tissue on mammography

•Most, but not all

–Lack of insurance coverage if not at registered pharmacies

–Weight gain- < 5lbs

–Breast tenderness- over in 3 months

Conclusions about the WP

•Provides definite relief of vasomotor and menopausal symptoms

•Very effective for new bone mineralization

•Stabilizes or minimally improves lipid profile

•Improves of mood and quality of sleep

•Has similar effects of other reported E2

•Has promising future with further study

•Short term use in high risk oncology population does not appear to be detrimental

—***Clinical trials needed*** !!!

Senator SMITH. Thank you very much, Ms. Wiley. You have given us another view, and we respect that.

I guess the thing that leads to my questioning of you is clearly the FDA gives a black box warning for hormone therapy when even the slightest amounts or smallest amounts of hormones are used. They tell you to do it for a short duration.

You, however, developed a protocol that uses higher amounts and for longer periods, as I understand it, recommended for lifetime usage. We have heard differing views at this morning's hearing.

I wonder, your protocol's approach contradicts that held by the larger—the greater—medical community on hormone therapy. You have said you are not a medical doctor. Can you explain how your proposal doesn't put women at greater risk?

Ms. WILEY. Yes. Hormones, as I am sure Dr. Wartofsky could agree, are dose-dependent in their effects on cellular systems and different in every organ in the body.

The normal menstrual rhythm, or the normal production of hormones over the course of 28 days in a healthy young woman who does not have breast cancer, heart disease, Alzheimer's, arthritis, osteoporosis—we could go on for days—in those healthy young women, is a rhythmic production with a crescendo of estrogen on day 12 and a crescendo of progesterone on day 21.

In using bioidentical transdermal hormone creams, it is possible, through justification with blood work, to recreate a dosing schedule that mimics those normally rolling hormones that provoke something called apoptosis, which is cell suicide, in the progesterone phase, that in the estrogen phase on day 12 provoked the progesterone receptor so that apoptosis can happen.

Endocrinology is about pulsatility and amplitude. A diabetic, for example, would never take the same amount of insulin day-in and day-out. The diabetic responds to the meal the diabetic ate with the appropriate amount of insulin that his body might have produced could he produce it. I only suggest that women are treated the same way.

Senator SMITH. You obviously believe that the bioidentical products ought to have a medical definition.

Ms. WILEY. Yes, I do.

Senator SMITH. OK. It is not just a marketing term.

Ms. WILEY. No. Well, I think "bioidentical" is a marketing term. I think "biomimetic" is more accurate. But there are differences in the effects of the molecule of estradiol versus conjugated equine estrogens, very big differences, certainly on inflammatory response in cardiovascular events.

Senator SMITH. Thank you.

Dr. Manson, have you reviewed the Wiley Protocol?

Dr. MANSON. Yes, I have.

Senator SMITH. Do you have any problems or concerns?

Dr. MANSON. I think it is an interesting theory, and I would like to see it tested.

But I think we have to note that in the post-menopausal woman, there are not these levels of estrogen and progesterone that are achieved with this treatment, so it is not a natural state that is being induced.

We just don't know what the health effects are, especially of very long-term, indefinite use. We don't even know the short-term effects.

I would like to see funding of trials to look at hormone regimens that do more closely simulate what happens in a woman's natural, pre-menopausal state. I think that is very important to have that research and to do those studies. But at this point in time, I don't think we can reassure women that this is any safer, any more effective, without rigorous science.

I would ask the question, why would any woman agree to spend so much out-of-pocket to pay for the hormones, to pay for these blood or saliva tests, if she really understood that there was no evidence that these treatments were any more effective than treatments that could be covered by her health insurance; that there was really no rigorous evidence that these tests were useful in guiding her hormone therapy treatment, and also if she were aware of the concerns about dosage consistency and impurities?

So I think it is clear that women are not getting the information that they need, or else it seems very unlikely to me that this would become as popular as it has become.

Senator SMITH. Ms. Wiley, would you welcome a Federal scientific test of these things?

Ms. WILEY. Oh, absolutely.

Senator SMITH. A vigorous——

Ms. WILEY. Absolutely.

Right now, the University of Texas at Tyler, through the nursing school, is entertaining giving us an IRB number, an Internal Review Board number, so that we can be watched—the women who are on the Wiley Protocol now—in a longitudinal observational study. We would love to go head-to-head with the commercial products.

Senator SMITH. Are you tracking occurrences of any adverse effects?

Ms. WILEY. Absolutely. Dr. Julie Taguchi in Santa Barbara, CA, is in touch with all the doctors who will report to us. We track them not only through the doctors but through something——

Senator SMITH. There are adverse events?

Ms. WILEY. We have seen two blood clots in I would say we have watched over 1,000 women almost face-to-face in Santa Barbara. There are many more that report to us from Santa Fe, NM, for example. There are pockets of women all over the country——

Senator SMITH. What do you do with the information, you know, of an adverse event?

Ms. WILEY. Dr. Taguchi chronicles it and keeps it.

We right now have reported on cancer patients who have taken the Wiley Protocol post-diagnosis without active cancers. That was reported to a large group of doctors at the American Academy for the Advancement of Medicine, ACAM.

Senator SMITH. I understand that you require pharmacies to be certified——

Ms. WILEY. Well, I——

Senator SMITH [continuing]. Before they can dispense drugs.

Ms. WILEY. I found that for the Wiley Protocol I expected a certain rigor in compounding. I perceived that there is a process that

makes these hormones uniquely standardized. In other words, a woman in New Mexico can pick up the same Wiley Protocol as a woman in New York City if, in fact, she goes to a pharmacy that has agreed and committed to make them in this certain way.

I went for standardization because, obviously, it removes variables for the doctors in discerning what is going on with their patients. More importantly, I was aware that no large pharmaceutical company is going to sponsor clinical trials for the Wiley Protocol, and that clinical trials would be useless without a standardized compound.

So by engaging enough pharmacies and asking them to donate a percent of their volume that they do in the Wiley Protocol, ultimately, to a national trial, I would have a standardized product that could be looked at.

Senator SMITH. Do you have any relationship to the FDA? Do they monitor what you do?

Ms. WILEY. No. Other than they monitor the bulk substances that the Wiley Protocol, you know, derives from.

Senator SMITH. But they have investigated your products, I assume, and——

Ms. WILEY. I believe they only investigate the bulk material that pharmacists use, and then that is, as Dr. Allen said, a pharmacy-to-pharmacy case, whether or not FDA inspects——

Senator SMITH. Those women who sign up for the Wiley Protocol, you have found overwhelmingly good results?

Ms. WILEY. Surprisingly good results.

I don't know what I anticipated. I was just interested. The oncologist I have worked with for over 7, 8 years, and a very large group of doctors both in Santa Barbara and around the country, we are all surprised at how remarkably well the women seem to do.

Senator SMITH. Dr. Allen, how does the Wiley Protocol fit within your academy's view of things?

Dr. ALLEN. Well, I can address it from the formulation standpoint.

Physicians in prescribing a compounded preparation may want a certain effect, and so the pharmacist has some leeway in the different excipients, or non-active ingredients, that can be included. So for the Wiley Protocol, it is, as was explained, a set formulation so that it can be compared——

Senator SMITH. Which would be different from your members who might be coming up with their own formulations and having pharmacies produce them?

Dr. ALLEN. Yes. The individual physician, based upon what they want in their specific prescription for their specific patients, they have some flexibility in the different excipients that can be used, yes.

Senator SMITH. Dr. Manson and Dr. Wartofsky, if compounded products could be standardized, as Ms. Wiley has done with her products, would that alleviate your concerns?

Dr. WARTOFSKY. I would have——

Senator SMITH. Push your button there.

Dr. WARTOFSKY. Sorry. I would have residual concern. The concern with compounded products is that they may not be of suffi-

cient content, quality, purity, so that women might be either underdosed or overdosed.

So Dr. Allen's comment that the doctor should pick up these adverse effects really doesn't apply because some of these effects may take years, if not decades. For example, if an estrogenic compound is underdosed and leads to bone mineral loss and osteoporosis, that will show up 10, 20 years later. The doctor will not pick that up.

Ms. Wiley's standardization of her formulation that is going out across the country to different pharmacies to me is counterintuitive to customization. If she is customizing the dosage for the individual patient, how does this fit a standard protocol?

Her analogy to diabetes and insulin doesn't hold. In the case of diabetes, we have a very specific marker to follow in terms of the efficacy of insulin: the blood sugar.

As Dr. Manson mentioned, the test to measure hormones by saliva or blood tests are notoriously inaccurate and thrown off. So it is really impossible, as I mentioned in my statement, to truly customize to an individual woman what her estrogen levels or progesterone levels should be by some standard formulation analogous to insulin and blood sugar.

Ms. WILEY. May I respond?

Senator SMITH. Yes. Let me get Dr. Manson. Then we will give you the last word, like Bill O'Reilly. [Laughter.]

Dr. MANSON. I agree with all of the concerns expressed by Dr. Wartofsky. But I also want to emphasize that some of the risks of having an inadequate dose of the progesterone are very serious.

Women who have a uterus who are taking estrogen have increased growth of the lining of the uterus. It is very important that they receive an adequate dose of a progestogen, whether it is natural or synthetic, in order to avoid uterine cancer, endometrial cancer. So if there is an inadequate dose of the progestogen, then they are at an increased risk of uterine cancer.

So I think there are some very serious concerns about not having uniformity of dose or consistency, knowing exactly what doses are there.

Also, if women are being told about the lack of scientific studies, the lack of evidence that these custom-compounded hormones are any safer or more effective then, again, it seems unlikely that they would be paying as much out-of-pocket for them and having these tests done that have not been proven to have validity.

Senator SMITH. Ms. Wiley?

Ms. WILEY. Well, first of all, I am flattered that anyone could insinuate low doses with the Wiley Protocol because we use quite a bit at the Wiley Protocol.

I don't ever involve myself with individual patient response. That belongs to their doctor.

However, by testing potency four times a year at the registered pharmacies to make sure what is on the label is in the syringe—and we use syringes—by following these women with what seems to be a standardized dose—it is one dose not fits all, but starts all—the customization actually is true.

These women are all on a rhythm. I am very concerned about the curves in the rhythm. However, their doctors customize this—because it is a compounded product and not FDA-approved—they cus-

tomize the Wiley Protocol by raising or lowering the dose a couple of lines, maintaining the curves which conceptually was my concern.

As far as tests, we never use saliva. I, too, agree with all of you. It is not reliable.

However, we do use blood testing that has been standardized and considered a reasonable approach in medicine since the early 1950's—blood tests. We test for estradiol blood levels on day 12 and progesterone both, and then we test again for both on day 21.

Now, as far as expense goes, the Wiley Protocol is $75 a month, and most insurance companies do cover it, OK?

The testing is not onerous either. In the first 3 months, the woman's levels are checked to make sure she has optimum response, and her doctor can adjust it to her needs given symptoms, matching numbers.

So I think we have created something that is standardized and simultaneously customized for the first time in compounded medicine.

Senator SMITH. Well, thank you, Ms. Wiley.

Thanks to all of our witnesses. We respect your time and don't hesitate in telling you that you have each contributed, I think, wonderfully to the understanding of this Senator and to the U.S. Senate record.

This is an important issue, and what is at stake is women's health. That matters to this committee and it certainly ought to be of concern to Federal agencies charged with consumer protection and legitimacy in medicine.

This hearing has been most enlightening, and for that we thank you. We wish you all a very good day.

We are adjourned.

[Whereupon, at 11:47 a.m., the Committee was adjourned.]

APPENDIX

RESPONSES TO SENATOR SMITH QUESTIONS FROM JOANN MANSON

Question What does the April 19, 2007 *New England Journal of Medicine* report[1] mean for hormone therapy and women's health in general?

Answer. This study compared time trends in breast cancer incidence with time trends in hormone therapy use in the United States. The researchers speculated that the 7 percent decline in the incidence of breast cancer that occurred from 2002 to 2003 in this country was most likely a result of the dramatic reduction in the use of hormone therapy following the publication of the WHI estrogen-plus-progestin trial results in July 2002. However, studies of this type (i.e., time-trend ecologic studies, which compare variations in aggregate exposures and outcomes over time within a population) cannot definitively establish the existence of cause-and-effect relationships. We need more research to tease out the factors causing the drop in breast cancer rates. Declining use of hormone therapy is likely part of the answer, but the decreasing prevalence of use of screening mammography may also play a role.[2] If so, some of the apparent decline in breast cancer rates could simply reflect underdiagnosis, because fewer women are getting screened for the disease. A key question is whether deaths from breast cancer will also decline, and it will take years to answer this definitively. Additionally, another recent study suggests that breast cancer rates have been declining since 1999[3]—that is, well before the mid-2002 drop in hormone therapy use.

Nonetheless, the results of the *New England Journal of Medicine* report underscore the importance of adhering to current clinical guidelines regarding the use of hormone therapy. To minimize the increase in breast cancer risk associated with hormone therapy, use of such therapy, particularly estrogen plus progestogen, should be limited to no more than five years (and ideally no more than two or three years). It should be noted that available data, including the WHI trials, more strongly implicate estrogen plus progestogen than estrogen alone in raising breast cancer risk. (Indeed, the WHI estrogen-alone trial found no increase in risk of breast cancer after 7 years of estrogen use among women with hysterectomy.) Some data suggest that less frequent use of a progestogen (e.g., as in cyclic regimens, where the progestogen is taken for only 10–14 days per month, or even less frequently) may carry less risk than more frequent use of a progestogen (e.g., as in continuous regimens, where it is taken every day), but more research is needed on this topic.

Question. Can you clarify for the record your position on the use of the term "bioidentical"—in what circumstances would its use be appropriate or accurate?

Answer. "Bioidentical" hormone preparations properly refer to medications that contain hormones that are an exact chemical match to those made naturally by women's bodies. Bioidentical preparations fall into two broad categories: (1) FDA-approved medications that are available at commercial pharmacies in a range of standard doses, and (2) custom-compounded medications prepared according to an individualized prescription from a doctor by compounding pharmacies. This distinction must be made clear to women who are considering the use of bioidentical products. A growing number of bioidentical products have FDA approval and are widely available through retail pharmacies, so most women have no need to take on the unique risks of custom-compounded products to satisfy their preference for bioidentical over traditional hormone formulations. Another important point is that no type of menopausal hormone therapy, including bioidentical products, should be called

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[1] Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ, Edwards BK, Berry DA. The decrease in breast-cancer incidence in 2003 in the United States. *New England Journal of Medicine* 2007; 356:1670–4.

[2] Breen N, K AC, Meissner HI, Taplin SH, Tangka FK, Tiro JA, McNeel TS. Reported drop in mammography: is this cause for concern? *Cancer* 2007 [e-published on 14 May 2007]

[3] Jemal A, Ward E, Thun MJ. Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. *Breast Cancer Research* 2007; 9:R28.

"natural," because all lead to substantially higher blood levels of estrogen and/or progesterone than the levels that occur naturally in women after menopause. (also see response to question #3)

Question. Could you clarify for the record your position on the use of FDA-approved bioidentical versus custom-compounded hormone therapy products?

Answer. Provided that they are appropriate candidates for hormone therapy, women who prefer to use FDA-approved bioidentical hormone preparations (such as estradiol and micronized progesterone) rather than traditional hormone products (such as conjugated equine estrogens and synthetic progestins), or transdermal over oral delivery systems, can be encouraged to do so, as these products may offer some advantages over traditional ones. That said, until we have solid data from randomized clinical trials that indicate otherwise, the conservative and prudent approach is to assume that all FDA-approved hormone formulations confer a roughly similar balance of benefits and risks.

There is no evidence that custom-compounded bioidentical hormone products are safer than FDA-approved bioidentical products, and healthcare providers should clearly convey this message to their patients. Indeed, custom-compounded bioidentical products carry unique risks—insufficient quality control; unreliable information about benefits and risks; misleading advertising claims; and are often accompanied by unreliable and expensive saliva and blood tests;—and should not be used by most women. Few women have a legitimate need to select a custom-compounded hormone product over other hormone options. The main valid reasons for a woman to choose a custom-compounded hormone product are allergies to certain ingredients (e.g., peanut oil in Prometrium) or intolerance to doses of commercially available products. With the recent availability of many different dose levels, there should be even less need than in the past to select a custom-compounded hormone product.

Question. When you spoke of the need for clinical trials on bioidentical hormones, did you mean head-to-head studies between FDA-approved bioidentical hormone products and traditional conjugated equine products, or did you mean custom-compounded bioidentical hormones and traditional products? If you were referring to custom compounding, how could you have a controlled trial without having a "standardized" compound preparation?

Answer. There are two types of double-blinded randomized clinical trials that need to be done. First, we need clinical trials that directly compare FDA-approved bioidentical hormone products to traditional hormone therapies such as conjugated equine estrogens or other synthetic products. These studies should compare different hormone formulations, as well as routes of delivery (such as pill, patch, or cream), with respect to their effects on blood-based biomarkers (including levels of cholesterol, C-reactive protein and other markers of inflammation, and markers of thrombosis), intermediate endpoints (such as noninvasive measures of atherosclerotic build-up or mammographic density), and, eventually, hard clinical endpoints (such as heart attack or breast cancer). Second, we need clinical trials that directly compare FDA-approved bioidentical hormone products with custom-compounded bioidentical hormones to determine which type of therapy, if either, is more effective at relieving menopausal symptoms and improving quality of life and sleep. In the FDA-approved bioidentical hormone arm of such a trial, the dosing should be determined in the usual way—i.e., start with the lowest possible dose and then adjust the dose based on the symptoms subsequently reported by the participant. In the custom-compounded bioidentical hormone arm, the initial and subsequent dosing would be based on results of ongoing blood and saliva tests until hormone levels are "stabilized" according to a preset protocol. Both types of clinical trials are affordable and feasible; they can be conducted with relatively few women and in a short time span, providing answers to many of the research questions in 6 to 12 months of follow-up. If initial trials look promising, then serious consideration should be given to mounting a large-scale clinical trial to compare the effect of these various hormone products on clinical events.

RESPONSES TO SENATOR SMITH QUESTIONS FROM LEONARD WARTOFSKY

Question. In your testimony you referenced internet pharmacies going beyond proper professional bounds and doctors on the "fringe" who were prescribing compounded bioidenticals. Can you give the Committee any further information on these problems you've identified, i.e. where and how frequently this is happening?

Answer. Unfortunately, no hard data exists detailing how frequently physicians in the broader medical community are prescribing compounded bioidentical hormones. However, the vast majority of The Endocrine Society members support our position statement, providing evidence that most endocrinologists do not prescribe

these. Opportunities do exist for patients to obtain compounded bioidentical hormones without a prescription from their regular physicians. We have attached links to three websites that provide women with the names of physicians who are willing to prescribe bioidentical hormones for them if their primary physician is unwilling to do so. Although compounding pharmacies claim that they are only filling the prescriptions that are generated by physicians, pharmacies such as these provide the means for women to get a prescription without the assistance or oversight of the physicians with whom they have a medical relationship.

http://www.gethormones.com/physicians.html
http://www.womensinternational.com/resources.html
http://www.naturalwoman.org/

Question. In your testimony you mentioned the National Association of State Boards of Pharmacy had guidelines on compounding that were only adopted by a quarter of states to date—is that statistic available in a report or paper you could share with the Committee?

Answer. The National Association of State Boards of Pharmacy issued "Good Compounding Practices Applicable to State Licensed Pharmacies," which may be viewed through the link below. The model code provides State Boards of Pharmacy with a framework for developing requirements for compounding pharmacies. As of 2003, only 10 states had adopted this code, which was identified through the 2003 testimony of Steven Galson, Acting Director, Center for Drug Evaluation and Research, FDA, before the Senate Committee on Health, Education, Labor, and Pensions, "Some of the stakeholder groups with whom we have interacted are engaged in activities intended to provide greater confidence in the quality of compounded medications. For example, the NABP has a model code governing pharmacy compounding that substantially has been adopted by ten states. The model code provides State Boards of Pharmacy with a framework for developing requirements for compounding pharmacies."

(http://www.fda.gov/ola/2003/pharmacycompound1023.html) Current statistics on the number of states that have adopted this code were available.

http://www.nabp.net/ftpfiles/NABP01/ModelActFINAL.doc

Question. You have mentioned some concerns about compounded products that can be attained over the internet. Could you explain those concerns and share any examples of bad actors known to the Endocrine Society? What more needs to be done to ensure product quality and safety the area of internet available compounded products?

Answer. As we mentioned above, there are compounding pharmacies that will provide women with the names of physicians who have already agreed to provide prescriptions for compounded hormones, even if they are not regular patients. In my work on thyroid conditions, I have come across a number of websites that are providing questionable advice and medical supplements for "Wilson's Syndrome."* We have attached links to a few websites as examples that can easily be accessed through a Google search.

http://www.wilsonstemperaturesyndrome.com/index.html
www.netriceuticals.com/
www.naturalhealthconsult.com

However, we cannot say with any certainty whether the practices of these organizations or those mentioned in Question #1 go beyond the bounds of the ethical or legally allowed practices of the medical community. We do believe that the decision about the best hormone therapy for a patient should only be made by the patient and her physician. Only when this happens can a woman be assured that she is receiving the best therapy for her individual needs. In order to ensure that women have access to safe and effective treatments, greater regulation of the production and marketing of compounded bioidentical hormones is needed.*An invented "syndrome"by a Florida physician, Dr. Wilson, to promote sale of his products.

RESPONSE TO SENATOR MCCASKILL QUESTION FROM LEONARD WARTOFSKY

Question. What are the growth or development risks to children of exposure to bioidentical hormones their parent or caregiver is using?

Answer. A small number of cases of children's virilization have been reported since 1999 as a result of exposure to topical testosterone preparations used by their fathers. The articles referenced below provide case reports of the effects of these testosterone preparations on small children. In the study conducted by Kunz, et al, 5 of the 6 caretakers obtained the products through Internet sites or interstate phar-

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*An invented "syndrome" by a Florida physician, Dr. Wilson, to promote sale of his products.

maceutical commerce, often without a prescription. The children suffered from masculinization of the genitals and enlargement of the clitoris or penis, rapid linear growth and bone maturation, development of pubic hair and acne, and aggressive behavior. In almost all cases, the symptoms regressed after the men ceased use of the topical preparations.

Brachet C, Vermeulen J, Heinrichs C.
Children's virilization and the use of a testosterone gel by their fathers.
Eur J Pediatr. 2005 Oct;164(10):646–7. Epub 2005 Jul 16.
Kunz GJ, Klein KO, Clemons RD, Gottschalk ME, Jones KL.
Virilization of young children after topical androgen use by their parents.
Pediatrics. 2004 Jul;114(1):282–4.

RESPONSES TO SENATOR SMITH QUESTIONS FROM LOYD V. ALLEN

Question. In your testimony, you discussed the issue of labeling compounded products and expressed that you were generally supportive of a labeling requirement. I understand that there is potential for developing a centralized database for pharmacists to use in order to provide a patient printout that provides uniform information about his or her medication. Can you share with the Committee how this would work, why it would be helpful, and when nationwide availability of such a database could be feasible?

Answer. The U.S. Pharmacopoeia (USP) has developed the USP–DI, or USP Drug Information database. The database was developed by physicians and pharmacists over several years and is very comprehensive. It consists of three volumes: Volume I is Drug Information for the Health Care Professional; Volume II is Advice for the Patient (Drug Information in Lay Language); and Volume III is Approved Drug Products and Legal Requirements. These are currently being published by Thomson-Micromedex.

The specific database that can be of benefit for compounding pharmacy and patients is Volume II Advice for the Patient. This database is at the USP offices in Rockville, MD and can be modified to meet the needs for pharmacy compounding. The database can be reformatted and licensed to the various software vendors that supply the software programs to compounding pharmacists. As the label for a compounded prescription is printed, the patient advisory leaflet information that is given to the patient can also be printed. This is similar to what is currently used for commercially manufactured prescriptions that print the patient advisory leaflet for the commercial product along with the label for dispensing to the patient.

This is a workable solution and could be implemented relatively quickly as the database is already available.

Question. There was considerable discussion in the hearing about the use of the term "bioidentical" when describing that particular type of hormone therapy. What is your opinion on the use of bioidentical as a descriptive?

Answer. The word "bioidentical" is a contraction of the worlds "bios," meaning "life," and "identical," meaning "the same as". Therefore, "bioidentical" means "the same as life" or identical to what is in the living body. This is in contrast to those substances that are not the same as those that naturally occur in the human body, such as synthetic conjugated hormones. The term bioidentical is descriptive of reality but has been misused.

To resolve this, since we commonly use the official term "Human Insulin" for insulin that is identical to that which occurs in the human body, it may be better to use the term "Human Hormones" to designate those that are identical to those in the body. The non-human hormones (conjugated estrogens, etc.) could not use this designation. (This is appropriate because human insulin is derived from non-human sources but is altered to be chemically identical to that in the body, just like bioidentical hormones are derived from yams and soy but are chemically altered to be identical to those in the body, i.e. bioidentical). The American Diabetes Association and the American Medical Association both use the term "Human Insulin," and the official name in the USP is Human Insulin USP.

The term "natural" is another term that has been used in a confusing manner. Human hormones are those that occur naturally in the body. However, the starting point for the chemical preparation of some of these human hormones is the naturally grown soy beans, yams, etc. The precursor chemical is extracted from these plants and is then chemically modified to the hormones that are bioidentical to those human hormones that are naturally in the body. This tends to be confusing to many people. If one also looks at the marketing of some low dose progesterone products available in the market place, they use the term natural, generally referring to the source of the hormone. So, the term "natural" can refer to either the

human hormones that occur naturally in the body or to the natural source from which they are derived.

Question. How safe is "bioidentical" hormone therapy from a pharmacist's viewpoint?

As a pharmacist, many things that occur naturally in the body are used therapeutically, including water, electrolytes (sodium, potassium, etc.), thyroid, pancreatic enzymes and insulin. We are simply replacing what the body has lost.

Bioidentical hormones are available in commercially manufactured (e.g., Prometriuim, Estragel, Androgel) and compounded forms. These have been recognized as safe and effective by the Food and Drug Administration. Since these hormones are the same as what the body has been producing for years, they should be safe, effective and without adverse problems provided the dosing is done properly, which is worked out between the physician, patient and the pharmacist. So yes, in my opinion they are safe and effective when properly used.

Question. We have discussed how you believe that the states are in the best position to regulate the practice of pharmacy compounding. I am told one of the challenges facing state boards of pharmacy is the lack of sufficient staffing (and funding) to do the type of inspections and investigations that could provide a higher level of oversight.How many additional staff members would each state need to start making a greater enforcement impact, and how much would it potentially cost to provide the personnel and training that they need?

Answer. The practice of pharmacy should be regulated by the state boards of pharmacy. As pharmacy practice changes, the state boards adapt to these changes. The standards of the USP related to pharmacy compounding are being implemented by the states, either directly or by rewriting them on a state-by-state basis. Enclosed please find a document prepared about three years ago, entitled "Reasons the FDA Should Not Be Involved In Pharmacy Compounding."

The individual state boards of pharmacy may need some supplemental funding for additional inspectors, depending upon the needs of the individual states. This may range from 1 to 5 additional inspectors per state with an overall average estimate of 2 per state, or 100 new inspectors. At salary plus benefits of about $100,000 per year per position this amounts to $10 million dollars. This could be provided initially in the form of grants for the first few years, similar to other programs provided by the Federal Government, as the states eventually assume funding for these and the federal funds are decreased and eventually eliminated as the program becomes totally supported at the state level.

WHITE PAPER #1

DID YOU KNOW THAT WITHOUT PHARMACY COMPOUNDING:

- children would not have available to them syrups, elixirs, suspensions and emulsions for most drugs that would make it easier to take medications
- elders would not have access to new dosage forms to make it easier to take their medications
- patients, while hospitalized, would receive numerous different drugs individually instead of combined in a single intravenous admixture
- cancer drugs, if they could be given, would have to be given individually, rather than combined, which would result in longer administration times
- physicians would not have most nuclear pharmaceuticals available to diagnose or treat illnesses
- adults would be limited to very few strengths of drugs, unless they were willing to break the tablets apart to obtain the dose needed
- therapy of many types would not be available to patients, to include bioidentical hormone replacement therapy (BHRT)
- patients would need to take drugs orally or by injection instead of by the newer methods of delivery into the body, to include transdermal gels, etc.
- drugs that are discontinued due to "economic reasons" by a pharmaceutical manufacturer would no longer be available to patients
- drugs that are in short supply would not be available and this would interrupt a patient's therapy that took so long to stabilize
- orphan drugs would be available to limited patients only
- patients would not have the option of new therapeutic approaches that physicians would like to use
- patients who are allergic to a preservative, dye, flavor, or other ingredient in a commercial product would have no options
- individuals maintained on "intravenous feeding" would require several different individual components administered separately instead of a single, compounded mixture

- patients would not have available to them the options of gummy bears, popsicles, most of the transdermal gels, oral inhalation solutions, medication sticks, iontophoresis solutions, phonophoresis solutions, etc.

- infants who are born prematurely would not have available to them many lifesaving and life-sustaining drugs

- infants would not have available to them many drugs

[®]Loyd V. Allen, Jr., Ph.D., Editor-in-Chief, International Journal of Pharmaceutical Compounding, www.IJPC.com

WHITE PAPER #2

Pharmacy Compounding is Important in Today's Healthcare

In the past, Compounding Was Pharmacy! Throughout history, pharmacists have had to compound drugs for individualized dosages for patients when they were prescribed by physicians. In the early 1900s, however, the pharmaceutical industry began manufacturing a myriad of drugs and dosage forms for patients and the need for compounding diminished. Since the late 1900s, a lot has changed and the pharmaceutical industry no longer supplies all the medications needed by patients. Pharmacy Compounding is important for the following reasons:

1. **LIMITED DOSAGE STRENGTHS**: The pharmaceutical industry supplies only limited strengths of drugs. One size does not fit all and it is often *necessary* to change the strength of a drug for patients through compounding.

2. **LIMITED DOSAGE FORMS**: The pharmaceutical industry supplies only limited dosage forms; generally only an oral solid (tablet or capsule) and/or injection are manufactured. This does not address the needs of children, premature infants, the elderly, and special needs patients. In fact, Congress has made it possible for the industry to obtain additional patent protection if they manufacture a pediatric (children's) form of the drug, but most companies still do not do this because it is not economically feasible for them. Therefore, compounding is necessary.

3. **HOME HEALTH CARE**: A significant percentage of the needs of home healthcare patients are satisfied by compounded medications, including, for example, total parenteral nutrition (intravenous fats, sugars, and amino acids) necessary for the healing of colon disorders post-operatively. These patients cannot be satisfactorily medicated or sustain the nutritional status needed for healing with manufactured dosage forms.

4. **HOSPICE AND PALLIATIVE CARE PATIENTS**: End-of-life therapy involves the compounding of many different and unique dosage forms to allow patients to live out their lives free of pain and discomfort. Many combinations of drugs are used for these patients who cannot swallow medications and who don't have the muscle mass that is required to receive multiple injections each day. Other methods include compounded medications for oral inhalation, nasal administration, topical/transdermal, and rectal use.

5. **DISCONTINUED DRUGS**: The pharmaceutical industry has discontinued thousands of drug products over the past 25 years, many due to economic considerations. These were very effective and important medications. The only way they are now available is through pharmacy compounding.

6. **DRUG SHORTAGES**: With over 70% of all bulk drug chemicals being imported for the U.S. pharmaceutical industry and for compounding, commercially manufactured

drugs become unavailable for various reasons. In many cases, these can be compounded to help "bridge the gap" until the commercial product comes back on the market.

7. **INTRAVENOUS ADMIXTURES IN HOSPITALS**: Many, if not most, of the lifesaving intravenous drugs given in hospitals and clinics are compounded. This saves the hospital personnel time and the patient multiple injections or administrations. It is hard to imagine being in the hospital without intravenous admixtures being available.

8. **ORPHAN DRUGS**: When physicians prescribe drugs that are not on the market, they may be available as orphan drugs, either commercially or compounded.

9. **SPECIAL PATIENT POPULATIONS**: Included here would be *pain management* patients, *bioidentical hormone replacement therapy (BHRT)* patients, *sports injury* patients (professional, collegiate, Olympic and other amateur athletes), *dental* patients, *dermatological* patients, *environmentally and cosmetically sensitive* patients, and *other* patients who are being treated successfully with compounded medications prescribed by physicians. In fact, *cancer treatment* often involves compounded "cocktails", or mixtures of cancer drugs that would be unavailable if they could not be compounded. Specialty compounded drugs for eye surgery, bone surgery, etc. would not be available.

10. **NEW THERAPEUTIC APPROACHES**: If a physician desires to use a medication that is successfully used in other countries but is not commercially available in the U.S., that physician can prescribe a compounded formulation of the medication for patients. An FDA-approved oral therapy prescribed as a topical gel for arthritis treatment to avoid gastric bleeding could reduce the overall cost of healthcare by avoiding hospitalization from a gastric bleed.

11. **VETERINARY COMPOUNDING**: Animals can be grouped into various categories, including small, large, herd, exotic, and companion groups. There are actually relatively few medications available for animals, and those medications that are available are for specific species and diseases. In most cases, for an animal to be satisfactorily treated, a compounded medication may be necessary.

12. **CLINICAL STUDIES**: Pharmacists compound drugs that are not commercially available for use in various clinical studies.

13. **NUCLEAR COMPOUNDING:** A radioactive source is "tagged" to a compound that circulates throughout the body and eventually concentrates in the organ under exploration. With over 100 different types of nuclear procedures performed every day, the most commonly performed procedure is organ imaging; to determine blood flow and function of the heart, blockage of the gallbladder, measure lungs for respiratory and blood-flow problems, bones for fracture, infection, arthritis or tumor,

bleeding of the bowel, locate the presence of infection, measure thyroid function, and to determine the presence or spread of cancer.

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WHITE PAPER #3

RECENT ADVANCES IN QUALITY PHARMACY COMPOUNDING

In the past, Compounding Was Pharmacy! Throughout history, pharmacists have compounded drugs for individualized dosages for patients when they were prescribed by physicians. In the early 1900s however, the pharmaceutical industry began manufacturing a myriad of drugs and dosage forms for patients and the need for compounding diminished. Since the late 1900s however, a lot has changed and the pharmaceutical industry no longer supplies all the medications needed by patients. Pharmacy compounding has experienced tremendous growth. It has not, however, been without its detractors. True, there have been some difficulties along the way, but recently great strides have been made to enhance the quality of pharmacy compounding, including the following:

PHARMACY COMPOUNDING ACCREDITATION BOARD

A consortium of eight national pharmacy organizations have worked together to establish the Pharmacy Compounding Accreditation Board. Operating through the offices of the National Association of Boards of Pharmacy, this board began the process of accrediting compounding pharmacies in the spring of 2005. The accreditation standards are rigid and require comprehensive documentation of a quality operation. Although voluntary, there are potentially some distinct advantages to becoming an accredited compounding pharmacy.

U.S. PHARMACOPEIA-NATIONAL FORMULARY

Beginning in 1985 at the U.S. Pharmacopoeial Convention, a resolution regarding pharmacy compounding was passed, and this has been followed by resolutions at the 1990, 1995, 2000, and the 2005 conventions concerning increased efforts in establishing pharmacy compounding standards and especially efforts related to special populations (pediatrics). In recent years, two enforceable general chapters have been implemented, including *USP* Chapter <795> Pharmaceutical Compounding—Nonsterile Preparations, and *USP* Chapter <797> Pharmaceutical Compounding—Sterile Preparations. In addition, two additional *USP* informational chapters are in effect, including, *USP* Chapter <1075> Good Compounding Practices, and *USP* Chapter <1160> Pharmaceutical Calculations in Prescription Compounding. A new chapter on Quality Control in Pharmacy Compounding <1163> has been prepared. In addition to the General Chapters, the *USP-NF* currently contains approximately 225 monographs related to pharmacy compounded preparations.

U.S. PHARMACOPEIA-PHARMACISTS PHARMACOPEIA

The *U.S. Pharmacopeia* was originally developed for pharmacists. However, the emphasis of the current *USP-NF* is directed towards the pharmaceutical industry. The *USP-Pharmacists Pharmacopeia* was launched in the summer of 2005. This set of

compounding standards can be enforced by the State Boards of Pharmacy, as well as the US Food and Drug Administration. The *USP-Pharmacists Pharmacopeia* is divided into two sections. Section one contains monographs for compounding substances and excipients and monograph standards for compounded preparations, as well as general chapters related to compounding standards. Section two contains supportive information for quality pharmacy compounding. This compendium will be continually revised and updated.

AMERICAN COUNCIL ON PHARMACEUTICAL EDUCATION (ACPE)

The American Council on Pharmaceutical Education has requested performance outcomes related to pharmacy compounding. These will be presented to ACPE this spring for consideration for implementation in the curriculum of accredited Colleges of Pharmacy throughout the U.S. ACPE standards are required for accreditation of Colleges of Pharmacy.

AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY (AACP) -TEACHERS OF PHARMACEUTICS

The Teachers of Pharmaceutics section of AACP is surveying its membership to determine the current status of pharmaceutics and compounding in the curriculum. The in-depth survey is designed to identify course content that is either taught as separate, free-standing courses, or as an integrated component of other courses.

PHARMACY COMPOUNDING EDUCATIONAL PROGRAMS

Many pharmacy compounding support companies, as well as the *International Journal of Pharmaceutical Compounding*, provide programs and information on pharmacy compounding. In addition, there are several books and websites available (e.g., www.ijpc.com; www.compoundingtoday.com) that provide information to support pharmacists in all practice sites (community, hospital, home healthcare, etc.) in pharmacy compounding.

LABORATORY SUPPORT

Analytical support is provided by several laboratories throughout the U.S., many of which are FDA-registered and -inspected. Potency analysis, sterility and endotoxin testing is now commonplace. In addition to outsourcing to these laboratories, some pharmacies (community as well as hospital) use in-house testing when appropriate.

[5] Loyd V. Allen, Jr., Ph.D., Editor-in-Chief, International Journal of Pharmaceutical Compounding, www.IJPC.com

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3. **HOME HEALTH CARE**: A significant percentage of the needs of home healthcare patients is satisfied by compounded medications, including total parenteral nutrition (intravenous fats, sugars and amino acids) necessary for the healing of colon disorders post-operatively.

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WHITE PAPER #4

REASONS THE FDA SHOULD NOT BE INVOLVED IN PHARMACY COMPOUNDING

In the past, Compounding Was Pharmacy! Throughout history, pharmacists compounded drugs for patients as they were prescribed by physicians.

- In 1820, the U.S. Pharmacopeia established monographs for pharmacy compounding for the U.S. In 1906, the U.S. Pure Food and Drug Act established the *U.S. Pharmacopeia* and *National Formulary,* two of the official compendia of standards for pharmaceuticals in the U.S.

- In the early 1900s, however, the pharmaceutical industry began manufacturing most drugs and dosage forms for patients.

- The U.S. Food and Drug Administration (FDA) was established with the passage of the Federal Food, Drug and Cosmetic Act of 1938 to develop and enforce standards for manufactured drugs.

During the mid-1900s, with the large effort by the pharmaceutical industry to providing numerous strengths and dosage forms for drugs, the need for compounding diminished. Since the late 1900s a lot has changed and the pharmaceutical industry no longer supplies all the medications needed by patients. Pharmacy compounding has experienced tremendous growth. It has not, however, been without its detractors demanding that the FDA control compounding. The FDA recognizes the importance of, and need for pharmacy compounding. This is also true of the Supreme Court and the U.S. Congress; all recognize the contribution of pharmacy compounding to modern health care today.

Individual states enact laws to establish the various professions and their requirements. The State Boards of Pharmacy are established to enforce the components of these acts as they relate to pharmacy. ***Pharmacy compounding is addressed in state boards of pharmacy regulations or the laws within the states.*** This should be adequate and places the control and enforcement of pharmacy compounding at the state level, not the federal level. The FDA was created to enforce requirements on the pharmaceutical industry and not on pharmacy practices. However, the FDA has expanded its reach in recent years due to a blurring of the line between compounding and manufacturing. This gray area needs to be clarified for all involved through the state boards of pharmacy. This presentation does not necessarily address this gray area of compounding but it does address the role of pharmacy compounding in the relationship between a physician, patient and pharmacist.

The FDA should not be involved in pharmacy compounding for the following reasons:

1. The FDA's definition of a "New Drug" requires that all compounded formulations and any manipulation of a commercially manufactured product outside its officially, approved labeling, is an unapproved new drug. In fact, a significant percent of drugs are used for indications other than what their official labeling states.

2. It is impractical to require that each and every one of the thousands of formulations prescribed by physicians and compounded every day be submitted to the FDA as an Investigational New Drug with accompanying documentation (this includes hospital intravenous admixtures, etc). The current cost to get a single drug to market is from 200 to 500 million dollars.

3. No entity would be interested in financing all the clinical trials to support each and every one of the compounded formulations as there would be insufficient income from these compounded preparations to pay for the research and clinical studies. Already, many FDA-approved drugs are discontinued by the pharmaceutical manufacturers for "economic reasons" when sufficient profit is not gained from them.

4. A physician may prescribe a change in strength or delivery route that would, under these requirements, be considered another "New Drug" that has not been tested. Why should a physician be denied the right to prescribe a change in strength or delivery route and a patient be denied the right to adequate health care and treatment that could be cost-saving only because the FDA views it as another "New Drug"?

5. The time requirement and logistics of studies for these compounded formulations would be difficult, if not impossible. For example, providing patient populations for these thousands of studies would be a formidable, if not an impossible task.

6. A change in the vehicle, due to the preferences of different physicians, would again require additional New Drug applications.

7. There is no patent protection for these formulas since they are prescribed by physicians for individual patients. Therefore, there is no incentive to do it.

8. The FDA is a large, complex governmental agency where communication between departments seems somewhat limited.

9. It has become apparent in recent years that the FDA is not really charged with the responsibility of keeping the pharmaceutical supply intact in the U.S. They have closed down manufacturing facilities that eliminated the availability of numerous drugs which left physicians with no alternative source of the drugs other than to prescribe them as medications that need compounding.

10. FDA approval of a drug is no guarantee that adverse events, even deaths, will not occur.

11. The current mechanism(s) related to single patient INDs, orphan drugs, and compassionate use are not feasible for physicians to initiate, as many patients are "one of a kind" and the time required for the current mechanism(s) are unrealistic.

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ORIGINAL CONTRIBUTION JAMA-EXPRESS

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the Women's Health Initiative Investigators

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

Interventions Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

Main Outcomes Measures The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Results On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10000 person-years.

Conclusions Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

JAMA. 2002;288:321-333 www.jama.com

For editorial comment see p 366.

Author Information and Financial Disclosures appear at the end of this article.

The Women's Health Initiative (WHI) focuses on defining the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women. Between 1993 and 1998, the WHI enrolled 161809 postmenopausal women in the age range of 50 to 79 years into a set of clinical trials (trials of low-fat dietary pattern, calcium and vitamin D supplementation, and 2 trials of postmenopausal hormone use) and an observational study at 40 clinical centers in the United States.[1] This article reports principal results for the trial of combined estrogen and progestin in women with a uterus. The trial was stopped early based on health risks that exceeded health benefits over an average follow-up of 5.2 years. A parallel trial of estrogen alone in women who have had a hysterectomy is being continued, and the planned end of this trial is March 2005, by which time the average follow-up will be about 8.5 years.

The WHI clinical trials were designed in 1991-1992 using the accumulated evidence at that time. The primary outcome for the trial of estrogen plus progestin was designated as coronary heart disease (CHD). Potential cardioprotection was based on generally

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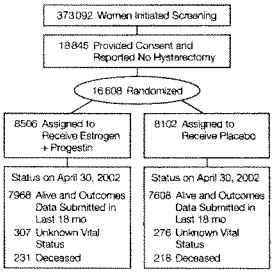
Figure 1. Profile of the Estrogen Plus Progestin Component of the Women's Health Initiative



supportive data on lipid levels in intermediate outcome clinical trials, trials in nonhuman primates, and a large body of observational studies suggesting a 40% to 50% reduction in risk among users of either estrogen alone or, less frequently, combined estrogen and progestin.[2-5] Hip fracture was designated as a secondary outcome, supported by observational data as well as clinical trials showing benefit for bone mineral density.[6,7] Invasive breast cancer was designated as a primary adverse outcome based on observational data.[3,8] Additional clinical outcomes chosen as secondary outcomes that may plausibly be affected by hormone therapy include other cardiovascular diseases; endometrial, colorectal, and other cancers; and other fractures.[3,6,9]

The effect of hormones on overall health was an important consideration in the design and conduct of the WHI clinical trial. In an attempt to summarize important aspects of health benefits vs risks, a global index was defined as the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other causes. Compared with total mortality, which may be too insensitive, this index assigns additional weight to the 7 listed diseases. Procedures for monitoring the trial involved semiannual comparisons of the estrogen plus progestin and placebo groups with respect to each of the elements of the global index and to the overall global index.

This report pertains primarily to estrogen plus progestin use among healthy postmenopausal women, since only 7.7% of participating women reported having had prior cardiovascular disease. During the course of the WHI trial, the Heart and Estrogen/progestin Replacement Study (HERS) reported its principal results.[10] HERS was another blinded, randomized controlled trial comparing the same regimen of estrogen plus progestin with placebo among women with a uterus; however, in HERS, all 2763 participating women had documented CHD prior to randomization. The HERS findings of no overall effect on CHD but an apparent increased risk in the first year after randomization seemed surprising given preceding observational studies of hormone use in women with CHD.[3] Subsequent to HERS, some investigators reanalyzed their observational study data and were able to detect an early elevation in CHD risk among women with prior CHD[11-13] but not in ostensibly healthy women,[14] prompting speculation that any early adverse effect of hormones on CHD incidence was confined to women who have experienced prior CHD events.

The WHI is the first randomized trial to directly address whether estrogen plus progestin has a favorable or unfavorable effect on CHD incidence and on overall risks and benefits in predominantly healthy women.

METHODS

Study Population

Detailed eligibility criteria and recruitment methods have been published.[1] Briefly, most women were recruited by population-based direct mailing campaigns to age-eligible women, in conjunction with media awareness programs. Eligibility was defined as age 50 to 79 years at initial screening, postmenopausal, likelihood of residence in the area for 3 years, and provision of written informed consent. A woman was considered postmenopausal if she had experienced no vaginal bleeding for 6 months (12 months for 50- to 54-year-olds), had had a hysterectomy, or had ever used postmenopausal hormones. Major exclusions were related to competing risks (any medical condition likely to be associated with a predicted survival of <3 years), safety (eg, prior breast cancer, other prior cancer within the last 10 years except nonmelanoma skin cancer, low hematocrit or platelet counts), and adherence and retention concerns (eg, alcoholism, dementia).

A 3-month washout period was required before baseline evaluation of women using postmenopausal hormones at initial screening. Women with an intact uterus at initial screening were eligible for the trial of combined postmenopausal hormones, while women with a prior hysterectomy were eligible for the trial of unopposed estrogen. This report is limited to the 16608 women with an intact uterus at baseline who were enrolled in the trial component of estrogen plus progestin vs placebo. The protocol and consent forms were approved by the institutional review boards for all participating institutions (see Acknowledgment).

Study Regimens, Randomization, and Blinding

Combined estrogen and progestin was provided in 1 daily tablet containing conjugated equine estrogen (CEE), 0.625 mg, and medroxyprogesterone acetate (MPA), 2.5 mg (Prempro, Wyeth Ayerst, Philadelphia, Pa). A matching placebo was provided to the control group. Eligible women were randomly assigned to receive estrogen plus progestin or placebo after eligibility was established and baseline assessments made (FIGURE 1). The randomization procedure was developed at the WHI Clinical Coordinating Center and implemented locally through a distributed study database, using a randomized permuted block algorithm, stratified by clinical center site and age group. All study medication bottles had a unique bottle number and bar code to allow for blinded dispensing.

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Initially, the design allowed women with a uterus to be randomized to receive unopposed estrogen, estrogen plus progestin, or placebo. After the release of the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial results[15] indicating that long-term adherence to unopposed estrogen was not feasible in women with a uterus, the WHI protocol was changed to randomize women with a uterus to only estrogen plus progestin or placebo in equal proportions. The 331 women previously randomized to unopposed estrogen were unblinded and reassigned to estrogen plus progestin. These women are included in the estrogen plus progestin group in this report, resulting in 8506 participants in the estrogen plus progestin group vs 8102 in the placebo group. Analysis of the data excluding the women randomized before this protocol change did not affect the results. Considerable effort was made to maintain blinding of other participants and clinic staff. When required for safety or symptom management, an unblinding officer provided the clinic gynecologist, who was not involved with study outcomes activities, with the treatment assignment.

Follow-up

Study participants were contacted by telephone 6 weeks after randomization to assess symptoms and reinforce adherence. Follow-up for clinical events occurred every 6 months, with annual in-clinic visits required. At each semiannual contact, a standardized interview collected information on designated symptoms and safety concerns, and initial reports of outcome events were obtained using a self-administered questionnaire. Adherence to study interventions was assessed by weighing of returned bottles. The study protocol required annual mammograms and clinical breast examinations; study medications were withheld if safety procedures were not performed, but these participants continued to be followed up. Electrocardiograms were collected at baseline and at follow-up years 3 and 6.

Data Collection, Management, and Quality Assurance

All data were collected on standardized study forms by certified staff according to documented study procedures. Study data were entered into a local clinical center database developed and maintained by the Clinical Coordinating Center and provided to each site in the form of a local area network connected to the Clinical Coordinating Center through a wide area network. Data quality was ensured through standard data entry mechanisms, routine reporting and database checks, random chart audits, and routine site visits.

Maintenance/Discontinuation of Study Medications

During the trial, some flexibility of the dosages of both estrogen and progestin was allowed to manage symptoms such as breast tenderness and vaginal bleeding. Vaginal bleeding was managed according to an algorithm that accounted for the time since randomization, severity of the bleeding, treatment assignment, and endometrial histology. Women who had a hysterectomy after randomization for indications other than cancer were switched to unopposed estrogen or the corresponding placebo without unblinding. These women are included in the original randomization group for analyses.

Permanent discontinuation of study medication was required by protocol for women who developed breast cancer, endometrial pathologic state (hyperplasia not responsive to treatment, atypia, or cancer), deep vein thrombosis (DVT) or PE, malignant melanoma, meningioma, triglyceride level greater than 1000 mg/dL (11.3 mmol/L), or prescription of estrogen, testosterone, or selective estrogen-receptor modulators by their personal physician. Medications were temporarily discontinued in participants who had acute myocardial infarction (MI), stroke, fracture, or major injury involving hospitalization, surgery involving use of anesthesia, any illness resulting in immobilization for more than 1 week, or any other severe illness in which hormone use is temporarily inappropriate.

Outcome Ascertainment

Cardiovascular Disease. Coronary heart disease was defined as acute MI requiring overnight hospitalization, silent MI determined from serial electrocardiograms (ECGs), or CHD death. The diagnosis of acute MI was established according to an algorithm adapted from standardized criteria[16] that included cardiac pain, cardiac enzyme and troponin levels, and ECG readings. The primary analyses included both definite and probable MIs as defined by the algorithm. Myocardial infarction occurring during surgery and aborted MIs were included. An aborted MI was defined as chest pain and ECG evidence of acute MI at presentation, an intervention (eg, thrombolysis) followed by resolution of ECG changes, and all cardiac enzyme levels within normal ranges. Silent MI was diagnosed by comparing baseline and follow-up ECGs at 3 and 6 years after randomization. Coronary death was defined as death consistent with CHD as underlying cause plus 1 or more of the following: preterminal hospitalization with MI within 28 days of death, previous angina or MI and no potentially lethal noncoronary disease, death resulting from a procedure related to coronary artery disease, or death certificate consistent with CHD as the underlying cause. Stroke diagnosis was based on rapid onset of a neurologic deficit lasting more than 24 hours, supported by imaging studies when available. Pulmonary emholism and DVT required clinical symptoms supported by relevant diagnostic studies.

Cancer. Breast, colorectal, endometrial, and other cancers were confirmed by pathological reports when available. Current data indicate that at least 98% of breast, colorectal, and endometrial cancers and 92% of other cancers were documented with pathological reports.

Fractures. Reports of hip, vertebral, and other osteoporotic fractures (including all fractures except those of

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Table 1. Baseline Characteristics of the Women's Health Initiative Estrogen Plus Progestin Trial Participants (N = 16 608) by Randomization Assignment*

Characteristics	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	P Value†
Age at screening, mean (SD), y	63.2 (7.1)	63.3 (7.1)	.39
Age group at screening, y			
50-59	2839 (33.4)	2683 (33.1)	
60-69	3853 (45.3)	3657 (45.1)	.80
70-79	1814 (21.3)	1762 (21.7)	
Race/ethnicity			
White	7140 (83.9)	6805 (84.0)	
Black	549 (6.5)	575 (7.1)	
Hispanic	472 (5.5)	416 (5.1)	.33
American Indian	26 (0.3)	30 (0.4)	
Asian/Pacific Islander	194 (2.3)	169 (2.1)	
Unknown	125 (1.5)	107 (1.3)	
Hormone use			
Never	6280 (73.9)	6024 (74.4)	
Past	1674 (19.7)	1588 (19.6)	.49
Current‡	548 (6.4)	487 (6.0)	
Duration of prior hormone use, y			
<5	1538 (69.1)	1467 (70.6)	
5-10	426 (19.1)	357 (17.2)	.25
≥10	262 (11.8)	253 (12.2)	
Body mass index, mean (SD), kg/m²§	28.5 (5.8)	28.5 (5.9)	.66
Body mass index, kg/m²			
<25	2579 (30.4)	2479 (30.8)	
25-29	2992 (35.3)	2834 (35.2)	.89
≥30	2899 (34.2)	2737 (34.0)	
Systolic BP, mean (SD), mm Hg	127.6 (17.6)	127.8 (17.5)	.51
Diastolic BP, mean (SD), mm Hg	75.6 (9.1)	75.8 (9.1)	.31
Smoking			
Never	4178 (49.6)	3999 (50.0)	
Past	3362 (39.9)	3157 (39.5)	.85
Current	880 (10.5)	838 (10.5)	
Parity			
Never pregnant/no term pregnancy	856 (10.1)	832 (10.3)	.67
≥1 term pregnancy	7609 (89.9)	7233 (89.7)	
Age at first birth, y‖			
<20	1122 (16.4)	1114 (17.4)	
20-29	4985 (73.0)	4685 (73.0)	.11
≥30	723 (10.6)	621 (9.7)	
Treated for diabetes	374 (4.4)	360 (4.4)	.88
Treated for hypertension or BP ≥140/90 mm Hg	3039 (35.7)	2949 (36.4)	.37
Elevated cholesterol levels requiring medication	944 (12.5)	962 (12.9)	.50
Statin use at baseline¶	590 (6.9)	548 (6.8)	.66
Aspirin use (≥80 mg/d) at baseline	1623 (19.1)	1631 (20.1)	.09
History of myocardial infarction	139 (1.6)	157 (1.9)	.14
History of angina	238 (2.8)	234 (2.9)	.73
History of CABG/PTCA	95 (1.1)	120 (1.5)	.04
History of stroke	61 (0.7)	77 (1.0)	.10
History of DVT or PE	79 (0.9)	62 (0.8)	.25
Female relative had breast cancer	1286 (16.0)	1175 (15.3)	.28
Fracture at age ≥55 y	1031 (13.5)	1029 (13.6)	.87

continued

the ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae) were routinely ascertained. All fracture outcomes were verified by radiology reports. Study radiographs were not obtained to ascertain subclinical vertebral fractures.

This report is based on outcomes adjudicated by clinical center physician adjudicators, as used for trial-monitoring purposes. Clinical center physician adjudicators were centrally trained and blinded to treatment assignment and participants' symptoms. Future communications will report results based on centrally adjudicated outcomes and will include a broader range of outcomes with more extensive explanatory analyses. Since this report is presented before the planned study closeout, outcome information is still being collected and adjudicated. Local adjudication is complete for approximately 96% of the designated self-reported events. To date, agreement rates between local and central adjudication are: MI, 84%; revascularization procedures, 97%; PE, 89%; DVT, 84%; stroke, 94%; invasive breast cancer, 98%; endometrial cancer, 96%; colorectal cancer, 98%; hip fracture, 95%; and specific cause of death, 82%. When related cardiovascular conditions are combined (eg, when unstable angina or congestive heart failure is grouped with MI), agreement rates exceed 94% for cardiovascular disease and 90% for specific cause of death.

Statistical Analyses

All primary analyses use time-to-event methods and are based on the intention-to-treat principle. For a given outcome, the time of event was defined as the number of days from randomization to the first postrandomization diagnosis, as determined by the local adjudicator. For silent MIs, the date of the follow-up ECG applied. Participants without a diagnosis were censored for that event at the time of last follow-up contact. Primary outcome comparisons are presented as hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional haz-

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ards analyses,[17] stratified by clinical center, age, prior disease, and randomization status in the low-fat diet trial.

Two forms of CIs are presented, nominal and adjusted. Nominal 95% CIs describe the variability in the estimates that would arise from a simple trial for a single outcome. Although traditional, these CIs do not account for the multiple statistical testing issues (across time and across outcome categories) that occurred in this trial, so the probability is greater than .05 that at least 1 of these CIs will exclude unity under an overall null hypothesis. The adjusted 95% CIs presented herein use group sequential methods to correct for multiple analyses over time. A Bonferroni correction for 7 outcomes as specified in the monitoring plan (described herein) was applied to all clinical outcomes other than CHD and breast cancer, the designated primary and primary adverse effect outcomes, and the global index. The adjusted CIs are closely related to the monitoring procedures and, as such, represent a conservative assessment of the evidence. This report focuses primarily on results using the unadjusted statistics and also relies on consistency across diagnostic categories, supportive data from other studies, and biologic plausibility for interpretation of the findings.

Data and Safety Monitoring

Trial monitoring guidelines for early stopping considerations were based on O'Brien-Fleming boundaries[18] using asymmetric upper and lower boundaries: a 1-sided, .025-level upper boundary for benefit and 1-sided, .05-level lower boundaries for adverse effects. The adverse-effect boundaries were further adjusted with a Bonferroni correction for the 7 major outcomes other than breast cancer that were specifically monitored (CHD, stroke, PE, colorectal cancer, endometrial cancer, hip fracture, and death due to other causes). The global index of monitored outcomes played a supportive role as a summary measure of the overall balance of risks and benefits. Trial monitoring for early stopping considerations was conducted semiannually by an independent data and safety monitoring board (DSMB). Aspects of the monitoring plan have been published.[19]

Table 1. Baseline Characteristics of the Women's Health Initiative Estrogen Plus Progestin Trial Participants (N = 16 608) by Randomization Assignment* (cont)

Characteristics	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	P Value
Gail model 5-year risk of breast cancer, %			
<1	1290 (15.2)	1271 (15.7)	.64
1-<2	5384 (63.3)	5139 (63.4)	
2-<5	1751 (20.6)	1621 (20.0)	
≥5	81 (1.0)	71 (0.9)	
No. of falls in last 12 mo			
0	5168 (66.2)	5172 (67.5)	.18
1	1643 (21.0)	1545 (20.2)	
2	651 (8.3)	645 (8.4)	
≥3	349 (4.5)	303 (4.0)	

*Data are presented as number (percentage) of patients unless otherwise noted. BP indicates blood pressure; CABG/PTCA, coronary artery bypass graft/percutaneous transluminal coronary angioplasty; DVT, deep vein thrombosis; and PE, pulmonary embolism.
†Based on χ^2 tests (categorical variables) or t tests (continuous variables).
‡Required a 3-month washout prior to randomization.
§Total number of participants with data available was 8470 for estrogen plus progestin and 8050 for placebo.
‖Among women who reported having a term pregnancy.
¶Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.

RESULTS

Trial Monitoring and Early Stopping

Formal monitoring began in the fall of 1997 with the expectation of final analysis in 2005 after an average of approximately 8.5 years of follow-up. Late in 1999, with 5 interim analyses completed, the DSMB observed small but consistent early adverse effects in cardiovascular outcomes and in the global index. None of the disease-specific boundaries had been crossed. In the spring of 2000 and again in the spring of 2001, at the direction of the DSMB, hormone trial participants were given information indicating that increases in MI, stroke, and PE/DVT had been observed and that the trial continued because the balance of risks and benefits remained uncertain.

In reviewing the data for the 10th interim analyses on May 31, 2002, the DSMB found that the adverse effects in cardiovascular diseases persisted, although these results were still within the monitoring boundaries. However, the design-specified weighted log-rank test statistic for breast cancer ($z=-3.19$) crossed the designated boundary ($z=-2.32$) and the global index was supportive of a finding of overall harm ($z=-1.62$). Updated analyses including 2 months of additional data, available by the time of the meeting, did not appreciably change the overall results. On the basis of these data, the DSMB concluded that the evidence for breast cancer harm, along with evidence for some increase in CHD, stroke, and PE, outweighed the evidence of benefit for fractures and possible benefit for colon cancer over the average 5.2-year follow-up period. Therefore, the DSMB recommended early stopping of the estrogen plus progestin component of the trial. Because the balance of risks and benefits in the unopposed-estrogen component remains uncertain, the DSMB recommended continuation of that component of the WHI. Individual trial participants have been informed.

Baseline Characteristics

There were no substantive differences between study groups at baseline; 8506 women were randomized into the estrogen plus progestin group and 8102 into the placebo group (TABLE 1). The mean (SD) age was 63.3 (7.1) years. Two thirds of the women who reported prior or current hormone use had taken combined hormones and one third had used unopposed estrogen.

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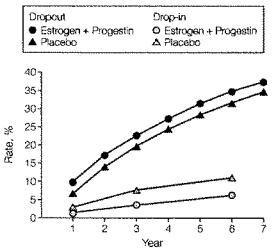
Figure 2. Cumulative Dropout and Drop-in Rates by Randomization Assignment and Follow-up Duration



Dropout refers to women who discontinued study medication; drop-in, women who discontinued study medication and received postmenopausal hormones through their own clinician.

Prevalence of prior cardiovascular disease was low and levels of cardiovascular risk factors were consistent with a generally healthy population of postmenopausal women. An assessment of commonly studied breast cancer risk factors, both individually and combined using the Gail model,[20] indicate that the cohort in general was not at increased risk of breast cancer.

Follow-up, Adherence, and Unblinding

Vital status is known for 16025 randomized participants (96.5%), including 449 (2.7%) known to be deceased. A total of 583 (3.5%) participants were lost to follow-up or stopped providing outcomes information for more than 18 months. The remaining 15576 (93.8%) provided recent outcome information (Figure 1).

At the time of this report, all women had been enrolled for at least 3.5 years, with an average follow-up of 5.2 years and a maximum of 8.5 years. A substantial number of women had stopped taking study drugs at some time (42% of estrogen plus progestin and 38% of placebo). Dropout rates over time (FIGURE 2) exceeded design projections, particularly early on, but compare favorably with community-based adherence to postmenopausal hormones.[21] Some women in both groups initiated hormone use through their own clinician (6.2% in the estrogen plus progestin group and 10.7% in the placebo group cumulatively by the sixth

Table 2. Clinical Outcomes by Randomization Assignment*

Outcomes	No. of Patients (Annualized %) Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	Hazard Ratio	Nominal 95% CI	Adjusted 95% CI
Follow-up time, mean (SD), mo	62.2 (16.1)	61.2 (15.0)	NA	NA	NA
Cardiovascular disease†					
CHD	164 (0.37)	122 (0.30)	1.29	1.02-1.63	0.85-1.97
CHD death	33 (0.07)	26 (0.06)	1.18	0.70-1.97	0.47-2.98
Nonfatal MI	133 (0.30)	96 (0.23)	1.32	1.02-1.72	0.82-2.13
CABG/PTCA	183 (0.42)	171 (0.41)	1.04	0.84-1.28	0.71-1.51
Stroke	127 (0.29)	85 (0.21)	1.41	1.07-1.85	0.86-2.31
Fatal	16 (0.04)	13 (0.03)	1.20	0.58-2.50	0.32-4.49
Nonfatal	94 (0.21)	59 (0.14)	1.50	1.08-2.08	0.83-2.70
Venous thromboembolic disease	151 (0.34)	67 (0.16)	2.11	1.58-2.82	1.26-3.55
Deep vein thrombosis	115 (0.26)	52 (0.13)	2.07	1.49-2.87	1.14-3.74
Pulmonary embolism	70 (0.16)	31 (0.08)	2.13	1.39-3.25	0.99-4.56
Total cardiovascular disease	694 (1.57)	546 (1.32)	1.22	1.09-1.36	1.00-1.49
Cancer					
Invasive breast	166 (0.38)	124 (0.30)	1.26	1.00-1.59	0.83-1.92
Endometrial	22 (0.05)	25 (0.06)	0.83	0.47-1.47	0.29-2.32
Colorectal	45 (0.10)	67 (0.16)	0.63	0.43-0.92	0.32-1.24
Total	502 (1.14)	458 (1.11)	1.03	0.90-1.17	0.86-1.22
Fractures					
Hip	44 (0.10)	62 (0.15)	0.66	0.45-0.98	0.33-1.33
Vertebral	41 (0.09)	60 (0.15)	0.66	0.44-0.98	0.32-1.34
Other osteoporotic‡	579 (1.31)	701 (1.70)	0.77	0.69-0.86	0.63-0.94
Total	650 (1.47)	788 (1.91)	0.76	0.69-0.85	0.63-0.92
Death					
Due to other causes	165 (0.37)	166 (0.40)	0.92	0.74-1.14	0.62-1.35
Total	231 (0.52)	218 (0.53)	0.98	0.82-1.18	0.70-1.37
Global index§	751 (1.70)	623 (1.51)	1.15	1.03-1.28	0.95-1.39

*CI indicates confidence interval; NA, not applicable; CHD, coronary heart disease; MI, myocardial infarction; CABG, coronary artery bypass grafting; and PTCA, percutaneous transluminal coronary angioplasty.

†CHD includes acute MI requiring hospitalization, silent MI determined from serial electrocardiograms, and coronary death. There were 8 silent MIs. Total cardiovascular disease is limited to events during hospitalization except venous thromboembolic disease reported after January 1, 2000.

‡Other osteoporotic fractures include all fractures other than chest/sternum, skull/face, fingers, toes, and cervical vertebrae, as well as hip and vertebral fractures reported separately.

§The global index represents the first event for each participant from among the following types: CHD, stroke, pulmonary embolism, breast cancer, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

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year). These "drop-in" rates were also greater than expected.

At the time of this report, clinic gynecologists had been unblinded to treatment assignment for 3444 women in the estrogen plus progestin group and 548 women in the placebo group, primarily to manage persistent vaginal bleeding. During the trial, 248 women in the estrogen plus progestin group and 183 in the placebo group had a hysterectomy.

Table 3. Cause of Death by Randomization Assignment

	No. (Annualized %)	
	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)
Total deaths	231 (0.52)	218 (0.53)
Adjudicated deaths	215 (0.49)	201 (0.49)
Cardiovascular	65 (0.15)	55 (0.13)
Breast cancer	3 (0.01)	2 (<0.01)
Other cancer	104 (0.24)	86 (0.21)
Other known cause	34 (0.08)	41 (0.10)
Unknown cause	9 (0.02)	17 (0.04)

Intermediate Cardiovascular Disease End Points

Blood lipid levels, assessed in an 8.6% subsample of fasting blood specimens collected from women at baseline and year 1, showed greater reductions in low-density lipoprotein cholesterol (−12.7%) and increases in high-density lipoprotein cholesterol (7.3%) and triglycerides (6.9%) with estrogen plus progestin relative to placebo (data not shown), consistent with HERS and PEPI.[10,22] Systolic blood pressure was, on average, 1.0 mm Hg higher in women taking estrogen plus progestin at 1 year, rising to 1.5 mm Hg at 2 years and beyond (data not shown). Diastolic blood pressures did not differ.

Clinical Outcomes

Cardiovascular Disease. Overall CHD rates were low (TABLE 2). The rate of women experiencing CHD events was increased by 29% for women taking estrogen plus progestin relative to placebo (37 vs 30 per 10000 person-years), reaching nominal statistical significance (at the .05 level). Most of the excess was in nonfatal MI. No significant differences were observed in CHD deaths or revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty). Stroke rates were also higher in women receiving estrogen plus progestin (41% increase; 29 vs 21 per 10000 person-years), with most of the elevation occurring in nonfatal events. Women in the estrogen plus progestin group had 2-fold greater rates of venous thromboembolism (VTE), as well as DVT and PE individually, with almost all associated CIs excluding 1. Rates of VTE were 34 and 16 per 10000 person-years in the estrogen plus progestin and placebo groups, respectively. Total cardiovascular disease, including other events requiring hospitalization, was increased by 22% in the estrogen plus progestin group.

Cancer. The invasive breast cancer rates in the placebo group were consistent with design expectations. The 26% increase (38 vs 30 per 10000 person-years) observed in the estrogen plus progestin group almost reached nominal statistical significance and, as noted herein, the weighted test statistic used for monitoring was highly significant. No significant difference was observed for in situ breast cancers. Follow-up rates for mammography were comparable in the estrogen plus progestin and placebo groups. Colorectal cancer rates were reduced by 37% (10 vs 16 per 10000 person-years), also reaching nominal statistical significance. Endometrial cancer incidence was not affected, nor was lung cancer incidence (54 vs 50; HR, 1.04; 95% CI, 0.71-1.53) or total cancer incidence.

Fractures. This cohort experienced low hip fracture rates (10 per 10000 person-years in the estrogen plus progestin group vs 15 per 10000 person-years in the placebo group). Estrogen plus progestin reduced the observed hip and clinical vertebral fracture rates by one third compared with placebo, both nominally significantly. The reductions in other osteoporotic fractures (23%) and total fractures (24%) were statistically significant (all associated CIs exclude 1).

The global index showed a nominally significant 15% increase in the estrogen plus progestin group (170 vs 151 per 10000 person-years). There were no differences in mortality or cause of death between groups (TABLE 3).

Time Trends

The Kaplan Meier estimates of cumulative hazards (FIGURE 3) for CHD indicate that the difference between treatment groups began to develop soon after randomization. These curves provide little evidence of convergence through 6 years of follow-up. The cumulative hazards for stroke begin to diverge between 1 and 2 years after randomization, and this difference persists beyond the fifth year. For PE, the curves separate soon after randomization and show continuing adverse effects throughout the observation period. For breast cancer, the cumulative hazard functions are comparable through the first 4 years, at which point the curve for estrogen plus progestin begins to rise more rapidly than that for placebo. Curves for colorectal cancer show benefit beginning at 3 years, and curves for hip fracture show increasing cumulative benefit over time. The difference in hazard rates for the global index (FIGURE 4) suggests a gradual increase in adverse effects compared with benefits for estrogen plus progestin through year 5, with a possible narrowing of the difference by year 6; however, HR estimates tend to be unstable beyond 6 years after randomization. Total mortality rates are indistinguishable between estrogen plus progestin and placebo.

Tests for linear trends with time since randomization, based on a Cox proportional hazards model with a time-

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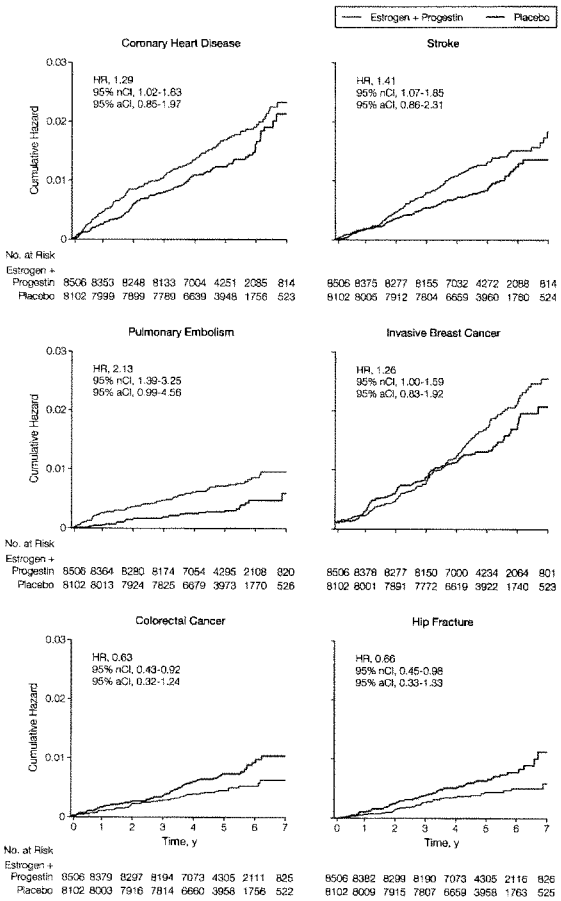
dependent covariate, detected no trend with time for CHD, stroke, colorectal cancer, hip fracture, total mortality, or the global index (TABLE 4). There was some evidence for an increasing risk of breast cancer over time with estrogen plus progestin ($z = 2.56$ compared with a nominal z score for statistical significance of 1.96) and a decreasing risk of VTE with time ($z = -2.45$). These results must be viewed cautiously because the number of events in each interval is modest, the data in later years are still incomplete, and later year comparisons are limited to women still at risk of their first event for that outcome.

Figure 3. Kaplan-Meier Estimates of Cumulative Hazards for Selected Clinical Outcomes



HR indicates hazard ratio; nCI, nominal confidence interval; and aCI, adjusted confidence interval.

Subgroup Analyses

Cardiovascular Disease. A small subset of women (n = 400; average follow-up, 57.4 months) in WHI reported conditions at baseline that would have made them eligible for HERS, ie, prior MI or revascularization procedures. Among these women with established coronary disease, the HR for subsequent CHD for estrogen plus progestin relative to placebo was 1.28 (95% CI, 0.64-2.56) with 19 vs 16 events. The remaining women, those without prior CHD, had an identical HR for CHD (145 vs 106; HR, 1.28; 95% CI, 1.00-1.65). Few women with a history of VTE were enrolled, but these data suggest a possibility that these women may be at greater risk of future VTE events when taking estrogen plus progestin (7 vs 1; HR, 4.90; 95% CI, 0.58-41.06) than those without a history of VTE (144 vs 66; HR, 2.06; 95% CI, 1.54-2.76). For stroke, prior history did not confer additional risk (1 vs 5 in women with prior stroke; HR, 0.46; 95% CI, 0.05-4.51; 126 vs 80 with no prior stroke; HR, 1.47; 95% CI, 1.11-1.95). No noteworthy interactions with age, race/ethnicity, body mass index, prior hormone use, smoking status, blood pressure, diabetes, aspirin use, or statin use were found for the effect of estrogen plus progestin on CHD, stroke, or VTE.

Breast Cancer. Women reporting prior postmenopausal hormone use had higher HRs for breast cancer associated with estrogen plus progestin use than those who never used postmenopausal hormones (among never users, 114 vs 102; HR, 1.06; 95% CI, 0.81-1.38; for women with <5 years of prior use, 32 vs 15; HR, 2.13; 95% CI, 1.15-3.94; for women with 5-10

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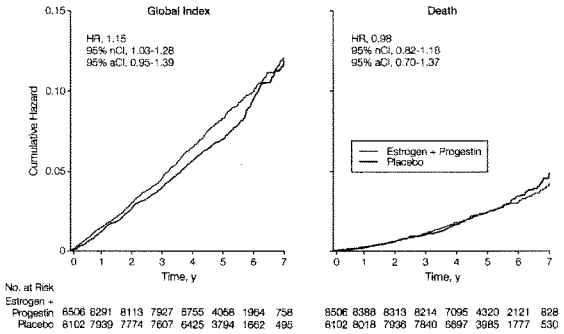
years of prior use, 11 vs 2; HR, 4.61; 95% CI, 1.01-21.02; and for women with ≥10 years of prior use, 9 vs 5; HR, 1.81; 95% CI, 0.60-5.43; test for trend, $z = 2.17$). No interactions between estrogen plus progestin and age, race/ethnicity, family history, parity, age at first birth, body mass index, or Gail-model risk score were observed for invasive breast cancer.

Further Analyses

Because a number of women stopped study medications during follow-up, several analyses were performed to examine the sensitivity of the principal HR estimates to actual use of study medications. Analyses that censored a woman's event history 6 months after becoming nonadherent (using <80% of or stopping study drugs) produced the largest changes to estimated effect sizes. This approach increased HRs to 1.51 for CHD, to 1.49 for breast cancer, to 1.67 for stroke, and to 3.29 for VTE. Analyses attributing events to actual hormone use ("as treated," allowing for a 6-month lag) produced more modest changes to these estimates. Analyses excluding women randomized during the period when the unopposed-estrogen component was open to women with a uterus and analyses stratifying by enrollment period did not substantially

Figure 4. Kaplan-Meier Estimates of Cumulative Hazards for Global Index and Death



HR indicates hazard ratio; nCI, nominal confidence interval; and aCI, adjusted confidence interval.

Table 4. Selected Clinical Outcomes by Follow-up Year and Randomization Assignment*

Outcomes	Year 1			Year 2			Year 3		
	E + P	Placebo	Ratio	E + P	Placebo	Ratio	E + P	Placebo	Ratio
No. of participant-years	8435	8050		8353	7980		8268	7888	
Coronary heart disease	43 (0.51)	23 (0.29)	1.78	36 (0.43)	30 (0.38)	1.15	20 (0.24)	18 (0.23)	1.06
Stroke	17 (0.20)	17 (0.21)	0.95	27 (0.32)	15 (0.19)	1.72	30 (0.36)	16 (0.20)	1.79
Venous thromboembolism	49 (0.58)	13 (0.16)	3.60	26 (0.31)	11 (0.14)	2.26	21 (0.25)	12 (0.15)	1.67
Invasive breast cancer	11 (0.13)	17 (0.21)	0.62	26 (0.31)	30 (0.38)	0.83	28 (0.34)	23 (0.29)	1.16
Endometrial cancer	2 (0.02)	2 (0.02)	0.95	4 (0.05)	4 (0.05)	0.96	4 (0.05)	5 (0.06)	0.76
Colorectal cancer	10 (0.12)	15 (0.19)	0.64	11 (0.13)	9 (0.11)	1.17	6 (0.07)	8 (0.10)	0.72
Hip fracture	6 (0.07)	9 (0.11)	0.64	8 (0.10)	13 (0.16)	0.59	11 (0.13)	12 (0.15)	0.87
Total death	22 (0.26)	17 (0.21)	1.24	30 (0.36)	30 (0.38)	0.96	39 (0.47)	35 (0.44)	1.06
Global index	123 (1.46)	96 (1.19)	1.22	134 (1.60)	117 (1.47)	1.09	127 (1.54)	107 (1.36)	1.13

Outcomes	Year 4			Year 5			Year 6 and Later			z Score for Trend†
	E + P	Placebo	Ratio	E + P	Placebo	Ratio	E + P	Placebo	Ratio	
No. of participant-years	7926	7562		5964	5566		5129	4243		
Coronary heart disease	25 (0.32)	24 (0.32)	0.99	23 (0.39)	9 (0.16)	2.38	17 (0.33)	18 (0.42)	0.78	−1.19
Stroke	25 (0.32)	14 (0.19)	1.70	16 (0.27)	8 (0.14)	1.87	12 (0.23)	15 (0.35)	0.66	−0.51
Venous thromboembolism	27 (0.34)	14 (0.19)	1.84	16 (0.27)	6 (0.11)	2.49	12 (0.23)	11 (0.26)	0.90	−2.45
Invasive breast cancer	40 (0.50)	22 (0.29)	1.73	34 (0.57)	12 (0.22)	2.64	27 (0.53)	20 (0.47)	1.12	2.56
Endometrial cancer	10 (0.13)	5 (0.07)	1.91	1 (0.02)	4 (0.07)	0.23	1 (0.02)	5 (0.12)	0.17	−1.58
Colorectal cancer	9 (0.11)	20 (0.26)	0.43	4 (0.07)	8 (0.14)	0.47	5 (0.10)	7 (0.16)	0.59	−0.81
Hip fracture	8 (0.10)	11 (0.15)	0.69	5 (0.08)	8 (0.14)	0.58	6 (0.12)	9 (0.21)	0.55	0.25
Total death	55 (0.69)	48 (0.63)	1.09	41 (0.69)	44 (0.79)	0.87	44 (0.86)	44 (1.04)	0.83	−0.79
Global index	155 (1.96)	127 (1.68)	1.16	112 (1.88)	77 (1.38)	1.36	100 (1.95)	99 (2.33)	0.84	−0.87

*E + P indicates estrogen plus progestin. All outcome data are number of patients (annualized percentage).
†Tests for trends are based on Cox proportional hazards models with time-dependent treatment effects. The z scores shown indicate trends across all years.

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affect the results. These analyses suggest that the intention-to-treat estimates of HRs may somewhat underestimate the effect sizes relative to what would be observed with full adherence to study medications.

COMMENT

The WHI provides evidence from a large randomized trial that addresses the important issue of whether most women with an intact uterus in the decades of life following menopause should consider hormone therapy to prevent chronic disease. The WHI enrolled a cohort of mostly healthy, ethnically diverse women, spanning a large age range (50-79 years at baseline). It is noteworthy that the increased risks for cardiovascular disease and invasive breast cancer were present across racial/ethnic and age strata and were not influenced by the antecedent risk status or prior disease. Hence, the results are likely to be generally applicable to healthy women in this age range. At the time the trial was stopped, the increases in numbers of invasive breast cancers, CHD, stroke, and PE made approximately equal contributions to harm in the estrogen plus progestin group compared with placebo, which were not counterbalanced by the smaller reductions in numbers of hip fractures and colorectal cancers.

Cardiovascular Disease

Even though the trial was stopped early for harm from breast cancer, a sufficient number of CHD events had occurred by 5.2 years of average follow-up to suggest that continuation to the planned end would have been unlikely to yield a favorable result for the primary outcome of CHD. Even if there were a reversal of direction toward benefit of a magnitude seen in the observational studies (ie, a risk reduction of 55%) during the remaining years, conditional power analyses indicate that less than 10% power remained for showing potential benefit if the trial continued.

The WHI finding that estrogen plus progestin does not confer benefit for preventing CHD among women with a uterus concurs with HERS findings among women with clinically apparent CHD,[10] with the Estrogen Replacement for Atherosclerosis trial, in which estrogen plus progestin did not inhibit progression,[23] and with a trial in women with unstable angina that did not observe a reduction in ischemic events.[24] The finding of an increased risk after initiation of treatment in WHI is similar to HERS. In HERS, after 4.1 and 6.8 years of follow-up, hormone therapy did not increase or decrease risk of cardiovascular events in women with CHD.[25] The WHI extends these findings to include a wider range of women, including younger women and those without clinically apparent CHD, and indicates that the risk may persist for some years.

Unlike CHD, the excess risk of stroke in the estrogen plus progestin group was not present in the first year but appeared during the second year and persisted through the fifth year. Preliminary analyses indicate that the modest difference in blood pressure between groups does not contribute much to an explanation of the increase in strokes (data not shown). The findings in WHI for stroke are consistent with but somewhat more extreme than those of HERS, which reported a nonsignificant 23% increase in the treatment group.[26] The results were also more extreme than those of the Women's Estrogen and Stroke Trial of estradiol (without progestin) in women with prior stroke, which found no effect of estrogen on recurrent strokes overall but some increase in the first 6 months.[27] Trials of the effect of estradiol on carotid intima-media thickness have yielded conflicting results.[28,29] At least 1 observational study has suggested that that use of estrogen plus progestin is associated with higher risk of stroke than estrogen alone.[14] In WHI, there was no indication that excess strokes due to estrogen plus progestin were more likely to occur in older women, in women with prior stroke history, by race/ethnicity, or in women with high blood pressure at baseline. Therefore, it appears that estrogen plus progestin increases the risk of strokes in apparently healthy women.

Venous thromboembolism is an expected complication of postmenopausal hormones, and the pattern over time in WHI is consistent with the findings from HERS and several observational studies.[30,31]

Cancer

The WHI is the first randomized controlled trial to confirm that combined estrogen plus progestin does increase the risk of incident breast cancer and to quantify the degree of risk. The WHI could not address the risk of death due to breast cancer because with the relatively short follow-up time, few women in the WHI have thus far died as a result of breast cancer (3 in the active treatment group and 2 in the placebo group). The risk of breast cancer emerged several years after randomization. After an average follow-up of about 5 years, the adverse effect on breast cancer had crossed the monitoring boundary. The 26% excess of breast cancer is consistent with estimates from pooled epidemiological data, which reported a 15% increase for estrogen plus progestin use for less than 5 years and a 53% increase for use for more than 5 years.[32] It is also consistent with the (nonsignificant) 27% increase found after 6.8 years of follow-up in HERS.[33]

With more common use of estrogen plus progestin, several epidemiological studies have reported that estrogen plus progestin appears to be associated with greater risk of breast cancer than estrogen alone.[34-37] In the PEPI trial, women in the 3 estrogen plus progestin groups had much greater increases in mammographic density (a predictor of breast cancer) than women in the estrogen or placebo groups.[38] In WHI, the HR for estrogen plus progestin was not higher in women with a family history or other risk factors for breast cancer, except for reported prior use of postmenopausal hormones. This may suggest a cumulative effect of years of exposure to postmenopausal hormones.

Endometrial cancer rates were low and were not increased by 5 years of es-

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trogen plus progestin exposure. Close monitoring for bleeding and treatment of hyperplasia may contribute to the absence of increased risk of endometrial cancer.

The reduction in colorectal cancer in the hormone group is consistent with observational studies, which have suggested fairly consistently that users of postmenopausal hormones may be at lower risk of colorectal cancer.[39] The mechanisms by which hormone use might reduce risk are unclear. Results from other trials of postmenopausal hormones will help resolve the effects of hormones on colorectal cancer.[40]

Fractures

The reductions in clinical vertebral fractures, other osteoporotic fractures, and combined fractures supported the benefit for hip fractures found in this trial. These findings are consistent with the observational data and limited data from clinical trials[41] and are also consistent with the known ability of estrogen (with or without progestin) to maintain hone mineral density.[42] The WHI is the first trial with definitive data supporting the ability of postmenopausal hormones to prevent fractures at the hip, vertebrae, and other sites.

Overall Risks and Benefits

At the end of the trial, the global index indicated that there were more harmful than beneficial outcomes in the estrogen plus progestin group vs the placeho group. The monitored outcomes included in the global index were selected to represent diseases of serious import that estrogen plus progestin treatment might affect, and do not include a variety of other conditions and measures that may be affected in unfavorable or favorable ways (eg, gallbladder disease, diabetes, quality of life, and cognitive function). The data on these and other outcomes will be the subject of future publications. All-cause mortality was balanced between the groups; however, longer follow-up may be needed to assess the impact of the incident diseases on total mortality.

The absolute excess risk (or risk reduction) attributable to estrogen plus progestin was low. Over 1 year, 10000 women taking estrogen plus progestin compared with placebo might experience 7 more CHD events, 8 more strokes, 8 more PEs, 8 more invasive hreast cancers, 6 fewer colorectal cancers, and 5 fewer hip fractures. Combining all the monitored outcomes, women taking estrogen plus progestin might expect 19 more events per year per 10000 women than women taking placebo. Over a longer period, more typical of the duration of treatment that would be needed to prevent chronic disease, the absolute numbers of excess outcomes would increase proportionately.

During the 5.2 years of this trial, the number of women experiencing a global index event was about 100 more per 10000 women taking estrogen plus progestin than taking placeho. If the current findings can be extrapolated to an even longer treatment duration, the absolute risks and benefits associated with estrogen plus progestin for each of these conditions could be substantial and on a population basis could account for tens of thousands of conditions caused, or prevented, by hormone use.

Limitations

This trial tested only 1 drug regimen, CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, in postmenopausal women with an intact uterus. The results do not necessarily apply to lower dosages of these drugs, to otber formulations of oral estrogens and progestins, or to estrogens and progestins administered through the transdermal route. It remains possible that transdermal estradiol with progesterone, which more closely mimics the normal physiology and metabolism of endogenous sex hormones, may provide a different risk-benefit profile. The WHI findings for CHD and VTE are supported by findings from HERS, but there is no other evidence from clinical trials for breast cancer and colorectal cancer, and only limited data from trials concerning fractures.

Importantly, this trial could not distinguish the effects of estrogen from those of progestin. The effects of progestin may be important for breast cancer and atherosclerotic diseases, including CHD and stroke. Per protocol, in a separate and adequately powered trial, WHI is testing the hypothesis of whether oral estrogen will prevent CHD in 10739 women who have had a hysterectomy. The monitoring of this trial is similar to that for the trial of estrogen plus progestin. At an average follow-up of 5.2 years, the DSMB has recommended that this trial continue because the balance of overall risks and benefits remains uncertain. These results are expected to be available in 2005, at the planned termination.

The relatively high rates of discontinuation in the active treatment arm (42%) and crossover to active treatment in the placebo arm (10.7%) are a limitation of the study; however, the lack of adherence would tend to decrease the observed treatment effects. Thus, the results presented here may underestimate the magnitude of both adverse effects on cardiovascular disease and breast cancer and the beneficial effects on fractures and colorectal cancer among women who adhere to treatment.

The fact that the trial was stopped early decreases the precision of estimates of long-term treatment effects. A longer intervention period might have shown more pronounced benefit for fractures and might have yielded a more precise test of the hypothesis that treatment reduces colorectal cancer. Nonetheless, it appears unlikely that benefit for CHD would have emerged by continuing the trial to its planned termination. The trial results indicate that treatment for up to 5.2 years is not beneficial overall and that there is early harm for CHD, continuing harm for stroke and VTE, and increasing harm for breast cancer with increasing duration of treatment. This risk-benefit profile is not consistent with the requirements for a viable intervention for the primary prevention of chronic diseases.

Implications

The WHI trial results provide the first definitive data on which to base treat-

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ment recommendations for healthy postmenopausal women with an intact uterus. This trial did not address the short-term risks and benefits of hormones given for the treatment of menopausal symptoms. On the basis of HERS and other secondary prevention trials, the American Heart Association recommended against initiating postmenopausal hormones for the secondary prevention of cardiovascular disease.[43] The American Heart Association made no firm recommendation for primary prevention while awaiting the results from randomized clinical trials such as WHI, and stated that continuation of the treatment should be considered on the basis of established noncoronary benefits and risks, possible coronary benefits and risks, and patient preference.

Results from WHI indicate that the combined postmenopausal hormones CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, should not be initiated or continued for the primary prevention of CHD. In addition, the substantial risks for cardiovascular disease and breast cancer must be weighed against the benefit for fracture in selecting from the available agents to prevent osteoporosis.

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Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy

The Women's Health Initiative Randomized Controlled Trial

The Women's Health Initiative Steering Committee*

Context Despite decades of use and considerable research, the role of estrogen alone in preventing chronic diseases in postmenopausal women remains uncertain.

Objective To assess the effects on major disease incidence rates of the most commonly used postmenopausal hormone therapy in the United States.

Design, Setting, and Participants A randomized, double-blind, placebo-controlled disease prevention trial (the estrogen-alone component of the Women's Health Initiative [WHI]) conducted in 40 US clinical centers beginning in 1993. Enrolled were 10739 postmenopausal women, aged 50-79 years, with prior hysterectomy, including 23% of minority race/ethnicity.

Intervention Women were randomly assigned to receive either 0.625 mg/d of conjugated equine estrogen (CEE) or placebo.

Main Outcome Measures The primary outcome was coronary heart disease (CHD) incidence (nonfatal myocardial infarction or CHD death). Invasive breast cancer incidence was the primary safety outcome. A global index of risks and benefits, including these primary outcomes plus stroke, pulmonary embolism (PE), colorectal cancer, hip fracture, and deaths from other causes, was used for summarizing overall effects.

Results In February 2004, after reviewing data through November 30, 2003, the National Institutes of Health (NIH) decided to end the intervention phase of the trial early. Estimated hazard ratios (HRs) (95% confidence intervals [CIs]) for CEE vs placebo for the major clinical outcomes available through February 29, 2004 (average follow-up 6.8 years), were: CHD, 0.91 (0.75-1.12) with 376 cases; breast cancer, 0.77 (0.59-1.01) with 218 cases; stroke, 1.39 (1.10-1.77) with 276 cases; PE, 1.34 (0.87-2.06) with 85 cases; colorectal cancer, 1.08 (0.75-1.55) with 119 cases; and hip fracture, 0.61 (0.41-0.91) with 102 cases. Corresponding results for composite outcomes were: total cardiovascular disease, 1.12 (1.01-1.24); total cancer, 0.93 (0.81-1.07); total fractures, 0.70 (0.63-0.79); total mortality, 1.04 (0.88-1.22), and the global index, 1.01 (0.91-1.12). For the outcomes significantly affected by CEE, there was an absolute excess risk of 12 additional strokes per 10000 person-years and an absolute risk reduction of 6 fewer hip fractures per 10000 person-years. The estimated excess risk for all monitored events in the global index was a nonsignificant 2 events per 10000 person-years.

Conclusions The use of CEE increases the risk of stroke, decreases the risk of hip fracture, and does not affect CHD incidence in postmenopausal women with prior hysterectomy over an average of 6.8 years. A possible reduction in breast cancer risk requires further investigation. The burden of incident disease events was equivalent in the CEE and placebo groups, indicating no overall benefit. Thus, CEE should not be recommended for chronic disease prevention in postmenopausal women.

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ESTROGEN THERAPY HAS BEEN available to postmenopausal women for more than 60 years. Proven benefits include relief of vasomotor symptoms and vaginal atrophy and prevention and treatment of osteoporosis. Observational studies primarily examining unopposed estrogen preparations have suggested a 30% to 50% reduction in coronary events,[1-3] and an 8% to 30% increase in breast cancer with extended use.[4-6]

The Women's Health Initiative (WHI) clinical trials of hormone therapy were designed in 1991-1992 using the accumulated evidence available at the time.[7] Two parallel randomized, double-blind, placebo-controlled clinical trials of hormone therapy were undertaken to determine whether conjugated equine estrogen (CEE) alone (for women with prior hysterectomy) or in combination with progestin (medroxyprogesterone acetate [MPA]) would reduce cardiovascular events in mostly healthy postmenopausal women. The WHI estrogen plus progestin trial was halted in July 2002 after a mean 5.2 years of follow-up because health risks exceeded benefits.[8] Coronary heart disease (CHD), stroke, and venous thromboembolic disease were all increased in women assigned to active treatment with estrogen plus progestin. Breast cancer was also increased while colorectal cancer, hip fracture, and other fractures were reduced. The lack of benefit for CHD was

For editorial comment see p 1769.

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supported by the Heart and Estrogen/progestin Replacement Study (HERS), which also tested CEE plus MPA in women with known coronary artery disease at baseline.[9]

Despite the early termination of the WHI estrogen plus progestin trial, the WHI estrogen-alone trial was continued with ongoing careful scrutiny by an independent data and safety monitoring board (DSMB) because the health risks and benefits had not been adequately determined. In February 2004, the National Institutes of Health (NIH) decided to terminate the intervention phase of the estrogen-alone study, prior to the scheduled close-out interval of October 2004 to March 2005. This report presents the results of the estrogen-alone trial using available data through February 29, 2004, prior to notifying participants of the decision on March 1, 2004. Subsequent detailed reports will include additional outcomes occurring between the participants' last routine follow-up and the date of trial termination. An ancillary study of dementia and cognitive function will be reported separately. Two remaining components of the WHI clinical trial, testing the effects of a low-fat eating pattern and, independently, the effects of calcium plus vitamin D supplementation, are continuing.

METHODS

Study Population and Randomization

Detailed eligibility criteria and recruitment methods have been published.[7,10] Briefly, most participants were recruited by population-based direct mailing campaigns to age-eligible women, in conjunction with local and national media awareness programs. Women were eligible if they were 50 to 79 years old at initial screening, had undergone hysterectomy (thereby considered postmenopausal for enrollment purposes), and were likely to reside in the area for 3 years. Major exclusions were related to competing risks (any medical condition likely to be associated with a predicted survival of <3 years), safety (eg, prior breast cancer, other prior cancer within the last 10 years except nonmelanoma skin cancer), adherence and retention concerns (eg, alcoholism, dementia, and transportation problems), or the clinical judgment of the participant's health care practitioner to continue hormone therapy in symptomatic or osteoporotic women. A 3-month washout period was required of women using postmenopausal hormones at initial screening. Prior to the 1997 HERS report,[11] which led to a change in eligibility criteria, 171 women with a history of venous thromboembolism (VTE) were enrolled. The protocol and consent forms were approved by the institutional review board for each participating institution (see the end of this article), and all women provided written informed consent.

Eligible women were randomly assigned to receive 0.625 mg/d of CEE (Premarin; Wyeth, St Davids, Pa) or a matching placebo, in equal proportions. The computerized randomization and blinding procedures have been described.[12] A small imbalance in the number of women in each group was a consequence of an early protocol change eliminating a CEE-alone intervention in women with a uterus.[8]

Follow-up and Data Collection

Study participants were contacted by telephone 6 weeks after randomization to assess symptoms and reinforce adherence. Follow-up contacts by telephone or clinic visit occurred every 6 months, with clinic visits required annually. At each contact, adherence to study medication was assessed, and information on symptoms, safety concerns, and outcomes was collected. Electrocardiograms were recorded at baseline and at visit years 3, 6, and 9. Annual mammograms and clinical breast examinations were required; study medication was withheld if these safety procedures were not performed or the results could not be verified. Participants were followed up from the date of entry until death, loss to follow-up, or the time of a request for no further contact, regardless of their adherence to study medication. Baseline and year 1 lipid levels were measured in fasting blood specimens from a random 8.6% subsample of women. Methods for subsampling, data collection and management, and quality assurance have been published.[12]

Maintenance/Discontinuation of Study Medications

During the trial, women with intolerable symptoms such as breast tenderness were managed by reducing the number of days per week that study medication was taken. Participants and study personnel remained blinded when these adjustments were made. Study medication was withheld in participants experiencing a myocardial infarction (MI), stroke, fracture or major injury involving hospitalization, surgery involving use of anesthesia, any illness resulting in immobilization for longer than 1 week, or any other severe illness in which hormone use was considered inappropriate. The decision to resume study medication after MI or stroke was left to the discretion of the clinical center, individual participant, and her health care clinician. Study medication was permanently discontinued in women who developed breast cancer; deep vein thrombosis (DVT) or pulmonary embolism (PE); malignant melanoma; meningioma; triglyceride level higher than 1000 mg/dL (>11.3 mmol/L); or who were treated by their personal health care practitioners with prescription estrogen, testosterone, or selective estrogen receptor modulators.

Outcome Ascertainment

Designated outcome events were evaluated by review of medical records by centrally trained physician adjudicators at each clinical center who were blinded to treatment assignment and symptoms related to study medication. Final adjudication of key cardiovascular and cancer outcomes, as well as hip fractures and deaths, was performed centrally by comparably blinded WHI physician adjudicators, neurologists, or cancer coders. Centrally adjudicated results are reported when available, with locally adjudicated events

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included when central adjudication has not yet been completed. Centrally adjudicated results are available for 95.7% of CHD events, 92.4% of strokes, 91.8% of PE cases, 97.2% of breast cancers, 99.2% of colorectal cancers, 89.2% of hip fractures, and 80.3% of deaths. Detailed outcome definitions and methods for ascertaining, documenting, and classifying outcomes have been published.[13]

Cardiovascular Disease. Coronary heart disease was defined as acute MI requiring overnight hospitalization, silent MI determined from serial electrocardiograms obtained every 3 years, or death due to CHD. Stroke was defined as the rapid onset of a neurologic deficit lasting more than 24 hours, supported by imaging studies in most cases (89.8% had computed tomography/magnetic resonance imaging [MRI] studies available). Venous thromboembolism was defined as PE or DVT and required clinical symptoms supported by relevant diagnostic studies. Total cardiovascular disease events include CHD, stroke, VTE, angina requiring hospitalization, coronary revascularization procedures, congestive heart failure, carotid artery disease, and peripheral vascular disease.

Cancer. All cancers other than nonmelanoma skin cancers were confirmed by pathology reports, available for 98.2% of invasive breast, 95.0% of colorectal, and 80.6% of other cancers.

Fractures. All reported clinical fractures other than those of the ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae were verified by review of radiology, MRI, or operative reports. WHI investigators did not obtain spine radiographs to ascertain subclinical vertebral fractures.

Global Index. A global index of risks and benefits was defined for each woman as the time to the first event among the monitored outcomes (CHD, stroke, PE, breast cancer, colorectal cancer, hip fractures, and death).[14]

Statistical Power and Analyses

The trial design assumed 12,375 women would need to be randomized to achieve 81% power to detect a 21% reduction in CHD rates over the projected 9-year average follow-up. This sample size would provide 65% power to detect a 20% reduction in hip fracture rates. An additional 5 years of follow-up without intervention was planned to achieve 79% power to detect a 22% increase in breast cancer risk.[7] Calculations based on the observed sample size and age distribution gave power estimates of 72%, 55%, and 71% for CHD, hip fracture, and breast cancer, respectively.[12]

Lack of adherence to study medication was summarized at each follow-up year as the cumulative proportion of randomized participants who had stopped taking study medications (dropouts) and similarly the proportion of women who began taking prescription menopausal hormones through their own health care practitioner (drop-ins), after excluding preceding deaths. Participants were classified by their most recent status with regard to study medications (stopped or not). Thus, women who temporarily stopped taking study medication were considered adherent in this analysis.

Event rate comparisons were based on the intent-to-treat principle using failure time methods. For a given outcome, the time of event was defined to be the number of days from randomization to the first postrandomization diagnosis of the designated event. For silent MIs, the date of the follow-up electrocardiogram was used as the event date. Follow-up time was censored at the time of the last documented follow-up contact or death. Comparisons of primary outcomes are presented as hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional hazard analyses,[15] stratified by age, prior disease, and randomization status in the low-fat diet trial. Cumulative hazard rates were estimated by the Kaplan-Meier method for each designated outcome.

Two forms of CIs were calculated, nominal and adjusted. This report primarily presents the nominal 95% CIs because they provide traditional estimates of variability and, as such, are comparable to most other reports of hormone therapy studies. To acknowledge multiple testing issues, adjusted CIs were calculated using group sequential methods, and for secondary outcomes a Bonferroni correction based on the data and safety monitoring plan (see below). Because the trial was nearing the planned termination, the impact of the group sequential adjustment on the width of the CIs is small. The Bonferroni correction reflects the study design and trial monitoring priorities and hence may be somewhat less relevant for interpreting the trial results. Unless otherwise indicated, all CIs and P values are nominal. Statistical analyses were performed using SAS version 9.0 (SAS Institute, Cary, NC) and significance was set at the .05 level.

The possibility of important subgroup effects was explored by testing for interactions in expanded Cox models. Because 23 interactions are reported, chance alone could produce a significant interaction at the .05 level for approximately 1 factor in the series. Sensitivity analyses were conducted to explore the possible impact of lack of adherence to study medications. In these "complier" analyses, the randomization assignment was preserved but follow-up for a woman was censored 6 months after she first became nonadherent (defined as taking <80% of study pills).

Data and Safety Monitoring

Statistical monitoring boundaries were based on O'Brien-Fleming group sequential procedures[16] with asymmetric boundaries for benefit (1-sided .025-level upper boundary for CHD) and adverse effects (1-sided .05-level lower boundary). The adverse effect boundary for the 6 monitored outcomes of CHD, stroke, PE, hip fractures, colorectal cancer, and death from causes other than the monitored disease outcomes incorporated a Bonferroni correction. The Bonferroni correction was not applied to breast cancer because it was the primary safety outcome. Early stopping was to be

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considered if a disease-specific boundary was crossed and the global index was supportive of the overall direction of CEE effects. Formal monitoring of disease rate comparisons began in the fall of 1997 with trial termination planned for March 2005. Additional aspects of the monitoring plan have been published.[14]

RESULTS

Trial Monitoring and Early Stopping

In early 2000 and again in 2001, after reviewing the data from the estrogen-alone and the estrogen plus progestin trials, the DSMB recommended that participants in both trials be informed of early increases in rates of heart disease, strokes, and blood clots in women taking active hormone pills. In 2002, with the early termination of the estrogen plus progestin trial, participants in the estrogen-alone trial were informed that no increase in breast cancer rates had been observed at that point in women taking CEE. The DSMB continued to closely monitor the estrogen-alone trial. The DSMB's review of the data for the 13th planned interim analysis through August 31, 2003, plus an unplanned analysis using data through November 30, 2003, did not lead to a consensus recommendation. None of the predefined stopping boundaries had been crossed, although the stroke comparison was approaching the adverse effect boundary.

On February 2, 2004, following subsequent reviews with additional advisors, the NIH decided to stop the intervention phase of the trial. The NIH concluded that with an average of nearly 7 years of follow-up completed, CEE does not appear to affect the risk of heart disease, the primary outcome of the study. Furthermore, the NIH found an increased risk of stroke that was similar to the risk reported from the estrogen plus progestin trial. Recognizing the risk of stroke, and the likelihood that neither cardioprotection nor breast cancer risk would be demonstrated in the remaining intervention period, the NIH deemed it unacceptable to subject healthy women in a prevention trial to this risk.[17] On March 1, 2004, participants were informed of the trial termination and advised to stop taking their study medication. Data available through February 29, 2004, by routine data collection are included in this report.

Table 1. Baseline Demographic and Clinical Characteristics of the Women's Health Initiative Estrogen-Alone Trial Participants With Prior Hysterectomy (N = 10 739) by Randomization Assignment*

Characteristics	CEE (n = 5310)	Placebo (n = 5429)
Age at screening, mean (SD), y	63.6 (7.3)	63.6 (7.3)
Age group at screening, y, No. (%)		
50-59	1637 (30.8)	1673 (30.8)
60-69	2387 (45.0)	2465 (45.4)
70-79	1286 (24.2)	1291 (23.8)
Race/ethnicity, No. (%)		
White	4007 (75.5)	4075 (75.1)
Black	782 (14.7)	835 (15.4)
Hispanic	322 (6.1)	333 (6.1)
American Indian	41 (0.8)	34 (0.6)
Asian/Pacific Islander	86 (1.6)	78 (1.4)
Unknown	72 (1.4)	74 (1.4)
Hormone use, No. (%)		
Never	2769 (52.2)	2770 (51.1)
Past	1871 (35.2)	1948 (35.9)
Current†	669 (12.6)	708 (13.0)
Duration of prior hormone use, y, No. (%)‡		
<5	1352 (53.2)	1412 (53.1)
5-<10	469 (18.5)	515 (19.4)
≥10	720 (28.3)	732 (27.5)
Body mass index, mean (SD)§	30.1 (6.1)	30.1 (6.2)
Body mass index, No. (%)		
<25	1110 (21.0)	1096 (20.3)
25-29	1795 (34.0)	1912 (35.5)
≥30	2376 (45.0)	2383 (44.2)
Systolic BP, mean (SD), mm Hg	130.4 (17.5)	130.2 (17.6)
Diastolic BP, mean (SD), mm Hg	76.5 (9.2)	76.5 (9.4)
Smoking, No. (%)		
Never	2723 (51.9)	2705 (50.4)
Past	1986 (37.8)	2089 (38.9)
Current	542 (10.3)	571 (10.6)
Parity, No. (%)		
Never pregnant/no term pregnancy	489 (9.3)	461 (8.5)
≥1 Term pregnancy	4779 (90.7)	4932 (91.5)
Age at first birth, y, No. (%)‖		
<20	1193 (28.1)	1234 (28.0)
20-29	2846 (67.0)	2914 (66.1)
≥30	210 (4.9)	260 (5.9)

Abbreviation: CEE, conjugated equine estrogen.
*Subgroup totals may not sum to number randomized because of missing data.
†Required a 3-month washout prior to randomization.
‡Among women reporting hormone use.
§Measured as weight in kilograms divided by height in meters squared. Data available for 5281 CEE and 5391 placebo participants.
‖Among women reporting ≥1 term pregnancy.

Baseline Characteristics

Between 1993 and 1998, a total of 10 739 women were randomized into the estrogen-alone trial. Demographic characteristics, medical history, and health behaviors of these women have been described in considerable detail.[18] In general, study participants were healthy and at average risk of CHD and breast cancer, although 441 (4.1%) with

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prior MI or coronary revascularization were enrolled. The intervention groups were well balanced at baseline on key demographic and disease risk factor characteristics (TABLE 1 and TABLE 2).

Follow-up, Adherence, and Unblinding

Vital status is known for 10176 (94.8%) of randomized participants, including 580 (5.4%) known to be deceased. Over the average 6.8 years of follow-up (range, 5.7-10.7 years), only 563 women (5.2%) withdrew, were considered lost to follow-up, or had stopped providing outcomes information for more than 18 months (FIGURE 1).

At the time of study termination, 53.8% of women had already stopped taking study medication. Dropout rates exceeded design projections, particularly early on, but did not differ significantly by randomization assignment and were stable after year 1, even with the termination of the estrogen plus progestin trial (FIGURE 2). Some women initiated hormone use through their own health care clinician: 5.7% of women in the CEE group and 9.1% in the placebo group by follow-up year 6. These drop-in rates in the placebo group were also somewhat greater than expected. Reasons for initiating hormone therapy outside of the study were not captured. Unblinding of the study gynecologist to randomization assignment was infrequent, occurring for only 100 women in the CEE group and 83 in the placebo group. Per protocol, the treatment assignment was not revealed to other study staff members or the study participants.

Intermediate Cardiovascular Disease End Points

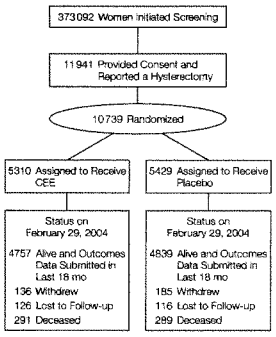
Fasting blood lipid levels, assessed in an 8.6% subsample of women at baseline and year 1, showed a greater reduction in low-density lipoprotein cholesterol (−13.7% vs −1.0%, $P<.001$) and a larger increase in high-density lipoprotein cholesterol (15.1% vs 1.1%, $P<.001$) in the CEE group compared with the placebo group. Reductions in total cholesterol from baseline to year 1 were comparable (−2.3% vs −1.4%, $P=.41$). Larger increases in triglyceride levels at year 1 were observed in the CEE group than in the placebo group (25.0% vs 3.0%, $P<.001$). Systolic blood pressure at 1 year was higher by a mean (SE) of 1.1 (0.4) mm Hg in women taking CEE than in women taking placebo ($P=.003$) and remained similarly elevated throughout follow-up. Diastolic blood pressures did not differ significantly between the study groups (data not shown).

Table 2. Baseline Medical History Characteristics of the Women's Health Initiative Estrogen-Alone Trial Participants With Prior Hysterectomy (N = 10 739) by Randomization Assignment*

Characteristics	CEE (n = 5310)	Placebo (n = 5429)
Age at hysterectomy, y, No. (%)		
<40	2100 (39.8)	2149 (39.8)
40-49	2281 (43.2)	2275 (42.2)
50-54	501 (9.5)	566 (10.5)
≥55	401 (7.6)	404 (7.5)
Bilateral oophorectomy, No. (%)	1938 (39.5)	2111 (42.0)
Medical treatment, No. (%)		
Treated for diabetes	410 (7.7)	411 (7.6)
Treated for hypertension or BP ≥140/90 mm Hg	2386 (48.0)	2387 (47.4)
Elevated cholesterol levels requiring medication	694 (14.5)	766 (15.9)
Statin use at baseline	394 (7.4)	427 (7.9)
Aspirin use (≥80 mg/d) at baseline	1030 (19.4)	1069 (19.7)
Medical history, No. (%)		
Myocardial infarction	165 (3.1)	172 (3.2)
Angina	308 (5.8)	306 (5.7)
CABG/PTCA	120 (2.3)	114 (2.1)
Stroke	76 (1.4)	92 (1.7)
DVT or PE	87 (1.6)	84 (1.5)
Female relative had breast cancer, No. (%)	893 (18.0)	870 (17.1)
Fracture at age ≥55 y, No. (%)	676 (14.0)	643 (13.2)
No. of falls in last 12 mo, No. (%)		
0	3300 (67.0)	3230 (64.8)
1	975 (19.8)	1024 (20.5)
2	422 (8.6)	478 (9.6)
≥3	231 (4.7)	255 (5.1)

Abbreviations: BP, blood pressure; CABG/PTCA, coronary artery bypass graft/percutaneous transluminal coronary angioplasty; CEE, conjugated equine estrogen; DVT, deep vein thrombosis; PE, pulmonary embolism.
*Subgroup totals may not sum to number randomized because of missing data.

Figure 1. Participant Flow in the Estrogen-Alone Component of the Women's Health Initiative



CEE indicates conjugated equine estrogen.

Clinical Outcomes

Cardiovascular Disease. The primary outcome for this trial was the rate of CHD. The observed CHD incidence rate of 51 per 10000 person-years was 15% lower than projected in the design. No significant effect of CEE was observed on CHD rates compared with placebo

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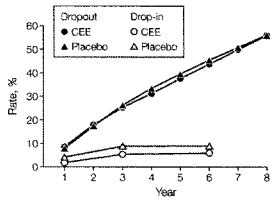
(49 vs 54 per 10000 person-years; 9% reduction) (TABLE 3). These data rule out a reduction in CHD rates with CEE of more than 25% during the trial period. The incidence of stroke was increased by 39% in the CEE group (44 vs 32 per 10000 person-years, $z=-2.72$, $P=.007$), which crossed the adverse effect monitoring boundary for the 14th planned interim analysis (defined as $z=-2.69$). The risk of VTE, including both DVT and PE, was increased for women taking CEE (28 vs 21 per 10000 person-years; 33% increase), although only the increased rate of DVT reached statistical significance ($P=.03$). Total cardiovascular disease event rates, including stroke, were 12% higher in women taking CEE (225 vs 201 per 10000 person-years, $P=.02$).

Figure 2. Cumulative Drop-in and Dropout Rates by Randomization Assignment and Follow-up Duration



CEE indicates conjugated equine estrogen. Use of nonstudy hormones to estimate drop-ins was routinely surveyed only in follow-up years 1, 3, and 6.

Cancer. Invasive breast cancer, the primary safety outcome for this trial, was diagnosed at a 23% lower rate in the CEE group than in the placebo group (26 vs 33 per 10000 person-years) and this comparison narrowly missed statistical significance ($P=.06$). No significant differences were found in rates of colorectal cancer for CEE vs placebo (17 vs 16 per 10000 person-years) or total cancer (103 vs 110 per 10000 person-years) (Table 3).

Fractures. Use of CEE reduced the rates of fractures by 30% to 39%. Hip fracture rates were 11 vs 17 per 10000 person-years ($P=.01$); clinical vertebral fractures, 11 vs 17 per 10000 person-years ($P=.02$); and total osteoporotic fractures, 139 vs 195 per 10000 person-years ($P<.001$) (Table 3).

Summary Measures. The global index of health risks and benefits was balanced overall (HR, 1.01; 95% CI, 0.91-1.12). Of the 580 reported deaths, 94.8% have been adjudicated. Use of

Table 3. Clinical Outcomes by Randomization Assignment

Outcomes	No. of Patients (Annualized %) CEE (n = 5310)	Placebo (n = 5429)	Hazard Ratio*	Nominal 95% CI	Adjusted 95% CI
Follow-up time, mean (SD), mo	81.6 (19.3)	81.9 (19.7)	NA	NA	NA
Cardiovascular disease†					
CHD	177 (0.49)	199 (0.54)	0.91	0.75-1.12	0.72-1.15
CHD death	54 (0.15)	59 (0.16)	0.94	0.65-1.36	0.54-1.63
Nonfatal MI	132 (0.37)	153 (0.41)	0.89	0.70-1.12	0.63-1.26
Stroke	158 (0.44)	118 (0.32)	1.39	1.10-1.77	0.97-1.99
Fatal	15 (0.04)	14 (0.04)	1.13	0.54-2.34	0.38-3.36
Nonfatal	114 (0.32)	85 (0.23)	1.39	1.05-1.84	0.91-2.12
Venous thromboembolic disease	101 (0.28)	78 (0.21)	1.33	0.99-1.79	0.86-2.08
Deep vein thrombosis	77 (0.21)	54 (0.15)	1.47	1.04-2.08	0.87-2.47
Pulmonary embolism	48 (0.13)	37 (0.10)	1.34	0.87-2.06	0.70-2.55
Total cardiovascular disease	811 (2.25)	746 (2.01)	1.12	1.01-1.24	0.97-1.30
Cancer					
Invasive breast	94 (0.26)	124 (0.33)	0.77	0.59-1.01	0.57-1.06
Colorectal	61 (0.17)	58 (0.16)	1.08	0.75-1.55	0.63-1.86
Total	372 (1.03)	408 (1.10)	0.93	0.81-1.07	0.75-1.15
Fractures					
Hip	38 (0.11)	64 (0.17)	0.61	0.41-0.91	0.33-1.11
Vertebral	39 (0.11)	64 (0.17)	0.62	0.42-0.93	0.34-1.13
Total	503 (1.39)	724 (1.95)	0.70	0.63-0.79	0.59-0.83
Death					
Due to other causes‡	193 (0.53)	185 (0.50)	1.08	0.88-1.32	0.79-1.46
Total	291 (0.81)	289 (0.78)	1.04	0.88-1.22	0.81-1.32
Global index§	692 (1.92)	705 (1.90)	1.01	0.91-1.12	0.89-1.14

Abbreviations: CEE, conjugated equine estrogen; CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; NA, not applicable.
*From Cox proportional hazards model stratified by age, prior disease, and randomization status in the dietary modification trial.
†CHD includes acute MI requiring hospitalization, silent MI determined from serial electrocardiograms, and coronary death. There were 14 silent MIs. Total cardiovascular disease is limited to events requiring or during hospitalization except venous thromboembolic disease reported after January 1, 2000.
‡All deaths except those from breast or colorectal cancer, definite/probable CHD, pulmonary embolism, or cerebrovascular disease.
§The global index represents the first event for each participant from among the following: CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, hip fracture, or death due to other causes.

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CEE did not significantly affect total mortality rates or cause-specific mortality (TABLE 4).

Time Trends

Differences in cumulative hazards for stroke and to a lesser extent for hip fracture began to emerge early in the intervention period and persisted throughout follow-up (FIGURE 3). Cumulative breast cancer hazard rates appeared to separate beginning in year 2. Similar displays for the global index and death (FIGURE 4) reinforce the comparability of these rates across treatment groups. Tests for trends with time since randomization were computed for all of the monitored and composite outcomes using a Cox proportional hazards model with a time-dependent treatment interaction term. Coronary heart disease was the only outcome with a statistically significant trend ($P = .02$) of slightly elevated HRs in the early follow-up period that diminished over time (year 1, 1.16; year 2, 1.20; year 3, 0.89; year 4, 0.79; year 5, 1.28; year 6, 1.24, and year ≥7, 0.42).

Further Analyses

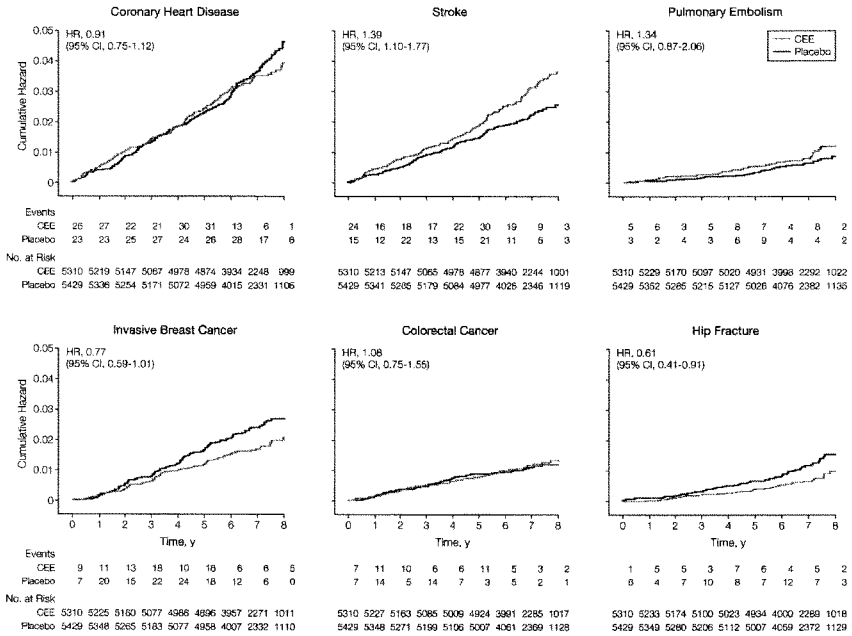
Exploratory analyses were conducted to determine whether selected participant characteristics modified CEE effects on major clinical outcome event rates. There were no significant interactions between CEE and race/

Table 4. Causes of Death

	No. (Annualized %)	
	CEE (n = 5310)	Placebo (n = 5429)
Total deaths	291 (0.81)	289 (0.78)
Adjudicated deaths	278 (0.77)	272 (0.73)
Cardiovascular	93 (0.26)	95 (0.26)
Breast cancer	4 (0.01)	8 (0.02)
Other cancer	110 (0.30)	118 (0.32)
Other known cause	51 (0.14)	38 (0.10)
Unknown cause	20 (0.06)	13 (0.04)

Abbreviation: CEE, conjugated equine estrogen.

Figure 3. Kaplan-Meier Estimates of Cumulative Hazards for Selected Clinical Outcomes



CEE indicates conjugated equine estrogen; HR, hazard ratio; CI, confidence interval. Events shown are occurring during 1-year intervals through year 8 and beyond year 8.

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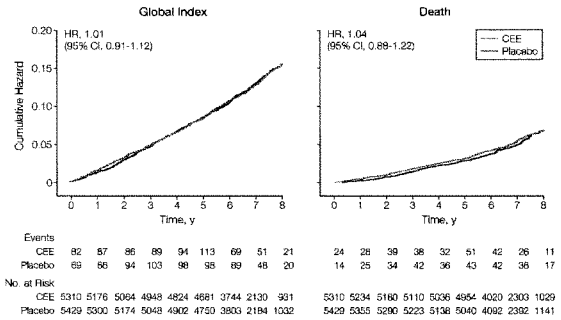
Figure 4. Kaplan-Meier Estimates of Cumulative Hazards for Global Index and Death



CEE indicates conjugated equine estrogen; HR, hazard ratio; CI, confidence interval. Events shown are occurring during 1-year intervals through year 8 and beyond year 8.

ethnicity or body mass index on risk of CHD, stroke, VTE, breast cancer, colorectal cancer, hip fracture, or total osteoporotic fracture (data not shown). Of particular interest for all outcomes was age at enrollment (FIGURE 5). The only treatment × age interaction reaching statistical significance was for colorectal cancer ($P=.048$), for which increasing age was associated with increasing risk with CEE use.

The effect of prior disease on cardiovascular event rates was also evaluated. Among the 441 women enrolled with prior MI or revascularization procedures, the effect of CEE relative to placebo (33 vs 31; HR, 1.04; 95% CI, 0.63-1.71) did not differ significantly from the CEE effect in women without documented CHD (143 vs 162; HR, 0.91; 95% CI, 0.73-1.14) ($P=.55$). Similarly, in 168 women reporting prior stroke, the HR for subsequent stroke (6 vs 6; HR, 1.67; 95% CI, 0.52-5.36) did not differ from the HR in women without a history of stroke (152 vs 112; HR, 1.39; 95% CI, 1.09-1.78) ($P=.77$). Removing from analysis the few participants with a history of PE did not alter the hazard ratio for PE substantially (47 vs 37; HR, 1.31; 95% CI, 0.85-2.01).

Sensitivity analyses were conducted to provide an indication of the potential impact of lack of adherence to assigned study medication. Compared with the primary intent-to-treat analyses (Table 3), the "complier" models estimated greater risks of stroke (HR, 1.74), pulmonary embolism (HR, 1.99), and total mortality (HR, 1.26) but lower risks of breast cancer (HR, 0.65), hip fracture (HR, 0.48), and colorectal cancer (HR, 0.92). The HRs for CHD (HR, 0.89) and the global index (HR, 1.06) were essentially unchanged.

COMMENT

The WHI estrogen-alone study was a large-scale, randomized, double-blind, placebo-controlled trial designed to test the effects of the most commonly used postmenopausal hormone therapy preparation in the United States[19] on chronic disease incidence in a diverse population of mostly healthy postmenopausal women aged 50 to 79 years. As conceived, the study had adequate power to detect moderate effects on CHD, hip fractures, and with longer-term follow-up, breast cancer among women across the broad age range relevant for disease prevention hypotheses. This trial demonstrated that CEE increases the risk of stroke, reduces the risk of hip and other fractures, but does not significantly affect the incidence of CHD (the primary outcome) or overall mortality. A nonsignificant reduction in breast cancer incidence requires additional investigation. These observed risks and benefits of CEE for chronic disease rates appear to be balanced over an average 6.8-year follow-up period.

The lack of effect of CEE on CHD risk is substantially different from the favorable reports from observational studies that motivated this trial, and was observed despite an improvement in cholesterol levels. However, these results are consistent with several recent secondary prevention trials that showed no benefit of hormone therapy on atherosclerosis or clinical events.[20-24] The current study suggests that younger women who use CEE may be at reduced risk of CHD but this possible association may be due to chance.

These CHD results for CEE also differ importantly from 2 previous trials of estrogen plus progestin. In both the WHI estrogen plus progestin trial[25] and HERS,[26] the risk of CHD was significantly elevated in the first year of treatment and the cumulative effects of estrogen plus progestin never appeared beneficial. In the current study, a smaller, nonsignificant increase was observed in the first year of CEE exposure but the cumulative effect suggests a possible modest benefit with longer-term use. Potential explanations for this discrepancy include the role of progestin, differences in the study populations in baseline risk factors,[18] duration of intervention and follow-up time, and the role of chance.

The observed adverse effect of CEE on the risk of stroke is consistent with the risks reported by the WHI and HERS estrogen plus progestin trials.[27,28] In addition, the use of estradiol in women after ischemic stroke resulted in no change in mortality but a higher rate of recurrent nonfatal stroke and a suggestion of more severe functional deficits.[29] The small but persistent increase in systolic

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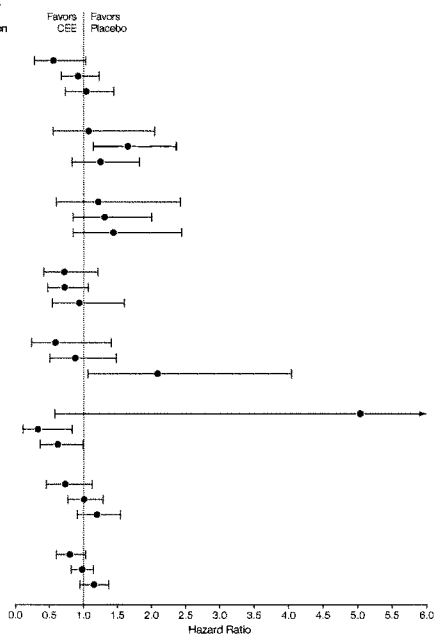
blood pressure in women taking CEE is one possible contributor to this effect because relatively small differences in systolic blood pressure have been positively associated with differences in stroke and cardiovascular disease rates.[30,31]

The WHI estrogen-alone trial provides strong evidence that CEE reduces the risk of hip, clinical vertebral, and other fractures. These reductions were of similar magnitude to those observed in the WHI estrogen plus progestin trial[32] and are consistent with findings from prior observational studies[33,34] and recent meta-analyses.[35-37]

The trend toward a reduction in breast cancer incidence was unanticipated and is opposite of that observed in the WHI estrogen plus progestin trial, which reported a 24% increased risk.[38] These results also appear contrary to the preponderance of observational study results,[4,39] including those from the recent Million Women Study.[40] When examining breast cancer risk by type of hormone therapy, most of these studies have reported a modest increase in breast cancer risk with estrogen alone but a greater risk for estrogen plus progestin. Still others have recently found little or no effect of estrogen alone on breast cancer risk.[41] Differences in breast cancer screening between the CEE and placebo groups do not explain the observed breast cancer effects because the WHI protocol mandated annual mammography and clinical breast examinations. The possibility that diagnostic delay could account for this reduction seems remote because the effect of CEE alone on breast density is minimal.[42] Longer-term effects of CEE on breast cancer risk remain uncertain. Extended follow-up, as is currently planned, and analyses of breast cancer characteristics similar to those reported for the estrogen

Figure 5. Selected Clinical Outcomes by Participant Age and Randomization Assignment

Outcome by Age, y	No. of Cases (Annualized %) CEE	No. of Cases (Annualized %) Placebo	Hazard Ratio (95% CI)	P Value for Interaction
Coronary Heart Disease				
50-59	16 (0.14)	29 (0.24)	0.56 (0.30-1.03)	
60-69	87 (0.54)	98 (0.59)	0.92 (0.69-1.23)	.14
70-79	74 (0.88)	72 (0.84)	1.04 (0.75-1.44)	
Stroke				
50-59	19 (0.16)	19 (0.16)	1.08 (0.57-2.04)	
60-69	79 (0.49)	50 (0.30)	1.65 (1.16-2.36)	.59
70-79	60 (0.71)	49 (0.57)	1.25 (0.85-1.82)	
Venous Thromboembolism				
50-59	18 (0.15)	15 (0.13)	1.22 (0.62-2.42)	
60-69	49 (0.31)	39 (0.23)	1.31 (0.86-2.00)	.39
70-79	34 (0.40)	24 (0.28)	1.44 (0.86-2.44)	
Invasive Breast Cancer				
50-59	25 (0.21)	35 (0.29)	0.72 (0.43-1.21)	
60-69	42 (0.26)	60 (0.36)	0.72 (0.49-1.07)	.51
70-79	27 (0.32)	29 (0.34)	0.94 (0.56-1.60)	
Colorectal Cancer				
50-59	8 (0.07)	14 (0.12)	0.59 (0.25-1.41)	
60-69	26 (0.16)	31 (0.19)	0.88 (0.52-1.48)	.048
70-79	27 (0.32)	13 (0.15)	2.09 (1.08-4.04)	
Hip Fracture				
50-59	5 (0.04)	1 (0.01)	5.04 (0.59-43.17)	
60-69	6 (0.04)	19 (0.11)	0.33 (0.13-0.83)	.39
70-79	27 (0.32)	44 (0.52)	0.62 (0.38-1.00)	
Total Death				
50-59	34 (0.29)	47 (0.39)	0.73 (0.47-1.13)	
60-69	127 (0.79)	131 (0.79)	1.01 (0.79-1.29)	.19
70-79	130 (1.54)	111 (1.30)	1.20 (0.93-1.54)	
Global Index				
50-59	104 (0.89)	132 (1.11)	0.80 (0.62-1.03)	
60-69	312 (1.95)	327 (1.97)	0.98 (0.84-1.15)	.08
70-79	276 (3.28)	246 (2.88)	1.16 (0.97-1.37)	



CEE indicates conjugated equine estrogen; CI, confidence interval. Data are plotted as hazard ratios with error bars showing 95% CIs.

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plus progestin study[38] may provide additional insight.

In preliminary subgroup analyses, the estimated HRs for CEE for several monitored outcomes, including the global index, were lower for women aged 50 to 59 years, although differences in HRs across age groups were not statistically significant. While these results suggest that CEE may be somewhat more favorable in younger than in older women, these subgroup analyses must be interpreted with caution; we cannot exclude the role of chance or limited power.

Limitations

This trial was designed to test only one unopposed estrogen preparation at a single dose, administered orally. We cannot determine whether these results would apply to other formulations, doses, or routes of administration. Care is needed in making comparisons of these estrogen-alone trial results to those of the estrogen plus progestin trial, even though this is of considerable interest. The differences between these 2 study populations in their baseline characteristics,[18,43] their event rates, the length of intervention and follow-up time, and the completeness of data at this initial report are sufficient to make simple contrasts potentially misleading. More detailed analyses of these parallel trials are planned.

The high rates of discontinuation of study medications and higher than expected crossover from placebo to active hormone use are further limitations. The rate of discontinuation is less than what is usually observed in clinical practice[44] and was similar in the 2 groups. The somewhat higher drop-in rate in the placebo group is not explained by unblinding, which was infrequent (1.5%) and similar in the 2 groups. Sensitivity analyses suggest that the lack of adherence to assigned study medication may have diluted the CEE effects, both positive and negative, relative to what might be observed with full adherence, but it did not distort the overall balance of effects.

Lower than anticipated event rates for some outcomes, particularly CHD and hip fractures, reduce the power relative to what was originally projected but reinforce the generally healthy status of these participants. The fact that the trial was stopped early further decreases the precision of the estimated effects. A longer intervention period may have provided stronger statistical evidence of CEE effects, particularly for CHD, for which some evidence of a trend with time was observed, and for breast cancer, for which the cumulative effect of long-term exposure remains uncertain. Additional data could have allowed for more informative subgroup analyses. Extended follow-up of these women without further intervention is planned.

Clinical Implications

In women aged 50 to 79 years reporting a prior hysterectomy, CEE did not affect CHD rates but did increase the risk of stroke, accounting for an excess risk of 12 cases per 10000 person-years, and reduced the risk of hip fractures, resulting in 6 fewer cases per 10000 person-years. Unexpectedly, women taking CEE also appeared to be diagnosed as having breast cancer at a lower rate than women taking placebo, but the estimated 7 fewer cases per 10000 person-years did not reach statistical significance. The totality of monitored effects, as summarized in the prespecified global index, suggests an overall balance of risks and benefits and importantly no effect on total mortality.

Based on these findings, women and their health care professionals now have usable risk estimates for the benefits and harms of CEE alone. Women considering taking CEE should be counseled about an increased risk of stroke but can be reassured about no excess risk of heart disease or breast cancer for at least 6.8 years of use. At present, these data demonstrate no overall benefit of CEE for chronic disease prevention in postmenopausal women and thus argue against its use in this setting. Overall, these data support the current US Food and Drug Administration recommendations for postmenopausal women to use CEE only for menopausal symptoms at the smallest effective dose for the shortest possible time.[45]

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20 Postmenopausal hormone therapy and cardiovascular disease

Jacques E Rossouw

Gender and cardiovascular disease

In the United States the number of women who die annually from cardiovascular disease is higher than men. The cardiovascular disease burden is particularly high in older women. In women aged 55 and older, major cardiovascular diseases (ICD 390–448·9) accounted for 473 569 deaths in 1997 compared to 402 310 deaths in older men.[1] Major cardiovascular diseases accounted for 44% of all deaths in older women and 40% of all deaths in older men. The number of deaths from coronary heart disease (CHD) was only slightly higher in older women (229 628) than in men (223 246), but the number of deaths from stroke was considerably higher in women (88 768 compared to 55 149 respectively). There were 4607 deaths from pulmonary embolism in older women compared to 3465 in men. As exemplified by these absolute numbers of deaths, cardiovascular disease now represents a larger health problem in older women than in older men.

CHD in particular occurs at a later age in women than in men, and this is one reason why early trials (including estrogen trials) attempting to prevent "premature" CHD focused on middle-aged men. On average, death from CHD occurs about 10 years later in women (Figure 20.1) than in men. The incidence rate of CHD mortality rises after the age of 65, and rises particularly steeply after 75 years when the great majority of CHD events occur. Though their incidence rates remain lower at any age than in men, the fact that older women with CHD outnumber men explains why the absolute number of CHD deaths is higher in women. Deaths from strokes and pulmonary embolism also rise markedly with age. Since CHD and strokes are the major contributors to overall cardiovascular disease rates, the effects of estrogen on these conditions will dominate the overall cardiovascular outcome.

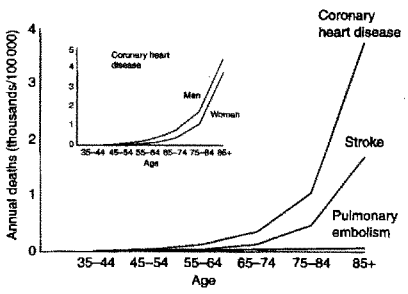


Figure 20.1 Annual mortality rates by 10 year age groups for CHD, stroke, and pulmonary embolism in US women, 1997.[1] Inset: Comparison of coronary heart disease mortality rates by age for men and women.

The sex differential in the age of onset of CHD is also one of the reasons why estrogen is of interest as a potential preventive treatment for CHD. Lipid levels in children of both sexes are similar until puberty, when high density lipoprotein (HDL) cholesterol levels fall by about 10 mg/dl in boys only, while low density lipoprotein (LDL) cholesterol levels decrease by about 5 mg/dl in girls.[2] These changes may be attributable to rising androgen and estrogen levels in boys and girls respectively. The sex differential for HDL cholesterol persists through adult life, but is less marked in older persons. LDL cholesterol levels rise during adulthood, and in older women LDL cholesterol levels eventually catch up with those in men. Estrogen levels in women gradually decline, starting some years before the menopause, during which time LDL cholesterol levels rise and HDL cholesterol levels decrease.[3] These lipid changes may underlie the lower CHD risk in premenopausal women, and the gradual increase in postmenopausal women. However, the menopause does not represent a sharp demarcation in risk; some longitudinal studies have not shown changes in risk factors over the menopause, and the rise in coronary rates may simply reflect the effects of aging itself, as suggested when the data for coronary deaths are plotted on a semi-logarithmic scale (Figure 20.2).[1,4] Nonetheless, premature menopause due to oophorectomy is associated with a higher CHD risk, and oophorectomy followed by estrogen therapy is not associated with increased risk for CHD.[5] When exogenous estrogen is administered via the oral route to postmenopausal women, LDL cholesterol levels decrease, HDL cholesterol levels increase, triglyceride levels increase, and lipoprotein (a) levels decrease.[6–10] However, exogenous oral estrogen has multiple non-lipid effects. Some changes in coagulation factors are potentially favorable (for example,

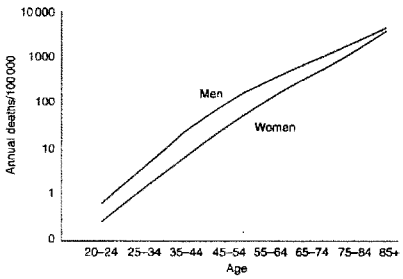


Figure 20.2 Annual mortality rates for CHD by age for US men and women on a semi-logarithmic scale

a decrease in fibrinogen level[7–9]) while others are potentially unfavorable (for example, an increase in factor VII[8,9]), and the net effect of estrogen on coagulation is uncertain. Similarly, some effects on markers of inflammation are potentially unfavorable (for example, increases in C-reactive protein) and others favorable (for example, decreases in vascular endothelial adhesion molecules).[11,12] Other potential influences of estrogen on vascular biology include direct effects on the vessel wall, which improve blood flow,[13,14] and antioxidant properties that may slow the early stages of atherosclerosis.[15] It should be noted that many, but not all, of the biologic effects of estrogen are counteracted by the progestins, which are now routinely prescribed in combination with estrogen in women with intact uterus.[7–9]

Thus, there is a plethora of potential mechanisms by which estrogen may reduce the risk of CHD.[16] Unfortunately, the existence of mechanisms does not necessarily translate into clinical benefit. A treatment that has a favorable effect on an intermediate mechanism may decrease the incidence of target clinical events, or may turn out to have no effect, or may actually increase the event rates. The treatment may also have unanticipated adverse effects on other clinical events.[17] For example, a number of early lipid lowering drugs, such as thyroxin and estrogen, were abandoned after it was found that, although these drugs decrease cholesterol levels, they also increase the cardiovascular morbidity and mortality in men.[18]

Box 20.1

- Cardiovascular disease is a major health problem in older women.
- Coronary heart disease occurs at a later age in women than in men.
- The later onset of coronary disease may be due to gender-specific hormone-induced changes in blood lipid levels.
- Increased rates of coronary heart disease after the menopause may be due to declining estrogens or may be due to aging.

Coronary heart disease

Throughout this chapter, the term postmenopausal hormone therapy (sometimes shortened to hormone therapy) is used to describe the use of estrogen or estrogen plus a progestin in postmenopausal women. The term hormone replacement therapy is not used, because this term implies a judgment that postmenopausal women suffer from a hormone "deficiency" that needs treatment.

More than 30 observational studies have suggested that women who are taking estrogen appear to have a lower risk of heart disease, and several have shown similar apparent risk reductions for estrogen when it is used in combination with progestin.[19–23] Only a few key studies will be reviewed in detail, since they illustrate sufficiently the findings from observational studies, and their limitations. "Primary prevention" studies are those in which women with prevalent coronary artery disease (CAD) were removed from the cohort, while "secondary prevention" studies followed only those women with a history or other evidence of CAD at baseline. The growing body of evidence from clinical trials with surrogate outcomes and clinical trials, with "hard" clinical outcomes for secondary prevention, will be reviewed in detail. Thus far, these secondary prevention trials have failed to confirm the cardiovascular benefit predicted from observational studies, and in fact the trials suggest that there is likely to be harm in the first few months to years after initiation of hormone therapy. Substantive data from primary prevention trials have yet to be published.

Primary prevention

Observational studies

With the exception of the initial report from Framingham on this issue, all the observational studies of healthy postmenopausal women comparing hormone users with non-users described an association of hormone use (particularly current hormone use) with lower risk for CHD.[19–24] However, as reviewed elsewhere, the consistency of these results may be due to powerful systematic biases in observational studies, which may lead to an overestimation of benefit and an underestimation of harm associated with hormone use.[25,26]

The Nurses' Health Study is representative of the observational studies, and the women in this study comprise one of the largest and best studied cohorts in the USA.[21] The 1976 baseline examination included 121 700 nurses aged 30–55 years of whom 21 726 were postmenopausal. With the passage of time a progressively larger proportion entered the menopause and these women contributed data to a series of papers on the associations between menopause, hormone therapy, and cardiovascular disease. Data on

hormone use and health status were updated biennially by questionnaire. The most recent analysis included 70 533 women with up to 20 years average follow up for a total experience of 808 825 person-years during which time the study accrued 1258 major coronary events (non-fatal myocardial infarction or coronary death).[21] There were 662 major coronary events during the 358 125 person-years of never users, 337 events during the 185 497 person-years of past users, and 259 events during the 265 203 person-years of current users of postmenopausal hormone therapy. Conjugated equine estrogen (CEE) accounted for about two thirds of the estrogen used. Proportional hazards models were used to calculate relative risks for incidence of clinical outcomes, using women who had never used hormones as the reference group. Multivariate adjustments were made for age, body mass index, history of diabetes, hypertension, high cholesterol level, cigarette smoking, and parental history of premature heart disease.

The adjusted relative risk of major coronary disease in current users compared to never users was 0·61 (95% CI 0·52–0·71), and in past users it was 0·82 (95% CI 0·72–0·94). Current users of CEE alone had a relative risk of 0·55 (95% CI 0·45–0·68), and current users of CEE with medroxyprogesterone acetate (MPA) had a relative risk of 0·55 (95% CI 0·49–0·85). Duration of hormone use appeared to have little influence; however the relative risk appeared to be lowest in current users for less than 1 year (0·41, 95% CI 0·21–0·77) (Figure 20.3). The reduced risk for CHD was observed at all estrogen doses, but appeared to be more marked at the doses of 0·3 mg conjugated equine estrogen (0·58, 95% CI 0·37–0·92) and 0·625 mg (0·54, 95% CI 0·44–0·67) than at the dose of 1·25 mg or higher (0·70, 95% CI 0·51–0·97) (Figure 20.3).

An earlier publication from the Nurses' Health Study noted that the rates of coronary revascularization did not differ between current users and non-users.[27] Since it differs from the findings for fatal and non-fatal myocardial infarction, this observation argues against an immediate beneficial effect of estrogen on the vessel wall. Most patients undergo revascularization for symptoms and, if estrogens had a direct effect, symptoms would have been less likely in users. The data as regards to revascularization have implications for the interpretation of the data for CHD events: if estrogen confers no immediate benefit, the finding of lower CHD rates in current users may be due to the compliance bias known to operate in subjects who are regularly taking medications, or to selection bias as to who goes onto estrogen and who is removed from therapy.

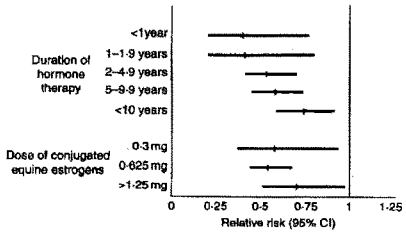


Figure 20.3 Relative risks and 95% confidence intervals for CHD by duration and dose of current hormone use in the Nurses' Health Study[21]

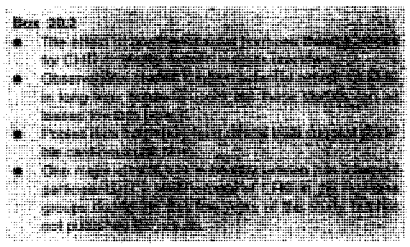
Data on risk for CHD in healthy women soon after initiation of estrogen therapy are sparse and inconsistent, although most studies suggest reduced initial risk in estrogen users. As noted above, the Nurses' Health Study observed the lowest relative risk during the first year of use.[21] Several other studies found little or no association of hormone use with risk in the first year or two after initiating therapy,[28–30] while two suggested some early increase in risk.[31,32] By contrast (see below) the data for secondary prevention are much more consistent in suggesting cardiovascular harm after initiation of therapy.

Clinical trials

A pooled analysis of 23 randomized controlled trials, which were done for the study of non-cardiovascular short-term effects of hormone therapy but which recorded numbers of clinical events, found twelve cardiovascular (arterial) events in the hormone groups and five in the control groups.[33] Though not statistically significant, the results were in the opposite direction to that predicted by the observational studies.

Large clinical trials of estrogen in healthy women with sufficient statistical power to provide a definitive answer to the question of benefit for cardiovascular disease are underway (Table 20.1). The first of these forms part of the Women's Health Initiative (WHI) in the USA. The WHI enrolled 27 347 women aged 50–79 in the trials of menopausal hormone therapy during 1993–1998 and will be completed in 2005 after 8·4 years average follow up.[34] The study comprises two randomized controlled clinical trials: the 16 608 women with an intact uterus randomized to CEE 0·625 mg/day plus MPA 2·5 mg/day or placebo, and the 10 739 women with a hysterectomy randomized to CEE 0·625 mg/day or placebo. No results have yet been published, but in 2000 the trial participants were advised that during the first 2 years after randomization small excesses in numbers of heart attacks, strokes, and blood clots in the lungs were observed in the active treatment groups.[35] In 2001 a follow up communication to participants stated that small absolute excesses of these conditions persisted beyond the first 2 years, but that the trials will continue because the overall risk and benefit remained uncertain.[35]

A second large trial being conducted in the United Kingdom and New Zealand, known as the Women's Intervention Study of long-Duration Oestrogen after the Menopause (WISDOM), is enrolling women aged 50–64 and randomizing women with a uterus to CEE 0·625 mg/day plus MPA 2·5 mg/day or placebo, and women who have had a hysterectomy to CEE 0·625 mg/day, CEE 0·635 mg/day plus MPA 2·5 mg/day, or placebo.[36] Up to 34 000 women will be enrolled. The primary analysis will compare CEE plus MPA to placebo, and the secondary analysis will compare CEE plus MPA to CEE alone. The primary outcome of interest is combined CHD and stroke.



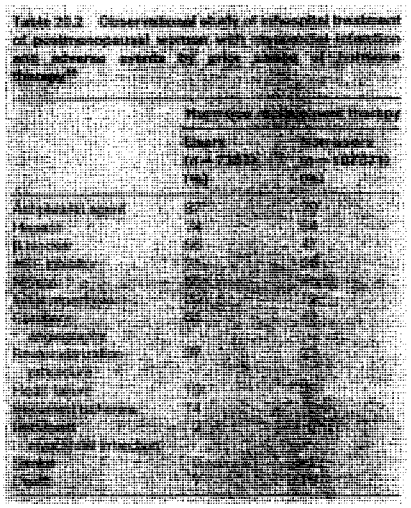
Secondary prevention

Observational studies

Observational studies in women undergoing angioplasty or coronary artery bypass grafting (CABG) have found that use of postmenopausal hormone therapy was associated with lower rates of cardiovascular events and improved survival.[37–40] A retrospective analysis of postmenopausal women undergoing angioplasty found that 12% of patients taking hormones had cardiovascular events over 7 years of follow up, compared to 35% of non-users.[37] A second similar study found that inhospital and 2 year mortality after angioplasty was lower in hormone users.[38] In women undergoing CABG, one study found that hormone use was associated with a 62% survival benefit; however, this was not confirmed in a subsequent study.[39,40] Several observational studies have compared the experience of women currently on hormone therapy and who suffer a myocardial infarction with those who were not on hormone therapy at the time of the myocardial infarction.[41–44] These studies have consistently found better outcomes for women who were currently on hormone therapy at the time of the event.

The largest study of inhospital mortality was performed prospectively in 114 724 women aged over 55 who were entered into the National Registry of Myocardial Infarction-3.[41] At the time of hospitalization, 6·4% of women reported current use of hormone therapy. There were significant differences between hormone users and non-users. Hormone users were younger, more likely to be white, less likely to have a history of diabetes, heart failure, prior myocardial infarction, and prior stroke compared to non-users, but were more likely to have high blood cholesterol and family history of CAD, or to smoke. Hormone users were also more likely to receive aggressive inhospital care including angiography, angioplasty, bypass grafting, reperfusion therapy, aspirin, heparin, β blockers, and nitrates (Table 20.2). Complication rates were similar in users and non-users; however, after adjustment for the potential confounders, hormone use was associated with a reduced odds of inhospital mortality (0·65, 95% CI 0·59–0·72). The association was strongest in the youngest group of women (age 55–64 years). The authors acknowledge that some or all of this apparent survival benefit could be due to one or more sources of bias – for example, residual differences between users and non-users or the healthier profile that decreased mortality may also have increased the likelihood of taking hormone therapy; or the hormone users may have received care at hospitals with greater experience of myocardial infarction care; or hormone users may have been better at compliance with treatment and may thus have an improved survival. The many differences in patient characteristics and inhospital treatment observed between hormone users and non-users illustrate the difficulties of interpretation of observational studies.

Three observational studies have suggested that recent initiation of hormones after the index myocardial infarction



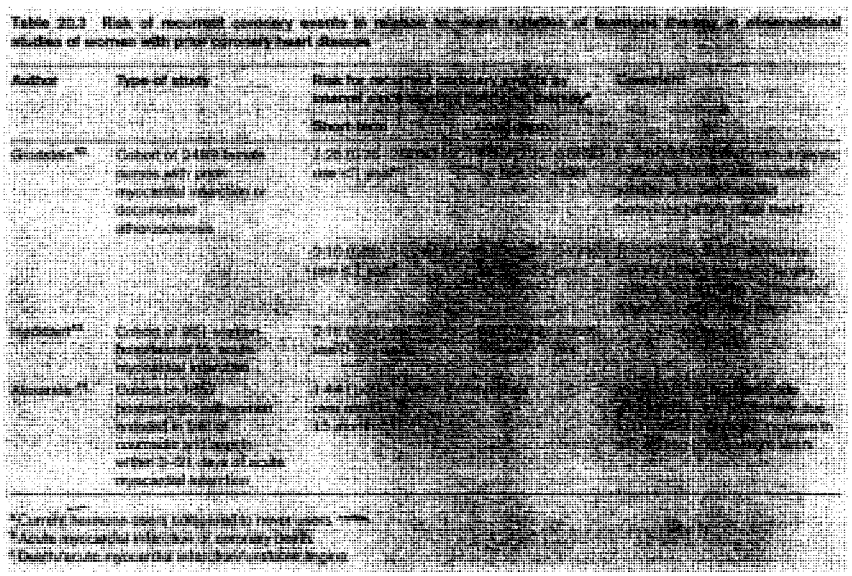
is associated with an increased risk for recurrent events in the short term; two of these studies provided data suggesting a possible decreased risk in later years among the survivors (Table 20.3).[42–44] This pattern of increased risk in the first year with apparently reduced risk in later years is similar to that observed in several randomized controlled clinical trials, notably the Heart and Estrogen/progestin Replacement Study (HERS).[45] It should be noted that these analyses of risk by recency of hormone use were performed after publication of the HERS results; therefore the possibility of publication bias cannot be excluded.

Clinical trials with surrogate outcomes

The primary outcome of the Estrogen Replacement and Atherosclerosis (ERA) trial was change in the angiographic minimal diameter of coronary artery lesions.[46] Women ($n = 309$) with angiographically defined CAD were randomized to one of three groups: CEE 0·625 mg, CEE 0·625 mg plus MPA 2.5 mg, or placebo. At the end of the trial, compliance ranged from 74% in the estrogen-only group to 84–86% in the other groups. Over the mean treatment duration of 3·2 years, all three groups showed a decrease in minimal coronary artery diameter and there were no differences between the groups. In other words, treatment with estrogen with or without MPA failed to arrest the progression of existing coronary artery lesions, even though the estrogen and estrogen plus MPA treatments lowered LDL cholesterol by 9·4 and 16·5%, and raised HDL cholesterol levels by 18·8 and 14·2%, respectively. Several additional clinical trials with angiographic outcomes are underway.

Clinical trials

A randomized controlled clinical trial in 293 postmenopausal women with unstable angina, aged 43–93, failed to demonstrate benefit with estrogen or estrogen plus progestin for reduction in number of ischemic episodes.[47] The premise of the trial was that endothelial dysfunction with subsequent impairment of coronary blood flow has an important pathophysiologic role in acute coronary syndromes, and that reversal of the endothelial dysfunction by estrogen would improve the clinical outcome. Participants received one of three study treatments within 24 hours of the onset of symptoms: an infusion of 1·25 mg of CEE followed by oral CEE 1·25 mg/day for 21 days, or an infusion of CEE followed by oral CEE plus MPA 2·5 mg/day, or an infusion of placebo followed by oral placebo. The trial was



stopped short of its planned enrollment of 351 when the Data and Safety Board determined that there was no difference between treatment groups. During the first 48 hours the mean number of ischemic episodes per patient recorded by ambulatory ECG monitoring was 0·74, 0·86, and 0·74 in the estrogen, estrogen plus progestin, and placebo groups respectively, and symptomatic ischemia occurred in 39%, 52%, and 42%. Inhospital incidence of refractory ischemia, death, myocardial infarction, and revascularization procedures were similar in the three groups (Table 20.4). The groups did not differ at 21 days for ischemia, or at 6 months for clinical events. The authors cite several possible reasons for the failure of the estrogen therapy to improve ischemia: lack of functional estrogen receptors in advanced lesions or with age, countervailing adverse effects of estrogen on thrombosis or inflammation, and the fact that participants almost uniformly received standard anti-ischemia therapy (including heparin, aspirin, β blockers, and nitroglycerin). The numbers of ischemic episodes were also lower than anticipated in the power calculations. From this study it would appear that acute estrogen therapy is not a useful addition to the standard therapy for acute coronary syndromes.

HERS is a landmark study, as it represents the first substantive test of the hypothesis that hormone therapy prevents coronary events in women with existing disease (Table 20.1).[45] The 2763 postmenopausal women aged 44–79 who enrolled all had established CAD and had not had a hysterectomy. They were randomized to CEE 0·625 mg/day plus MPA 2·5 mg/day or to placebo. The hormones induced the expected lipid changes, reducing LDL cholesterol by 11%, raising HDL cholesterol by 10%, and raising triglycerides by 8% compared to placebo. Over the average study duration of 4·1 years there was no net benefit for the principal outcome of CHD (non-fatal myocardial infarction plus coronary death) with 172 cases in the placebo group and 176 cases in the active treatment group.

However, in the first year of HERS there was a nominally significant ($P < 0·05$) 52% excess of coronary events in the treatment group compared to the placebo group (Figure 20.4). In the second year there was no difference in event rates and thereafter there was a trend towards a reduction in the active treatment group, mainly due to a reduction in non-fatal myocardial infarction. The trend for coronary heart disease risk over time was significant ($P = 0·009$). However, it should be noted that the significance of the trend depended on the adverse direction of events in the first year, and that events after the first year were recorded in survivors of the first year (that is, after the first year the arms were no longer balanced). There was no benefit for any other cardiovascular outcome, including angina or revascularization procedures. Other important findings were a significant increase in venous thromboembolism and a marginally significant increase in gallbladder disease (84 in hormone

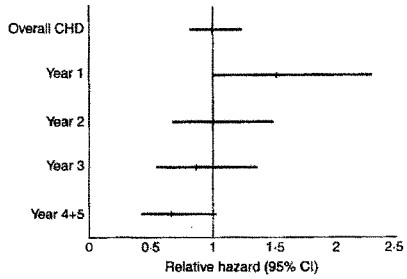
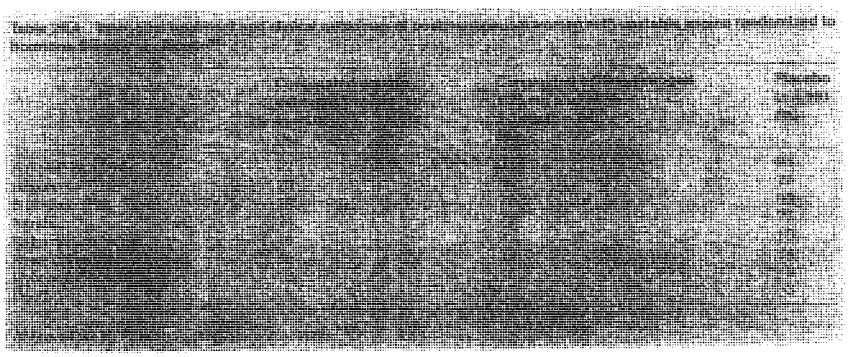


Figure 20.4 Relative hazard and 95% confidence intervals for CHD in HERS over the entire trial duration and by year since randomization[45]



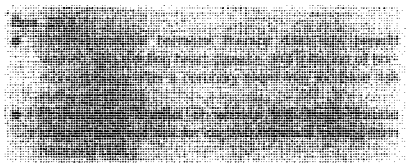
group and 62 in the placebo group, $P = 0{\cdot}05$). There was no reduction in fractures (130 compared to 138).

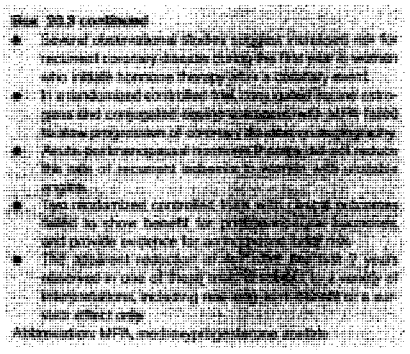
Thus, HERS provided some results for hormone therapy that were expected (increased risk for venous thromboembolism and gallbladder disease) and some that were unexpected (no overall reduction in CHD, and no reduction in fractures). The trend over time for coronary disease was also unexpected, and in fact the investigators anticipated that the immediate effects of estrogen – for example, on fibrinolysis and vascular reactivity – might have led to early benefit, sustained in later years by beneficial changes in plasma lipid concentrations. The observed early adverse effect needs to be explained: possibilities include that hormone therapy induces inflammatory changes in unstable plaques, or that a procoagulant effect predominates early on. There is no doubt that menopausal hormone therapy is procoagulant, as shown by the excess of venous thromboembolism. The findings may be explained by the existence of a subset of women who are particularly susceptible to one or more of the adverse metabolic or local tissue changes induced by hormone therapy, and that the remaining women who did not have an early event reap the later benefit of lipid lowering. Alternatively, there may be no real benefit, and the apparent later benefit may simply reflect a survivor effect in that women most susceptible to an adverse effect of the treatment have been removed from the cohort. A post-hoc analysis of HERS data indicated that women with higher lipoprotein (a) levels were less likely to have an initial adverse outcome, and were more likely to benefit in later years, presumably because some of the adverse effects of the hormones were counteracted by a reduction in high lipoprotein (a) levels.[10]

One possible explanation for the HERS findings is that MPA negated any possible benefit from estrogen, for example by blocking the direct vascular effects of estrogen and blunting the rise in HDL cholesterol induced by estrogen. (However, it is noted that HDL cholesterol levels in fact increased by 10%.) Another explanation might be that many participants were receiving medications that would lower risk for recurrent coronary events (for example, aspirin, β blockers, lipid lowering medications, and to a lesser extent angiotensin-converting enzyme [ACE] inhibitors), thus masking any potential for benefit from estrogen. This seems unlikely, but even if true the trial still demonstrates that hormone therapy is not a useful adjunct to established secondary prevention treatments. Other possible explanations offered are that the women in HERS were too old and their arteries too diseased to benefit from hormone therapy, or that the type and dose of hormones was not optimal.[48–50] These explanations ignore the fact that the observational studies suggesting benefit and which prompted the need for HERS were conducted in populations similar to that studied in HERS, and the hormones were the same as those tested in HERS.

Though unexpected and controversial, the pattern of early harm observed in HERS has found support in two other secondary prevention trials for coronary disease and one for stroke (and as noted above, in the WHI primary prevention trial, a pooled analysis of short-term studies, and in several observational studies).[35,42–44,51–53] Stimulated by the HERS findings, a re-analysis of data from an earlier trial of CEE 2·5 mg/day in men with existing heart disease revealed a pattern of no overall benefit but with increased risk for CHD in the first 4 months after randomization (relative hazard 1·58, 95% CI 1·04–2·40) similar to that found in HERS for the same period (2·29, 95% CI 0·94–5·56).[51] A trial of transdermal estradiol (with cyclic norethisterone for women with a uterus) was stopped after an average of 2·5 years follow up for reasons of futility and possible harm (Table 20.1).[52] At the time of stopping this trial, 255 women with angiographically defined CAD had been enrolled and only 61% of women were still on estrogen. Though clearly underpowered, with short follow up, and reported only in abstract form, the results were nonetheless consistent with HERS in that there was a 23% ($P = 0{\cdot}3$) excess of unstable angina, myocardial infarction, and death. Finally, the Women's Estrogen for Stroke Trial (WEST) in women with a recent stroke found that oral estradiol did not prevent recurrent strokes overall, and compared to placebo there was a higher risk for fatal strokes, and a higher risk for all strokes in the first 6 months.[53] The combined data from these clinical trials leave little room for doubt that, at least in women with existing arterial disease (coronary or cerebrovascular), estrogen use for up to 4 years is unlikely to result in benefit, and in the first few months to a year is associated with an increased risk for arterial complications.

One other trial testing estradiol valerate versus placebo in 1017 women with CHD is due to report results soon.[54] A secondary analysis of safety data from a trial of raloxifene (a selective estrogen receptor modulator) in 7705 women with osteoporosis showed no benefit for cardiovascular outcomes over 4 years of treatment, but suggested a risk reduction of 40% (95% CI 5–62) in a subset of 1035 women with increased cardiovascular risk at baseline.[55] A randomized controlled clinical trial of raloxifene (a selective estrogen receptor modulator) versus placebo is underway in several countries in order to test whether raloxifene reduces the risk for CHD and breast cancer in women with existing heart disease or who are at high risk for heart disease.[56] This trial has enrolled 10 101 women and the study is planned to end after 1670 participants have experienced a coronary event (expected in 2005).





Cerebrovascular disease

Primary prevention

Because stroke may be fatal, and often leaves the survivors cognitively and functionally impaired, primary prevention is of the greatest importance.

Observational studies

As reviewed elsewhere, the data for stroke are less consistent than those for CHD.[57] Five case–control studies of risk for incidence of all stroke or ischemic stroke reported essentially null results, and six of 16 internally controlled cohort studies reported a significant reduction in risk while two reported significantly increased risk among hormone users. Data on stroke subtypes are scanty and variable. Among current users in five cohort studies, three studies found essentially no effect on ischemic stroke while one each found an increased risk and the other a decreased risk. Similarly, the data on duration and type of hormone therapy (estrogen alone or combined with progestin) are variable. Data for thromboembolic, intracerebral hemorrhage, and subarachnoid hemorrhage stroke subtypes are very scanty.

A meta-analysis of stroke studies suggested that, in aggregate, estrogen users had the same risk for all incident strokes as non-users; however, this meta-analysis antedated the most recent data from the large Nurses' Health Study.[19] Examination of the 20 year follow up data from the Nurses' Health Study is not entirely reassuring.[27] The relative risk for all strokes (767 strokes during 808 825 person-years) in current hormone users compared to never users was 1·13 (95% CI 0·94–1·35), but for ischemic strokes (432 cases) the relative risk was somewhat higher (1·26, 95% CI 1·00–1·61). Furthermore, for all strokes and for ischemic strokes there was a significant increase in relative risk at the usual dose of 0·625 mg, with a further increase at the higher dose of 1·25 mg or greater (Figure 20.5). For example, at the most commonly used dose of 0·625 mg/day the relative risk for all stroke was 1·35 (95% CI 1·08–1·68) and for ischemic stroke it was 1·44 (95% CI 1·07–1·93). The association of stroke with hormone use was stronger in women who used estrogen combined with progestin (1·45, 95% CI 1·10–1·92) than in women who used estrogen alone (1·18, 95% CI 0·95–1·46). There was no excess of strokes in past users. Unlike in CHD, duration of hormone therapy did not appear to influence the risk for stroke (Figure 20.5).

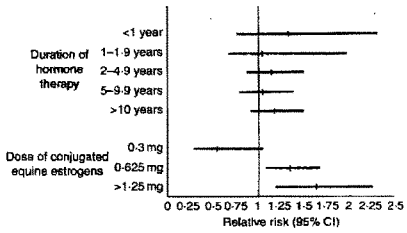


Figure 20.5 Relative risks and 95% confidence intervals for stroke by duration and dose of current hormone use in the Nurses' Health Study[21]

Data for fatal stroke are somewhat more consistent across studies in suggesting an association with reduced risk in current users. Of nine internally controlled cohort studies, there was a significantly reduced risk in three, and with one exception the point estimates for the remaining six studies were below unity.[56]

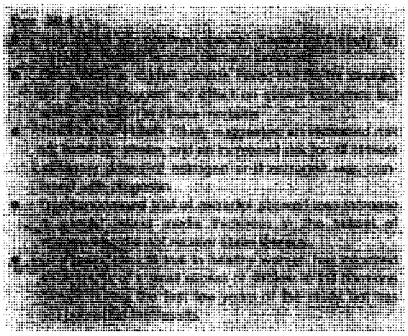
Clinical trials with surrogate outcomes

A randomized placebo-controlled trial of oral estradiol in 202 (199 with evaluable outcomes) healthy postmenopausal women aged 46–80 years found that the rate of progression of carotid intima media thickness (IMT) over 2 years was lower in those taking unopposed estradiol than in those on placebo ($P = 0·046$).[58] Adherence to study medications was very good (95% in estradiol group and 92% in placebo group). Per protocol, 122 participants received lipid lowering medications (primarily statins) because their LDL cholesterol values exceeded 160 mg/dl. The numbers were similar in the estradiol and placebo groups. The participants in the estradiol group who received lipid lowering medications lowered their LDL cholesterol levels by 20%, compared to 15·1% change in the placebo group ($P = 0·02$), and both estradiol and placebo groups experienced some regression of intima media thickness. In the 77 participants who did not receive lipid-lowering therapy, estradiol lowered LDL cholesterol by 10·5% compared to 1·1% in the placebo

group ($P = 0{\cdot}001$), and in this subgroup the estradiol group but not the placebo group showed regression ($P = 0{\cdot}002$ for difference). The authors conclude that reduction in the progression of subclinical carotid atherosclerosis was seen in women who did not take lipid lowering medication but not in those who took these medications. From these results, it would appear that estrogens would not augment the known benefits of statins for inhibiting atherosclerosis.

Clinical trials

WHI is the only clinical trial of healthy women that has provided any indication of the effect of hormone therapy on strokes. As noted above, study participants have been informed of a small absolute increase in the number of strokes in the hormone groups compared to the placebo groups during the first few years of the trial.[35] Stroke is also a predefined outcome of interest in the WISDOM trial.[36]



Secondary prevention

Clinical trials with surrogate outcomes

A randomized trial of oral estradiol 1 mg with standard dose progestin (gestodene 0·025 mg 12 days every month), or estradiol with low-dose progestin (gestodene 0·025 mg 12 days every third month), or placebo for 4 years in 321 women aged 40–70 at high risk for cardiovascular disease (that is, carotid IMT >1 mm) failed to show any benefit for reducing the rate of progression of subclinical atherosclerosis in the carotid arteries.[59] Exclusion of the small number of subjects (14%) who received lipid lowering therapy did not alter these results. LDL cholesterol decreased by 13% in the active treatment groups and fibrinogen by 20%. Adherence was good with only 12–20% of participants discontinuing study medications; compliance was 98% in the remaining participants. Reasons for the difference in outcome of this study with the study of Hodis *et al*[58] are not known. It is possible that the addition of a progestin to the estradiol may have negated the effects of estradiol, but the fact that the results in the standard and low-dose gestodene groups did not differ argues against that possibility. Though this study is regarded as secondary prevention, the distinction is somewhat artificial and is based on the entry level of carotid IMT.

Clinical trials

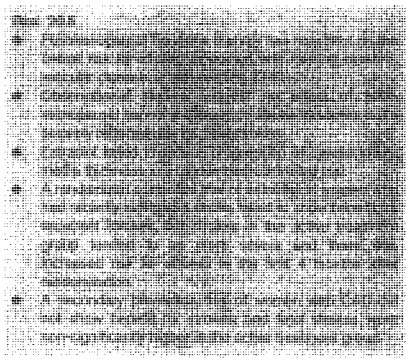
Where HERS examined the effect of hormone therapy on recurrent coronary disease, WEST is its counterpart for recurrent stroke.[53] There are important parallels between the two trials, and also a few differences. WEST randomized 664 women aged 46–91 who had suffered a transient ischemic attack or stroke in the previous 90 days to receive oral estradiol 1 mg or placebo and followed them for an average of 2·8 years. By the end of the trial 34% had stopped estradiol and 24% had stopped placebo. Compared to placebo, estradiol had no effect on the primary outcome of combined non-fatal stroke and all-cause mortality, or on non-fatal stroke or death individually (Table 20.5). However, estradiol increased the risk for fatal stroke (relative risk 2·9, 95% CI 0·9–9·0) and the non-fatal strokes in the estradiol group were associated with more functional and neurologic deficits. A post-hoc analysis of strokes by time since randomization indicated that during the first 6 months, there were three fatal strokes and eighteen non-fatal strokes in the estradiol group, compared to one fatal and eight non-fatal strokes in the placebo group (relative risk for any stroke 2·3, 95% CI 1·1–5·0). There were no differences in the rates of transient ischemic attacks or myocardial infarction.

Table 20.5 Selected outcomes according to treatment assignment in the WEST[53]

Outcome	Estradiol group ($n = 337$)	Placebo group ($n = 327$)	Relative hazard (95% CI)
Death or non-fatal stroke	99	98	1·1 (0·8–1·4)
Death	43	41	1·2 (0·8–1·8)
fatal stroke	12	4	2·9 (0·9–9·0)
CHD	11	13	0·8 (0·4–1·8)
Non-fatal stroke	57	52	1·0 (0·7–1·4)
Non-fatal myocardial infarction	14	12	1·2 (0·5–2·5)

HERS has published a more complete analysis of the stroke data, which indicated that there was no significant effect of hormone therapy on any category of stroke (fatal, non-fatal, ischemic, hemorrhagic, any stroke, transient ischemic attack).[60] However, the point estimate was above

unity for each category except transient ischemic attack (0·90, 95% CI 0·57–1·42), and the highest relative risk was for fatal stroke (1·61, 95% CI 0·73–3·55). The trend towards an excess of more severe strokes in the hormone group is similar to that observed in WEST.



Venous thromboembolism

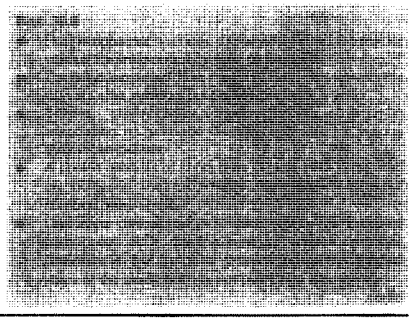
Observational studies

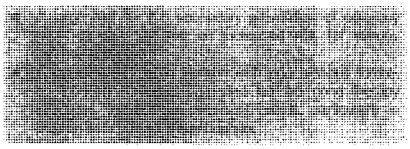
Early observational studies did not suggest an increased risk for venous thromboembolism (deep vein thrombosis or pulmonary embolism) in postmenopausal hormone users; however, as reviewed elsewhere, several more recent studies have found a two- to fourfold increased risk in hormone users.[61] The studies are consistent in showing an increased relative risk for current but not past use of hormones. Recent onset of current use conferred higher risk than long duration of use, consistent with an immediate effect on coagulation factors. Some but not all studies reported a dose-response relationship. Estrogen alone, as well as estrogen with progestin, appeared to be associated with higher risk. Though transdermal estradiol causes less perturbation of coagulation proteins than oral estrogen, one study suggested that the risk for venous thromboembolism was present for this formulation also.

Clinical trials

Venous thromboembolism is usually recorded as an adverse effect in clinical trials of hormone therapy. A pooled analysis of short-term trials found five thromboembolic events in the hormone groups and one in the control groups.[33] HERS found a significant, almost threefold increase in the risk for venous thromboembolism (34 in the hormone group and 13 in the placebo group, relative hazard 2·7, 95% CI 1·4–5·0, $P = 0·003$).[62] The trend towards higher excess risk in the first few years was not significant, and some excess persisted over the duration of the study. These findings on ar adverse event from a clinical trial are very similar to those from the observational studies. In exploratory analyses, other risl factors for venous thromboembolism included older age a menopause, lower extremity fractures, cancer, being withir 90 days of inpatient surgery, or non-surgical hospitalization After non-fatal MI the risk was increased for 90 days. Use o statins or aspirin appeared to decrease risk; it should be noted however, that these were non-randomized comparisons anc that the large number of comparisons performed may have lec to chance findings. The WEST study investigators stated tha there were no differences in venous thromboembolism between treatment groups.[53] As noted above, healthy women in the WHI have been informed of an excess risk during the first few years of the study.[35] Some trials with intermediate o surrogate outcomes (for example, the Postmenopausa Estrogen-Progestin Interventions and ERA) have also notec small numbers of venous events, with more events in the active treatment groups than the placebo groups, although numbers were too small for statistical testing.[7,46]

One randomized controlled trial, initiated before it was known that estrogen increases risk for venous thrombo embolism, strongly suggested that hormone therapy increases the risk for recurrent events.[63] Women with prior venous thromboembolism ($n = 140$) received either ora estradiol 2 mg and norethisterone acetate 1 mg or placebc for 2 years. Though predefined stopping boundaries had no been crossed, the trial was stopped prematurely because o the emergence of data from observational studies and clini cal trials, and the clustering of end points (recurrent venous thromboembolism) in one treatment group. There were eight events in the active treatment group (10·7%) and one in the placebo group (2·3%) indicating a 4·6-fold increase in the hormone group. All of the recurrent events in the active treatment group occurred during the 9 months, while the single event in the placebo group occurred at 14 months. Five of the eight cases with recurrent events in the hormone group also had familial thrombophilia (three with factor V Leiden, two with anticardiolipin antibodies).





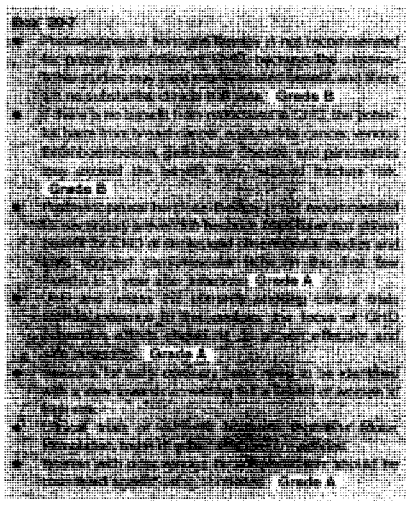
Treatment recommendations

Based on current evidence, postmenopausal hormone therapy is not recommended for prevention or treatment of CHD or stroke.[64] For primary prevention, the American Heart Association (AHA) states that firm recommendations should await the results of ongoing randomized clinical trials, and that there are currently insufficient data to suggest that hormone therapy should be initiated for the sole purpose of primary prevention of cardiovascular disease.[64] The AHA makes a stronger statement that hormone therapy should not be initiated for the secondary prevention of cardiovascular disease; however women on hormone therapy for several years do not necessarily have to stop since they have presumably passed through the period of initial increased risk. Women with a prior history of venous thromboembolism should be counseled against using hormone therapy.[62]

Because the trials have failed to show benefit for secondary prevention, and there are no published trial data for primary prevention, in both instances decisions about hormone therapy should be based on established non-cardiovascular risks and benefits.[64] The major proven benefits of estrogen are relief of the symptoms accompanying the menopause, urogenital atrophy, and prevention of osteoporosis. Known risks include endometrial cancer, venous thromboembolism, pancreatitis (in women with high blood triglycerides), and gallbladder disease. At the average age of menopause, the risk for cardiovascular and non-cardiovascular disease conditions is low, and therefore, the short-term use of estrogens to manage the menopause is not at issue.[65]

However, long-term use (5 years or more) of hormone therapy is more problematic, given the possible increase in breast cancer associated with prolonged use.[65] Calculations show that in older women and with prolonged use, the potential risks for breast cancer, stroke, and venous thromboembolism, may outweigh the potential benefit for reduction in fractures if the treatment does not reduce risk for CHD.[66] Since CHD and stroke are by far the most common causes of disease and death in older women, the clinical trial data on the long-term effects of hormone therapy on cardiovascular disease will provide the key information on whether long-term estrogen should be prescribed for any indication in older women. If these trials show that long-term use confers cardiovascular benefit (and if methods are found to screen out women at high initial risk for cardiovascular complications), then hormone therapy may in future play a more prominent role as a viable prevention strategy.

However, until these clinical trial data are known, it may be wise to consider alternatives to hormone therapy even for proven indications such as prevention of osteoporosis.[65] For osteoporosis prevention, exercise, diet, calcium, and vitamin D may be recommended, and for treatment the bisphosphonates and raloxifene have been shown to prevent fractures. Lifestyle measures and medical management of risk factors such as high blood cholesterol and high blood pressure will prevent many cases of CHD and stroke, and for secondary prevention of CHD aspirin, statins, β blockers, and ACE inhibitors have all been found to be effective.[64] The AHA statement acknowledges that the current recommendations are based mainly on data from trials using standard doses of conjugated equine estrogens and medroxyprogesterone, and that evidence is insufficient for different preparations, routes of delivery, and doses that may have a more favorable or more adverse effect on cardiovascular outcomes.



Addendum

On July 9, 2002, the National Heart, Lung, and Blood Institute announced that the WHI trial[67] of estrogen plus progestin versus placebo in 16 608 healthy women with an intact uterus had been stopped early, after an average of

5·2 years of follow up rather than the planned 8·5 years. The reasons for stopping were that an increased risk for breast cancer started emerging at 4 years, which by 5 years had crossed the prespecified monitoring boundary. In addition, there was evidence of overall harm. At the time of stopping, the hazard ratios (HR) for the major adverse effects were: breast cancer 1·26 (95% CI 1·00–1·59), CHD 1·29 (95% CI 1·02–1·63), stroke 1·41 (95% CI 1·07–1·85), and pulmonary embolism 2·13 (95% CI 1·39–3·25). There were benefits for colorectal cancer, HR 0·63 (95% CI 0·43–0·93), and for hip fracture, HR 0·66 (95% CI 0·45–0·98), while endometrial cancer and all-cause mortality were not affected. The investigators conclude that the risk-benefit profile found in this trial is not consistent with the requirements for a viable prevention treatment, and in particular that this regimen should not be initiated or continued for the primary prevention of CHD. In addition, the substantial risks for cardiovascular disease and breast cancer must be weighed against the benefit for fracture in selecting from the available agents for osteoporosis. WHI has answered the question of whether combined estrogen plus progestin, given by mouth for several years, prevents cardiovascular disease: it does not, and it does in fact increase the risk. However, as stated by the investigators, the use for a few years (less than 4 years) to treat the symptoms of menopause may be reasonable, since the benefits may outweigh the small absolute risk of cardiovascular disease in younger women. Of importance, the WHI trial of estrogen only in women who have had a hysterectomy is continuing, because the overall balance of benefits and risks remains uncertain.

Disclaimer

The views expressed in this chapter are those of the author and do not necessarily reflect the views or policy of the National Heart, Lung, and Blood Institute, or of the Steering Committee of the Women's Health Initiative. The conclusions are based on a review of the published literature and public documents, and not on any confidential or unpublished information to which the author might have access.

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ORIGINAL CONTRIBUTION

Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause

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Context The timing of initiation of hormone therapy may influence its effect on cardiovascular disease.

Objective To explore whether the effects of hormone therapy on risk of cardiovascular disease vary by age or years since menopause began.

Design, Setting, and Participants Secondary analysis of the Women's Health Initiative (WHI) randomized controlled trials of hormone therapy in which 10 739 postmenopausal women who had undergone a hysterectomy were randomized to conjugated equine estrogens (CEE) or placebo and 16 608 postmenopausal women who had not had a hysterectomy were randomized to CEE plus medroxyprogesterone acetate (CEE + MPA) or placebo. Women aged 50 to 79 years were recruited to the study from 40 US clinical centers between September 1993 and October 1998.

Main Outcome Measures Statistical test for trend of the effect of hormone therapy on coronary heart disease (CHD) and stroke across categories of age and years since menopause in the combined trials.

Results In the combined trials, there were 396 cases of CHD and 327 cases of stroke in the hormone therapy group vs 379 cases of CHD and 239 cases of stroke in the placebo group. For women with less than 10 years since menopause began, the hazard ratio (HR) for CHD was 0.76 (95% confidence interval [CI], 0.50-1.16); 10 to 19 years, 1.10 (95% CI, 0.84-1.45); and 20 or more years, 1.28 (95% CI, 1.03-1.58) (P for trend = .02). The estimated absolute excess risk for CHD for women within 10 years of menopause was −6 per 10 000 person-years; for women 10 to 19 years since menopause began, 4 per 10 000 person-years; and for women 20 or more years from menopause onset, 17 per 10 000 person-years. For the age group of 50 to 59 years, the HR for CHD was 0.93 (95% CI, 0.65-1.33) and the absolute excess risk was −2 per 10 000 person-years; 60 to 69 years, 0.98 (95% CI, 0.79-1.21) and −1 per 10 000 person-years; and 70 to 79 years, 1.26 (95% CI, 1.00-1.59) and 19 per 10 000 person-years (P for trend = .16). Hormone therapy increased the risk of stroke (HR, 1.32; 95% CI, 1.12-1.56). Risk did not vary significantly by age or time since menopause. There was a nonsignificant tendency for the effects of hormone therapy on total mortality to be more favorable in younger than older women (HR of 0.70 for 50-59 years; 1.05 for 60-69 years, and 1.14 for 70-79 years; P for trend = .06).

Conclusions Women who initiated hormone therapy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause, but this trend test did not meet our criterion for statistical significance. A similar nonsignificant trend was observed for total mortality but the risk of stroke was elevated regardless of years since menopause. These data should be considered in regard to the short-term treatment of menopausal symptoms.

Trial Registration clinicaltrials.gov Identifier: NCT00000611

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In observational studies of women with and without existing coronary heart disease (CHD), the use of postmenopausal hormone therapy is associated with a reduced risk of CHD events.[1] In contrast, clinical trials have shown no benefit and some trials have suggested an increased risk of CHD during the first year after randomization.[2,3] The Women's Health Initiative (WHI) reported a hazard ratio (HR) for CHD of 0.95 (95% confidence interval [CI], 0.70-1.16) in the trial of conjugated equine estrogens (CEE) and an HR of 1.24 (95% CI, 1.00-1.54) in the trial of CEE plus medroxyprogesterone acetate (CEE + MPA).[3,4] While observational studies have evidently overestimated benefit due to confounding, selection biases, and other limitations,[5,6] an additional source of discrepancy may be the timing of initiation of hormone therapy in relation to the underlying state of the vasculature. Some investigators have hypothesized

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that estrogen may delay the onset of the earliest stages of atherosclerosis, which are more likely to be present in younger women, but it may be ineffective or even trigger events in the presence of existing advanced lesions such as those found in older women.[7] The potential existence of a window of opportunity to reduce cardiovascular disease is supported by animal and laboratory studies.[6]

Compared with observational studies of hormone therapy use among healthy women such as the Nurses' Health Study, most women in the randomized hormone trials were older and the majority commenced study hormones more than a decade after menopause began.[3,4,8] Subgroup analyses in the 2 WHI trials of hormone therapy suggested a nonsignificant reduction in risk of CHD in women aged 50 to 59 years in the trial of CEE[4] or in women with less than 10 years since menopause in the trial of CEE + MPA.[3] Risk of stroke did not appear to be reduced in these subgroups.[9,10] The numbers of events in the subgroups in the individual trials were too small to provide definitive answers but the similar direction of the findings supports the idea that pooling the trials could yield clearer answers.

In this secondary analysis, statistical power was improved by the use of techniques that allow combining the trial data to examine trends in the effects of hormone therapy on CHD and stroke across categories of age and years since menopause. These results could apply to a population similar to the women enrolled in the WHI trials, which included 40% of women taking unopposed estrogen (CEE) or placeho and 60% of women taking estrogen plus progestin (CEE + MPA) or placebo. Total mortality and a predefined global index were examined to capture the overall effects of hormone therapy on disease outcomes. Combined hormone therapy trial analyses and subgroup analyses by age were prespecified in the WHI protocol; other analyses were not prespecified. The subgroup and secondary analyses are exploratory; however, given that these are the best available data, the potential clinical implications of our findings also are examined.

METHODS

Study Participants and Outcomes

The WHI trials enrolled 27 347 predominantly healthy postmenopausal women aged 50 to 79 years from September 1993 to October 1998 at 40 US clinical centers based on hysterectomy status. Of these women, 10 739 had undergone a hysterectomy and were randomized to 0.625 mg/d of CEE or placebo and 16 608 had not had a hysterectomy and were randomized to 0.625 mg/d of CEE plus 2.5 mg/d of MPA or placebo. Details have been published elswhere.[11,12]

The trials were reviewed and approved by the institutional review boards at each clinical center and all participants provided written informed consent. All outcomes were centrally adjudicated. The main outcomes for the current analyses were CHD (defined as nonfatal myocardial infarction, CHD death, or silent myocardial infarction) and stroke. Other outcomes were mortality and a global index (defined as the first occurrence of CHD, stroke, pulmonary embolism, hreast cancer, colorectal cancer, endometrial cancer [CEE + MPA trial only], hip fracture, or death from other causes) used for trial monitoring. Clinical events that were self-reported by participants prior to unblinding at trial closure and subsequently adjudicated were included. Due to the compressed timeline for the initial publications,[3,11] 13 additional adjudicated cases each of CHD and stroke from the CEE + MPA trial were available for this analysis.

Statistical Analysis

Age at menopause was defined by the age at which a woman last had any menstrual bleeding, bilateral oophorectomy, or began using menopausal hormone therapy. For hysterectomy without bilateral oophorectomy, the age at menopause was the age at which a woman either began using hormone therapy or first had vasomotor symptoms (ie, hot flashes, night sweats). For women who had a hysterectomy without bilateral oophorectomy at age 50 years or older but no use of hormone therapy or symptoms, the age at menopause was defined as the age when the hysterectomy was performed. If the algorithm defined an age at menopause as older than 60 years, it was recoded as 60 years. Any misclassification of age at menopause is likely to he nondifferential and would tend to bias the results toward the null. Age at menopause could not be defined (due to missing values) in 1420 (8.5%) women who had not had a hysterectomy and in 1610 (15%) women who had a hysterectomy. These women were excluded from the years since menopause analyses, which included 24 317 participants.

Study participants completed a questionnaire at baseline that included a probe for the presence of vasomotor symptoms (hot flashes or night sweats) during the prior 4 weeks. If present, participants were asked how bothersome the symptom was. Mild indicated that the symptom did not interfere with usual activities; moderate, the symptom interfered somewhat with usual activities; and severe, the symptom was so severe that usual activities could not be performed.

Event rate comparisons were based on the intent-to-treat principle using failure time methods. For a given outcome, the time to event was the number of days from randomization to the first diagnosis of the designated event. Comparisons of outcomes are presented as HRs and 95% CIs stratified by prior cardiovascular disease (defined as history of myocardial infarction, angina, coronary or carotid revascularization, stroke, transient ischemic attack, or peripheral arterial disease) and randomization status in the Dietary Modification Trial. The stratified models allow for flexible (and possibly different) hazard functions between strata and hence more accurately capture the effects of hormone therapy. Preliminary analyses

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showed no striking differences in HRs across categories of age or years since menopause in women with and without prior cardiovascular disease, or in unadjusted models and models adjusted for baseline risk factors (race/ethnicity, education, physical activity, prior hormone use, body mass index [calculated as weight in kilograms divided by height in meters squared], left ventricular hypertrophy by electrocardiographic criteria, current smoking, hypertension, treated diabetes, and treated high serum cholesterol level). Therefore, the results of unadjusted models for all women are presented. For consistency with the display of HRs within categories of age or years since menopause, the estimated absolute excess risks were obtained by applying the HR in each category to the observed annualized incidence in the placebo group. The 95% CIs were calculated by bootstrap methods. Likelihood ratio tests were used to test for differences between the age categories and the categories for years since menopause.

The primary analyses of this study were based on the 2 trials combined. Separate tests for trend were performed to examine differences in hormone effects across 3 preselected, coded categories of age (50-59, 60-69, 70-79 years) or years since menopause (<10, 10-19, and ≥20) using Cox regression model interaction terms.[13] The tests stratified the baseline disease rates for the CEE and CEE + MPA cohorts by active vs placebo (4 strata), while leaving the form of the (marginal) HR for hormone therapy unspecified as a function of time from randomization. The marginal HR dependence on age or years since menopause also was unrestricted through the separate inclusion for each trial cohort of indicator variables for the upper 2 age group categories or years since menopause categories in the log HR models.

The models included regression terms for interaction between cohorts and coded indicator variables for the 3 categories of age or years since menopause. The categories were assigned an ordinal number (1, 2, 3) and then the resulting variable was fitted as a continuous linear variable in the risk models. Interaction terms between age or years since menopause and active vs placebo groups tested whether there were differential effects of hormone therapy as a function of age or years since menopause. These models allow the data for the 2 trials to be combined because they do not make assumptions about baseline risk or the overall treatment effect of hormone therapy in each of the trials. Analyses also were performed for each of the trials separately. The method used to test HR interactions differs slightly from that used in previous publications,[3,4,12] in that age and years since menopause are modeled as coded rather than as continuous variables. Models using coded variables are likely to be less sensitive to the effects of extreme values but may occasionally yield different results than the models using continuous variables.

Other analyses were defined for the purposes of this study based on a priori considerations of biologic plausibility. These included analyses aimed at separating out the effects of age and years since menopause by including terms for both variables as well as an interaction term. Models allowing the HRs and baseline disease incidence to vary by risk factor status were used to directly compare the HRs between the 2 trials. Further analyses tested whether the trends in the effect of hormone therapy by age or years since menopause varied with several factors potentially related to hormone status (eg, prior hormone use [never, past, current]; oophorectomy; presence or absence of vasomotor symptoms [never, mild, moderate or severe] at baseline). Tests were performed by including appropriate additional product interaction terms (eg, 3-way interaction of vasomotor symptoms, age, and hormone therapy treatment effect). The possibility that interactions between age and years since menopause could vary by duration of hormone therapy was examined in models and included additional product terms for duration of therapy. Adherence-adjusted sensitivity analyses censored a woman's event history 6 months after becoming nonadherent (defined as taking <80% of study drugs or completely stopping use). Analyses of the effects of hormone therapy also were performed by years since last exposure to either endogenous or exogenous hormones (years since menopause or last use of hormone therapy).

Statistical tests were undertaken at the .01 level to partially account for multiple testing issues and the post hoc nature of some of the tests. Forty-two tests for trend, 33 additional interaction tests, and 62 comparisons of HRs were performed (a total of 137 tests). Two P values were significant (1-2 were expected by chance). For consistency with previous WHI studies, HRs and 95% CIs were used. An HR of less than 1 favored hormone therapy and greater than 1 favored placebo. The 95% CIs were estimated in 182 subgroups. Of these 182, 19 did not include 1 (9 were expected by chance). Statistical analyses were performed using SAS version 9 (SAS Institute Inc, Cary, NC).

RESULTS

Baseline Characteristics

As previously reported, women in the CEE trial had a more adverse cardiovascular risk profile than women in the CEE + MPA trial, with a higher prevalence of obesity, left ventricular hypertrophy by electrocardiogram, hypertension, diabetes, hypercholesterolemia, and prior history of cardiovascular disease.[3,4,9-12] Previous use of postmenopausal hormones was reported by 61% and 41% of women with and without a prior bilateral oophorectomy, respectively, in the CEE trial compared with 26% of women who had not had a hysterectomy in the CEE + MPA trial. Vasomotor symptoms were reported in 43% (17% moderate or severe) of CEE participants and 38% (12% moderate or severe) of CEE + MPA participants, and were more frequent in women who initiated therapy closer to the onset of

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menopause (TABLE 1 and TABLE 2). Coronary risk factors (except smoking) and prior cardiovascular disease increased markedly with increasing age and years since menopause (data not shown).

Overall Effects of Hormone Therapy (All Participants)

Consistent with previous WHI studies,[3,4] hormone therapy did not reduce overall risk of CHD (TABLE 3). As before, the HR for CHD was lower when participants were taking CEE than when taking CEE + MPA (0.95 vs 1.23; $P = .02$ after adjusting for risk factors).[4] Risk of stroke was increased (HR, 1.32; 95% CI, 1.12-1.56) in the combined trials, with no difference between the individual trials. Individual trial results were similar to those described in previous publications using centrally coded data.[3,4,9,10,12] Estimated absolute excess risks per 10 000 person-years were approximately 3 for CHD, 9 for stroke, 1 for total mortality, and 14.5 for the global index in the combined trials, under a constant HR model for each trial.

Effects of Hormone Therapy by Age at Randomization

The numbers of events increased with increasing age but there was no statistically significant additional effect of hormone therapy by age for any outcome in the combined trials (TABLE 4). The trends in HRs for CHD appeared to be somewhat more pronounced in women without prior cardiovascular disease with HRs of 0.91, 0.97, and 1.33 across the 3 age groups (535 cases; P for trend = .10) compared with 0.99, 0.98, and 1.12 in women with prior cardiovascular disease

Table 1. Selected Baseline Characteristics of Participants in the Trial of Conjugated Equine Estrogens (CEE) (n = 10 739)*

	No. (%) of Participants							
	Randomization Assignment		Age at Randomization			Years Since Menopause		
	CEE (n = 5310)	Placebo (n = 5429)	50-59 y (n = 3310)	60-69 y (n = 4852)	70-79 y (n = 2577)	<10 (n = 1643)	10-19 (n = 2936)	≥20 (n = 4550)
Years since menopause								
<10	826 (15.6)	817 (15.0)	1237 (37.4)	406 (8.4)	0			
10-19	1436 (27.0)	1500 (27.6)	1030 (31.1)	1564 (32.2)	342 (13.3)			
≥20	2231 (42.0)	2319 (42.7)	524 (15.8)	2150 (44.3)	1876 (72.8)			
Age group, y								
50-59						1237 (75.3)	1030 (35.1)	524 (11.5)
60-69						406 (24.7)	1564 (53.3)	2150 (47.3)
70-79						0	342 (11.6)	1876 (41.2)
Vasomotor symptoms								
None	2962 (55.8)	3004 (55.3)	1245 (37.6)	2850 (58.7)	1871 (72.6)	770 (46.8)	1834 (62.4)	3067 (68.9)
Mild	1377 (25.9)	1442 (26.6)	1132 (34.2)	1243 (25.6)	444 (17.2)	531 (32.3)	686 (23.3)	955 (21.4)
Moderate or severe	913 (17.2)	917 (16.9)	903 (27.3)	706 (14.6)	221 (8.6)	342 (20.8)	416 (14.1)	528 (11.8)
Prior use of hormone therapy								
Never	2769 (52.1)	2770 (51.0)	1671 (50.5)	2498 (51.5)	1370 (53.2)	835 (50.8)	1383 (47.1)	1711 (37.6)
Past	1871 (35.2)	1948 (35.9)	935 (28.2)	1247 (36.0)	626 (24.3)	452 (27.5)	1036 (35.3)	2331 (51.2)
Current	669 (12.6)	708 (13.0)	359 (18.0)	603 (12.4)	389 (15.1)	356 (21.7)	516 (17.6)	505 (11.1)
Duration of prior hormone therapy use, y								
<5	1352 (25.5)	1412 (26.0)	935 (28.2)	1203 (24.8)	626 (24.3)	579 (35.2)	786 (26.8)	1399 (30.7)
5-9	469 (8.8)	515 (9.5)	359 (10.8)	433 (8.9)	192 (7.5)	223 (13.6)	295 (10.0)	466 (10.2)
≥10	720 (13.6)	732 (13.5)	345 (10.4)	718 (14.8)	389 (15.1)	6 (0.4)	472 (16.1)	974 (21.4)
Prior bilateral oophorectomy								
No	2973 (56.0)	2917 (53.7)	2006 (60.6)	2578 (53.1)	1306 (50.7)	1216 (74.0)	1473 (50.2)	1816 (39.9)
Yes	1938 (36.5)	2111 (38.9)	1128 (34.1)	1904 (39.2)	1017 (39.5)	334 (20.3)	1279 (43.6)	2431 (53.4)
Hormone therapy use among participants with bilateral oophorectomy								
Never	737 (38.0)	829 (39.3)	352 (31.2)	755 (39.7)	459 (45.1)	104 (31.1)	537 (42.0)	920 (37.8)
Past	894 (46.1)	968 (45.9)	508 (45.0)	870 (45.7)	484 (47.6)	132 (39.5)	491 (38.4)	1239 (51.0)
Current	307 (15.8)	313 (14.8)	268 (23.8)	278 (14.6)	74 (7.3)	98 (29.3)	250 (19.5)	271 (11.2)
Hormone therapy use among participants without bilateral oophorectomy								
Never	1783 (60.1)	1699 (58.2)	1209 (60.3)	1525 (59.2)	752 (57.6)	679 (55.8)	755 (51.3)	667 (36.7)
Past	861 (29.0)	857 (29.4)	485 (24.1)	767 (29.8)	466 (35.7)	298 (24.5)	477 (32.4)	943 (51.9)
Current	324 (10.9)	359 (12.3)	312 (15.6)	283 (11.0)	88 (6.7)	239 (19.7)	241 (16.4)	203 (11.1)

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(214 cases; *P* for trend=.72); however, these trends did not differ significantly (*P* for interaction=.54). There were no significant increases in risk due to hormone therapy for any outcome at ages 50 to 59 years, but increases in risk for CHD, stroke, and global index events in some older age categories were noted. There was a reduction in total mortality in the age group of 50 to 59 years (HR, 0.70; 95% CI, 0.51-0.96), with a nonsignificant trend for increasing HRs across age groups (*P*=.06). In adjusted models, the HRs of CHD (*P*=.04) and global index events (*P*=.04) were nonsignificantly lower in the age group of 50 to 59 years for women taking CEE compared with women taking CEE + MPA but HRs were comparable at older ages (results not shown). The HR for the global index increased with age in the CEE trial (*P* for trend=.01). However, the trend statistics for CHD and global index did not differ between the trials.

Effects of Hormone Therapy by Years Since Menopause

The HR for CHD was 0.76 in women with less than 10 years since menopause, 1.10 for women with 10 to less than 20 years since menopause, and 1.28 for women with more than 20 years since menopause (*P* for trend=.02; TABLE 5). Hormone therapy increased the risk of CHD in women with 20 or more years since menopause (HR, 1.28; 95% CI, 1.03-1.58). In women without prior cardiovascular disease, the HRs across categories of years since menopause were 0.78, 1.10, and 1.35 (464 cases; *P* for trend=.02) and in women with prior cardiovascular disease they were 0.59, 1.08, and 1.14 (180 cases; *P* for trend=.44); these trends did not differ significantly (*P* for interaction=.68). In contrast to CHD, the effect of hormone therapy on stroke risk was similar in all categories of years since menopause, with a HR of 1.77 (95% CI, 1.05-2.98) in women with less than 10 years since menopause. In women with less than 10 years since menopause without prior cardiovascular disease, the HR for stroke was 1.64; after excluding women older than 60 years, the HR attenuated to 1.23 (all 95% CIs included 1). There were no significant differences in the HRs between the trials in any category of years since menopause in the adjusted models (results not shown), and the trend statistics for treatment effects by years since menopause also were similar for all outcomes.

Estimated Absolute Excess Risk

The combination of low incidence rates and modest HRs at ages 50 to 59 years led to low or no absolute excess risks of CHD, stroke, total mortality, or global index events due to hormone therapy in that age group (FIGURE 1). With increasing age, the higher incidence rates and larger HRs yielded progressively larger estimated absolute excess risks due to hormone therapy. At ages 50 to 59 years, there were 10 fewer deaths per 10 000 person-years compared with 16 additional deaths at ages 70 to 79 years

Table 2. Selected Baseline Characteristics of Participants in the Trial of Conjugated Equine Estrogens Plus Medroxyprogesterone Acetate (CEE + MPA) (n = 16 608)*

	No. (%) of Participants							
	Randomization Assignment		Age at Randomization			Years Since Menopause		
	CEE + MPA (n = 8506)	Placebo (n = 8102)	50-59 y (n = 5522)	60-69 y (n = 7510)	70-79 y (n = 3576)	<10 (n = 5494)	10-19 (n = 6041)	≥20 (n = 3653)
Years since menopause								
<10	2782 (32.7)	2712 (33.5)	4092 (74.1)	1402 (18.7)	0			
10-19	3947 (35.8)	2994 (37.0)	831 (15.0)	4320 (57.5)	890 (24.9)			
≥20	1850 (21.7)	1803 (22.3)	55 (1.0)	1145 (15.2)	2453 (68.6)			
Age group, y								
50-59						4092 (74.5)	831 (13.8)	55 (1.5)
60-69						1402 (25.5)	4320 (71.5)	1145 (31.3)
70-79						0	890 (14.7)	2453 (76.2)
Vasomotor symptoms								
None	5162 (60.7)	4928 (60.8)	2298 (41.6)	4974 (66.2)	2818 (78.8)	2411 (43.8)	4113 (68.0)	2827 (77.3)
Mild	2190 (25.8)	2115 (26.1)	1947 (35.3)	1804 (24.0)	554 (15.5)	1945 (32.3)	1384 (22.9)	628 (17.1)
Moderate or severe	1072 (12.6)	974 (12.0)	1224 (22.2)	650 (8.7)	172 (4.8)	1138 (20.7)	544 (9.0)	198 (5.4)
Prior use of hormone therapy								
Never	6277 (73.8)	6020 (74.3)	3937 (71.3)	5683 (75.7)	2677 (74.9)	3803 (69.2)	4558 (75.5)	2516 (68.9)
Past	1671 (19.6)	1588 (19.6)	1033 (18.7)	1418 (18.9)	808 (22.6)	1109 (20.2)	1126 (18.6)	1024 (28.0)
Current	554 (6.5)	491 (6.1)	552 (10.0)	403 (5.4)	90 (2.5)	581 (10.6)	354 (5.9)	110 (3.0)
Duration of prior hormone therapy use, y								
<5	1539 (18.1)	1470 (18.1)	1200 (21.7)	1239 (16.5)	570 (15.9)	1363 (24.8)	917 (15.2)	729 (20.0)
5-9	427 (5.0)	356 (4.4)	302 (5.5)	328 (4.4)	153 (4.3)	322 (5.9)	282 (4.7)	179 (4.9)
≥10	263 (3.1)	255 (3.1)	83 (1.5)	259 (3.4)	176 (4.9)	5 (0.1)	284 (4.7)	229 (6.3)

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Table 3. Overall Cardiovascular and Global Index Events

	No. of Cases (Annualized %)*			
	Hormone Therapy (n = 13 816)	Placebo (n = 13 531)	HR (95% CI)†	Estimated Absolute Excess Risk per 10 000 Person-Years (95% CI)‡
	Combined Trials			
CHD§	396 (0.46)	379 (0.44)	1.07 (0.92 to 1.23)	3.1 (−2.6 to 9.4)
Stroke	327 (0.38)	239 (0.29)	1.32 (1.12 to 1.56)	9.3 (3.4 to 15.1)
Total mortality	546 (0.63)	528 (0.63)	1.02 (0.90 to 1.15)	1.2 (−6.0 to 8.6)
Global index‖	1601 (1.94)	1467 (1.81)	1.08 (1.00 to 1.16)	14.5 (1.7 to 28.2)
	CEE Trial			
	CEE (n = 5310)	Placebo (n = 5429)		
CHD§	201 (0.54)	217 (0.57)	0.95 (0.78 to 1.16)	−2.9 (−13.2 to 8.3)
Stroke	166 (0.45)	127 (0.33)	1.33 (1.05 to 1.68)	10.9 (1.6 to 20.3)
Total mortality	297 (0.79)	292 (0.75)	1.04 (0.88 to 1.22)	3.2 (−8.9 to 16.0)
Global index‖	747 (2.06)	744 (2.01)	1.02 (0.92 to 1.13)	4.0 (−13.0 to 26.1)
	CEE + MPA Trial			
	CEE+MPA (n = 8506)	Placebo (n = 8102)		
CHD§	195 (0.41)	153 (0.34)	1.23 (0.99 to 1.53)	7.8 (−0.3 to 16.0)
Stroke	159 (0.33)	112 (0.25)	1.31 (1.03 to 1.68)	7.8 (0.8 to 14.2)
Total mortality	249 (0.52)	236 (0.52)	1.00 (0.83 to 1.19)	0 (−9.6 to 10.0)
Global index‖	854 (1.84)	723 (1.65)	1.13 (1.02 to 1.25)	21.5 (4.3 to 39.6)

Abbreviations: CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MPA, medroxyprogesterone acetate.
*Annualized percentage defined as cases per 100 person-years.
†Cox regression model stratified according to age (50-54, 55-59, 60-69, 70-79 years), prior cardiovascular disease, and randomization status in the Dietary Modification Trial.
‡Calculated as [annualized percentage in placebo group × (HR in placebo group − 1)] × 1000. The 95% CIs were estimated by bootstrap methods (however, bootstrap methods may introduce some inaccuracies).
§Defined as CHD death, nonfatal myocardial infarction, or definite silent myocardial infarction (Novacode 5.1 or 5.2).
‖Defined as CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer for CEE plus MPA trial only, hip fracture, or death from other causes.

(P=.03). The pattern of increasing absolute excess risks across age categories was observed in both trials. In the CEE trial, the higher absolute excess risks of death and global index events in the oldest age group appeared to differ from the reduced risks at ages 50 to 59 years (P=.02 and P=.01, respectively).

In women with less than 10 years since menopause, there were no apparent effects of hormone therapy on absolute excess risks of CHD, total mortality, or global index in the combined trials (FIGURE 2). However, there were excess risks of stroke in each category for years since menopause, and the 95% CI excluded 1 for the category of women with less than 10 years since menopause. Increasing absolute excess risks were observed for CHD, total mortality, and global index events in women more distant from menopause but only the 17 additional CHD events in women with 20 or more years since menopause approached statistical significance compared with the reduction of 6 events in women with less than 10 years since menopause (P=.03). The patterns across menopause categories were consistent across the 2 trials.

Additional Analyses

There was a high correlation between age and years since menopause (r=0.71). The nonsignificant modification of age relative to the effect of hormone therapy on CHD in the combined trials (P for trend=.16) became even weaker with additional adjustment on years since menopause (P for trend=.83). The relationship of years since menopause to the HR for CHD also was attenuated (from P=.02 to P=.07) with additional adjustment for age.

There were no significant trends for hormone therapy by years since last exposure to hormones (endogenous or exogenous) and no significant interactions of prior hormone use or oophorectomy status with in-trial hormone effects by age or by years since menopause. However, vasomotor symptoms at baseline may have influenced the results for CHD by both age and years since menopause. The possible 3-way interactions of vasomotor symptoms with hormone therapy effects on the HR trend by age (P=.04) and by years since menopause (P=.06) appeared to be due to trends across these categories in the 12% to 17% of women in the trials with moderate or severe vasomotor symptoms (P for trend <.01; TABLE 6 and TABLE 7). There were not any similar trends in the women with no or mild vasomotor symptoms at baseline (data not shown). There were no apparent effects of hormone therapy on CHD in women with vasomotor symptoms aged 50 to 59 years or in women with less than 10 years since menopause. Increased risks for CHD, stroke, and global index events were seen in women aged 70 to 79 years at baseline and for CHD and global index events in women with 20 or more years since menopause. The findings were similar for women taking CEE and CEE + MPA (data not shown).

The vasomotor symptoms in the older women appeared to be related to hormonal factors to a similar extent as those in younger women because a large majority reported their first symptoms starting at menopause. The vasomotor symptoms responded to hormone therapy in the trial to a similar extent, with the exception of a lesser response of night sweats to CEE + MPA in women aged 70 to 79 years or with 20 or more years since menopause (data not shown). Risk factors for CHD tended to be more adverse in the women with vasomotor symptoms in each age group and in each category for years since menopause. However, the results did not change when the analyses for interaction were repeated with adjustment for risk factors. Similarly, adjustment for adherence to study pills did not change the results.

Sensitivity analyses that censored the data when a woman became nonadherent generally increased the HRs for outcomes but did not show any substan-

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tial modification of hormone effects by age or years since menopause. Other models suggested a time-dependent effect of hormone therapy in the combined trials for CHD (but not stroke), with higher risks in the first 2 years and decreasing risk thereafter ($P = .01$). Even though power was limited by small numbers of events, the direction of time-dependent effects were similar within categories of age or years since menopause, and there were no interactions of time-dependent effects on HRs across the age or years since menopause categories.

COMMENT

Although not statistically significant, these secondary analyses suggest that the effect of hormones on CHD may be modified by years since menopause and by the presence of vasomotor symptoms, with the highest risks in women who were 20 or more years since menopause (or aged ≥70 years). Coronary heart disease tended to be nonsignificantly reduced by hormone therapy in younger women or women with less than 10 years since menopause, and the risk of total mortality was reduced in women aged 50 to 59 years. We did not have adequate statistical power to assess outcomes in the women aged 50 to 54 years or less than 5 years since menopause. As previously reported, CEE appeared to be associated with lower risk of CHD than CEE + MPA.[4] Importantly, the risk of stroke was not influenced by years since menopause, the presence of vasomotor symptoms, or drug regimen, although there was no increased risk of stroke in women aged 50 to 59 years.

Our findings are consistent with findings from observational studies of the association of years since menopause

Table 4. Cardiovascular and Global Index Events by Age at Baseline

	Age Group at Randomization									
	50-59 y			60-69 y			70-79 y			
	No. of Cases			No. of Cases			No. of Cases			
	Hormone Therapy (n = 4476)	Placebo (n = 4356)	HR (95% CI)*	Hormone Therapy (n = 6240)	Placebo (n = 6122)	HR (95% CI)*	Hormone Therapy (n = 3100)	Placebo (n = 3053)	HR (95% CI)*	P Value for Trend†
Combined Trials										
CHD‡	59	61	0.93 (0.65-1.33)	174	178	0.98 (0.79-1.21)	163	131	1.26 (1.00-1.59)	.16
Stroke	44	37	1.13 (0.73-1.76)	156	102	1.50 (1.17-1.92)	127	100	1.21 (0.93-1.58)	.97
Total mortality	69	95	0.70 (0.51-0.96)	240	225	1.05 (0.87-1.26)	237	208	1.14 (0.94-1.37)	.06
Global index§	278	278	0.96 (0.81-1.14)	717	661	1.08 (0.97-1.20)	606	528	1.14 (1.02-1.29)	.09
CEE Trial										
	CEE (n = 1637)	Placebo (n = 1673)		CEE (n = 2387)	Placebo (n = 2465)		CEE (n = 1286)	Placebo (n = 1291)		
CHD‡	21	34	0.63 (0.36-1.09)	96	106	0.94 (0.71-1.24)	84	77	1.13 (0.82-1.54)	.12
Stroke	18	21	0.89 (0.47-1.69)	84	54	1.62 (1.15-2.27)	66	52	1.21 (0.84-1.75)	.62
Total mortality	34	48	0.71 (0.46-1.11)	129	131	1.02 (0.80-1.30)	134	113	1.20 (0.93-1.55)	.18
Global index§	114	140	0.82 (0.64-1.05)	333	342	1.01 (0.86-1.17)	300	262	1.16 (0.98-1.37)	.01
CEE + MPA Trial										
	CEE+MPA (n = 2839)	Placebo (n = 2683)		CEE+MPA (n = 3853)	Placebo (n = 3657)		CEE+MPA (n = 1814)	Placebo (n = 1762)		
CHD‡	38	27	1.29 (0.79-2.12)	78	72	1.03 (0.74-1.43)	79	54	1.48 (1.04-2.11)	.70
Stroke	26	16	1.41 (0.75-2.65)	72	48	1.37 (0.95-1.97)	61	48	1.21 (0.82-1.78)	.56
Total mortality	35	47	0.69 (0.44-1.07)	111	94	1.09 (0.83-1.44)	103	95	1.06 (0.80-1.41)	.19
Global index§	164	138	1.10 (0.87-1.38)	384	319	1.15 (0.99-1.34)	306	266	1.13 (0.95-1.33)	.96

Abbreviations: CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MPA, medroxyprogesterone acetate.
*Cox regression models stratified according to prior cardiovascular disease and randomization status in the Dietary Modification Trial.
†Test for trend (interaction) using age as continuous (linear) form of categorical coded values. Cox regression models stratified according to active vs placebo and trial, including terms for age and the interaction between trials and age.
‡Defined as CHD death, nonfatal myocardial infarction, or definite silent myocardial infarction (Novacode 5.1 or 5.2).
§Defined as CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer for CEE plus MPA trial only, hip fracture, or death from other causes.

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with carotid intima-media thickness.[14,15] Although age and years since menopause are highly correlated, in our analyses years since menopause appeared to influence hormone effects on CHD somewhat more than chronological age. Estrogen may have dual and opposing actions, retarding the earlier stages of atherosclerosis through beneficial effects on endothelial function and blood lipids, but triggering acute events in the presence of advanced lesions through procoagulant and inflammatory mechanisms.[5,6] Our findings are consistent with a neutral effect of hormone therapy in women soon after menopause (who are likely to have fewer complicated lesions), but progressively more unfavorable effects on CHD risk in later years. The trends across categories of age and years since menopause appeared to be somewhat stronger in women without a history of prior cardiovascular disease (although this trend was not significantly different from women with prior cardiovascular disease, possibly due to small numbers). It is not known why the effects of hormone therapy on stroke overall, and in women close to menopause, differ from the effects of therapy on CHD. Risk of stroke on hormone therapy was elevated by 77% in women with 10 or less years since menopause but by a nonsignificant 13% in women aged 50 to 59 years. The risk for stroke in women with less than 10 years since menopause attenuated to a nonsignificant increase of 23% when those with prior cardiovascular disease and who were older than 60 years were excluded.

This analysis of the WHI data provides some convergence with information from observational studies, ani-

Table 5. Cardiovascular and Global Index Events by Years Since Menopause at Baseline

	Years Since Menopause									
	<10			10-19			≥20			
	No. of Cases			No. of Cases			No. of Cases			
	Hormone Therapy (n = 3608)	Placebo (n = 3529)	HR (95% CI)*	Hormone Therapy (n = 4483)	Placebo (n = 4494)	HR (95% CI)*	Hormone Therapy (n = 4081)	Placebo (n = 4122)	HR (95% CI)*	P Value for Trend†
	Combined Trials									
CHD‡	39	51	0.76 (0.50-1.16)	113	103	1.10 (0.84-1.45)	194	158	1.28 (1.03-1.58)	.02
Stroke	41	23	1.77 (1.05-2.98)	100	79	1.23 (0.92-1.66)	142	113	1.26 (0.98-1.62)	.36
Total mortality	53	67	0.76 (0.53-1.09)	142	149	0.98 (0.78-1.24)	267	240	1.14 (0.96-1.36)	.51
Global index§	222	203	1.05 (0.86-1.27)	482	440	1.12 (0.98-1.27)	675	632	1.09 (0.98-1.22)	.82
	CEE Trial									
	CEE (n = 826)	Placebo (n = 817)		CEE (n = 1436)	Placebo (n = 1500)		CEE (n = 2231)	Placebo (n = 2319)		
CHD‡	8	16	0.48 (0.20-1.17)	47	50	0.96 (0.64-1.44)	117	111	1.12 (0.86-1.46)	.15
Stroke	17	8	2.24 (0.92-5.44)	43	30	1.47 (0.92-2.35)	86	72	1.20 (0.87-1.65)	.24
Total mortality	14	21	0.65 (0.33-1.29)	63	70	0.93 (0.66-1.30)	169	152	1.16 (0.93-1.45)	.42
Global index§	60	62	0.94 (0.65-1.36)	179	177	1.05 (0.85-1.29)	391	381	1.07 (0.92-1.23)	.63
	CEE + MPA Trial									
	CEE+MPA (n = 2782)	Placebo (n = 2712)		CEE+MPA (n = 3047)	Placebo (n = 2994)		CEE+MPA (n = 1850)	Placebo (n = 1803)		
CHD‡	31	35	0.88 (0.54-1.43)	66	53	1.23 (0.85-1.77)	77	47	1.66 (1.14-2.41)	.05
Stroke	24	15	1.58 (0.81-3.05)	57	49	1.12 (0.76-1.64)	56	41	1.35 (0.89-2.03)	.87
Total mortality	39	46	0.81 (0.52-1.24)	79	79	1.03 (0.75-1.41)	98	88	1.11 (0.83-1.49)	.93
Global index§	162	141	1.09 (0.87-1.37)	303	263	1.17 (0.99-1.38)	284	251	1.13 (0.95-1.35)	.92

Abbreviations: CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MPA, medroxyprogesterone acetate.
*Cox regression models stratified according to prior cardiovascular diseases and randomization status in the Dietary Modification Trial.
†Test for trend (interaction) using age as continuous (linear) form of categorical coded values. Cox regression models stratified according to active vs placebo and trial, including terms for years since menopause and the interaction between trials and years since menopause.
‡Defined as CHD death, nonfatal myocardial infarction, or definite silent myocardial infarction (Novacode 5.1 or 5.2).
§Defined as CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer for CEE plus MPA trial only, hip fracture, or death from other causes.

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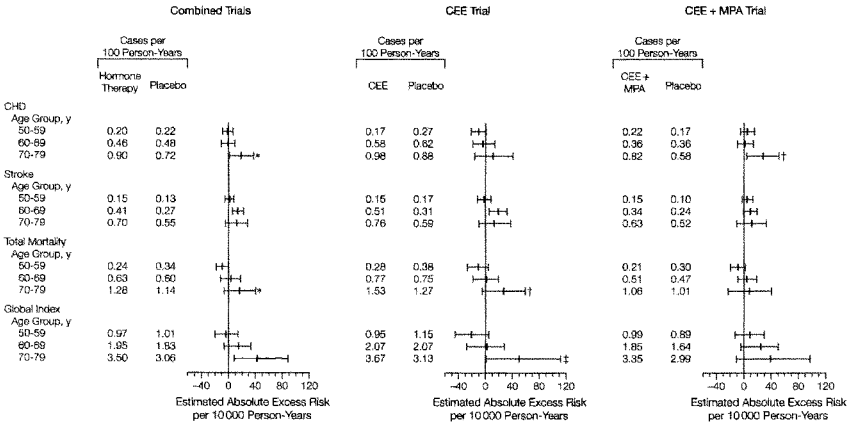
mal studies, and laboratory studies, which have focused mainly on the effects of estrogen on normal coronary arteries or women without clinical cardiovascular disease.[5,6,16] However, differences remain. One observational study examining this issue predicted a reduced risk of CHD in healthy women who commenced hormone therapy within 4 years since menopause, and no effect in women with 10 or more years since menopause,[7] while our combined trial data find a nonsignificant reduction in women starting hormone therapy during 10 or less years since menopause and increasing risks thereafter. Women's Health Initiative data suggest an advantage for CEE compared with CEE + MPA in regard to CHD, but the observational data would predict similar effects for these formulations (at least for CEE with the cyclical MPA more commonly used in observational studies).[1,7,16]

There is also a divergence in regard to secondary prevention, with observational study but not trial data on women with existing disease suggesting CHD benefit for hormone users.[1,2,17,18] The inclusion of a small proportion of women with prior disease in this analysis of trial data and in similar analyses of observational study data did not change the estimates of CHD risk on hormone therapy by age or years since menopause appreciably, possibly because there were relatively few such women in younger age categories, and in the older age categories the presence of prior CHD is but one of many other factors contributing to risk.[7] Some observational and trial data agree in predicting early harm in women after initiation of hormone therapy.[2,3,17-20] Confounding due to the healthier characteristics of hormone users, and failure to account for years since hormone therapy initiation, would lead to overestimation of benefit for CHD in observational studies, even after adjusting for measurable factors.[5]

Absolute risks may be more helpful than HRs to clinicians weighing the pros and cons of hormone therapy for particular patients. Because of low event rates in more recently menopausal women, the absolute excess risk will be very small, even in the presence of some increased relative risk due to hormone therapy. On the other hand the higher event rates in women more distant from menopause, together with their increased HRs, translate into large absolute excess risks. The low or absent excess risks of CHD in women with less than 10 years since menopause may be somewhat reassuring to women considering the use of hormones in the first few years after menopause. However, the increased absolute risk of stroke in this subgroup (although not apparent in women aged 50-59 years in the CEE trial and at-

Figure 1. Estimated Absolute Excess Risk per 10 000 Person-Years by Age Group at Baseline



The estimated absolute excess risk may differ slightly from the absolute excess risk derived from the differences in cases per 100 person-years between active hormone and placebo groups. Estimated absolute excess risk was per 10 000 person-years calculated as [annualized percentage in the placebo group × (hazard ratio in the placebo group − 1)] × 1000. Error bars indicate 95% confidence intervals, estimated using bootstrap methods. CEE indicates conjugated equine estrogens; CHD, coronary heart disease; MPA, medroxyprogesterone acetate.

*$P = .03$ compared with the age group of 50 to 59 years.

†$P = .02$ compared with the age group of 50 to 59 years.

‡$P = .01$ compared with the age group of 50 to 59 years.

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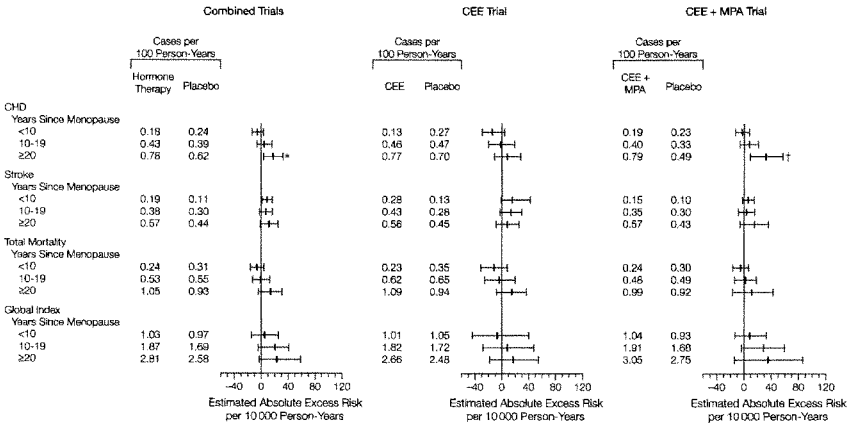
tenuated after excluding women older than 60 years in the years since menopause analyses) implies that, at a minimum, screening and treatment of risk factors for stroke would be advisable before considering hormone therapy.

For CEE + MPA, the risk of breast cancer also needs to be considered. In women with less than 10 years since

Figure 2. Estimated Absolute Excess Risk per 10 000 Person-Years by Years Since Menopause at Baseline



The estimated absolute excess risk may differ slightly from the absolute excess risk derived from the differences in cases per 100 person-years between active hormone and placebo groups. Estimated absolute excess risk per 10 000 person-years calculated as [annualized percentage in the placebo group × (hazard ratio in the placebo group − 1)] × 1000. Error bars indicate 95% confidence intervals, estimated using bootstrap methods. CEE indicates conjugated equine estrogens; CHD, coronary heart disease; MPA, medroxyprogesterone acetate.

*$P = .03$ compared with the less than 10 years since menopause group.

†$P = .04$ compared with the less than 10 years since menopause group.

Table 6. Cardiovascular and Global Index Events in Subgroup of Participants with Moderate or Severe Vasomotor Symptoms at Baseline in the Combined Trials

	Age Group at Randomization										
	50-59 y			60-69 y			70-79 y				
	No. of Cases			No. of Cases			No. of Cases			P Value	
	Hormone Therapy (n = 1097)	Placebo (n = 1030)	HR (95% CI)*	Hormone Therapy (n = 691)	Placebo (n = 665)	HR (95% CI)*	Hormone Therapy (n = 197)	Placebo (n = 196)	HR (95% CI)*	Trend†	Interaction With Vasomotor Symptoms‡
CHD§	17	19	0.86 (0.44-1.65)	31	25	1.20 (0.70-2.04)	27	6	5.08 (2.08-12.40)	<.01	.04
Stroke	14	11	1.09 (0.49-2.43)	16	20	0.75 (0.39-1.45)	12	3	3.94 (1.09-14.23)	.28	.34
Total mortality	20	22	0.85 (0.46-1.56)	35	27	1.27 (0.77-2.12)	24	15	1.56 (0.81-3.00)	.22	.72
Global index‖	69	66	0.98 (0.70-1.38)	88	85	1.02 (0.75-1.37)	62	32	2.10 (1.35-3.27)	.02	.15

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio.

*Cox regression models stratified according to prior cardiovascular disease and randomization status in the Dietary Modification Trial.

†Test for trend (interaction) using age as continuous (linear) form of categorical coded values. Cox regression models stratified according to active vs placebo and trial, including terms for age and the interaction between trials and age.

‡Likelihood ratio test for 3-way interaction among hormone therapy, age, and vasomotor symptoms (none vs mild vs moderate or severe).

§Defined as CHD death, nonfatal myocardial infarction, or definite silent myocardial infarction (Novacode 5.1 or 5.2).

‖Defined as CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer for CEE plus MPA trial only, hip fracture, or death from other causes.

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menopause, there were 72 (0.32%) cases of breast cancer while taking CEE + MPA compared with 57 (0.28%) cases while taking placebo (HR, 1.19; 95% CI, 0.84-1.70). By contrast, the increasing absolute risks of CHD in older women or women more distant from menopause (most marked in women aged >70 years or ≥20 years past menopause), together with their increased risks of stroke, breast cancer, and venous thromboembolism, would in general contraindicate the use of hormones for disease prevention in these groups.

The findings for vasomotor symptoms are intriguing and of potential importance to clinicians but need confirmation. The higher risks in women more distant from menopause appeared to be concentrated in the small subset of women with moderate or severe vasomotor symptoms. It is possible that vasomotor symptoms in recently menopausal women represent the reaction of vessels with normal endothelial function to estrogen withdrawal but persistent symptoms may signify something different in older women. If confirmed elsewhere (eg, by reanalyses of existing observational studies and clinical trials), the clinical implication might be that while treatment of vasomotor symptoms with hormone therapy in younger women remains an option, the reverse might apply to older women. Rather, the presence of moderate or severe vasomotor symptoms at older ages might signal the need for identification and treatment of risk factors for CHD. Although CHD risk factors were more frequent in women with vasomotor symptoms, analyses adjusting for these factors did not change the trend statistic, suggesting that hormone therapy interactions with other unmeasured risk factors in women with vasomotor symptoms may underlie the increasing risk in women more distant from menopause.

The current analyses are most pertinent to the effects of initiation of exogenous hormone use but also provide some limited information regarding the potential effects of prolonged use, taking into account indicators of hormone status at trial enrollment. Within the relatively short trial durations, CHD risk related to hormone therapy appeared to decrease over time. However, the significance of this trend over time depends on both the initial increase in risk, as well as the subsequent decrease, and hence may partially represent a survivor effect. In addition, the decreasing risk is confounded by diminishing compliance over time. Current or past hormone users and never users appeared to have similar trends toward increasing risks by years since menopause during the trial, providing indirect evidence that longer duration of use is not protective. It is not feasible to test hormone effects over very long periods of use in clinical trials, and observational studies have yielded conflicting results.[16,20] Unlike statin drugs, which have beneficial effects for both atherosclerosis and clinical events irrespective of the underlying state of the arteries,[21,22] hormone therapy has a putative beneficial effect on early atherosclerosis,[5,6] no effect on advanced atherosclerosis,[23,24] and an early increase in risk of CHD events when advanced atherosclerosis may be present.[2,3,25] Because age-related progression of atherosclerosis is likely to continue even in the face of hormone therapy, use over decades could potentially result in an eventual increase in CHD events. Hence, even if ongoing imaging trials confirm a slowing of early atherosclerosis,[26,27] it would be unwise to extrapolate such findings to clinical benefit with continued use into old age.

These analyses are based on systematically ascertained outcomes in a set-

Table 7. Cardiovascular and Global Index Events in Subgroup of Participants With Moderate or Severe Vasomotor Symptoms at Baseline in the Combined Trials

	Years Since Menopause										
	<10			10-19			≥20				
	No. of Cases			No. of Cases			No. of Cases			P Value	
	Hormone Therapy (n = 833)	Placebo (n = 757)	HR (95% CI)*	Hormone Therapy (n = 557)	Placebo (n = 555)	HR (95% CI)*	Hormone Therapy (n = 440)	Placebo (n = 459)	HR (95% CI)*	Trend†	Interaction With Vasomotor Symptoms‡
CHD§	13	17	0.84 (0.40-1.77)	17	13	1.38 (0.63-3.00)	39	16	2.76 (1.53-4.97)	<.01	.06
Stroke	10	3	3.36 (0.92-12.24)	13	11	1.02 (0.44-2.37)	16	16	0.92 (0.44-1.93)	.31	.59
Total mortality	14	16	0.93 (0.44-1.96)	17	15	1.21 (0.58-2.51)	42	29	1.60 (0.99-2.60)	.14	.41
Global index‖	55	47	1.15 (0.77-1.71)	59	47	1.23 (0.82-1.84)	85	72	1.30 (0.94-1.80)	.30	.48

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio.
*Cox regression models stratified according to prior cardiovascular disease and randomization status in the Dietary Modification Trial.
†Test for trend (interaction) using years since menopause as continuous (linear) form of categorical coded values. Cox regression models stratified according to active vs placebo and trial, including terms for years since menopause and the interaction between trials and years since menopause.
‡Likelihood ratio test for 3-way interaction among hormone therapy, years since menopause, and vasomotor symptoms (none vs mild vs moderate or severe).
§Defined as CHD death, nonfatal myocardial infarction, or definite silent myocardial infarction (Novacode 5.1 or 5.2).
‖Defined as CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer for CEE plus MPA trial only, hip fracture, or death from other causes.

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ting of randomized controlled trials, thus avoiding some of the potential biases of observational studies. The conclusions relating to harm in women more distant from menopause are more robust because of the larger numbers of clinical events. The conclusions based on the analyses of women closer to menopause are less robust due to smaller numbers, as are the analyses involving vasomotor symptoms. Time of menopause may not be accurately ascertained in women who have undergone a hysterectomy. Nonadherence may have affected the results. At the end of the trials, 54% of participants were no longer taking CEE and 42% were no longer taking CEE + MPA. The results are derived from relatively short durations of treatment but the average of 4 to 5 years of receiving treatment in the trials is longer than most women would need for treatment of vasomotor symptoms. Multiple statistical tests were performed, raising a distinct possibility that several of the positive findings occurred by chance. The possibility of type I error is increased by the fact that these analyses were partly stimulated by the initial findings from the trials. The results are dependent on the analytic approach used, which differs in this compared with previous publications from the WHI trials. In previous WHI studies using continuous variables, the significance of the interaction of years since hysterectomy on CHD in the trial of CEE was $P=.06$ compared with $P=.15$ for years since menopause in the current analysis using coded variables.[3] In the trial of CEE + MPA, the significance for years since menopause changed from $P=.33$ to $P=.05$.[4] Only one form of oral estrogen and one form of oral progestin taken daily were included in the trials, and it may be that different results would have been obtained if other regimens (eg, transdermal estradiol, progesterone, or cyclic therapy) were tested.

These analyses, although not definitive, suggest that the health consequences of hormone therapy may vary by distance from menopause, with no apparent increase in CHD risk for women close to menopause, and particularly high risks in women who are distant from menopause and have vasomotor symptoms. We did not identify any subgroup with reduced risk of CHD, although total mortality was reduced among women aged 50 to 59 years. The findings regarding potential modifying effects of vasomotor symptoms warrant further study. The absence of excess absolute risk of CHD and the suggestion of reduced total mortality in younger women offers some reassurance that hormones remain a reasonable option for the short-term treatment of menopausal symptoms, but does not necessarily imply an absence of harm over prolonged periods of hormone use. In contrast, risk of stroke did not depend on years since menopause or the presence of vasomotor symptoms. The findings are consistent with current recommendations that hormone therapy be used in the short-term for relief of moderate or severe vasomotor symptoms, but not in the longer term for prevention of cardiovascular disease.[28,29]

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ELITE: Early Versus Late Intervention Trial With Estradiol

This study is currently recruiting patients.
Verified by National Institute on Aging (NIA) February 2007

Sponsored by: National Institute on Aging (NIA)
Information provided by: National Institute on Aging (NIA)
ClinicalTrials.gov Identifier: NCT00114517

Purpose

The purpose of this study is to examine the effects of 17B-estradiol (estrogen) on the progression of early atherosclerosis in postmenopausal women.

Condition	Intervention	Phase
Atherosclerosis	Drug: 17B-estradiol	Phase II Phase III

MedlinePlus related topics: Vascular Diseases
Genetics Home Reference related topics: Vascular Diseases

Study Type: Interventional
Study Design: Treatment, Randomized, Double-Blind, Placebo Control, Factorial Assignment, Efficacy Study

Official Title: Biologic Response of Menopausal Women to 17B-Estradiol

Further study details as provided by National Institute on Aging (NIA):

Primary Outcomes: rate of change of distal common carotid artery (CCA) far wall intima-media thickness (IMT)
Secondary Outcomes: neurocognitive function
Expected Total Enrollment: 504

Study start: July 2004; Expected completion: June 2009

The primary hypothesis to be tested is that 17B-estradiol (estrogen) will reduce the progression of early atherosclerosis if initiated soon after menopause when the vascular endothelium (lining of blood vessels) is relatively healthy versus later when the endothelium has lost its responsiveness to estrogen. Ultrasonography will be used to measure the rate of change in the thickness of the carotid artery.

A total of 504 postmenopausal women will be randomized according to their number of years since menopause, less than 6 years or 10 years or more, to receive either oral 17B-estradiol 1 mg daily or a placebo. Women with a uterus will also use vaginal progesterone gel 4% (or a placebo gel) the last ten days of each month. The vaginal progesterone will be distributed in a double-blind fashion along with the

randomized treatment so that only women exposed to active treatment will receive active progesterone. Participants will receive ultrasonography at baseline and every 6 months throughout the 2 to 5 years (average 3 years) of randomized treatment.

Eligibility

Genders Eligible for Study: Female

Accepts Healthy Volunteers

Criteria

Inclusion Criteria:

- Women with a serum estradiol level 25 pg/ml or less
- No period for 6 months or more
- Postmenopausal less than 6 years, OR 10 years or longer

Exclusion Criteria:

- Clinical signs, symptoms, or personal history of cardiovascular disease
- Women who have had a hysterectomy only and no oophorectomy (since time from menopause cannot be determined)
- Diabetes mellitus or fasting serum glucose 140 mg/dL or greater
- Uncontrolled hypertension (diastolic blood pressure 110 mmHg or greater)
- Thyroid disease (untreated)
- Serum creatinine greater than 2.0 mg/dL
- Plasma triglyceride levels greater than 500 mg/dL
- Life threatening disease with prognosis less than 5 years
- Cirrhosis or liver disease
- History of deep vein thrombosis or pulmonary embolism
- History of breast cancer
- Current hormone replacement therapy (HRT)

Location and Contact Information

Please refer to this study by ClinicalTrials.gov identifier NCT00114517

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More Information

Clinical Trial: ELITE: Early Versus Late Intervention Trial With Estradiol

USC Atherosclerosis Research Unit ELITE Trial

Study ID Numbers: AG0025; R01AG024154
Last Updated: February 15, 2007
Record first received: June 15, 2005
ClinicalTrials.gov Identifier: NCT00114517
Health Authority: United States: Federal Government
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Kronos Early Estrogen Prevention Study (KEEPS)

This study is currently recruiting patients.
Verified by Kronos Longevity Research Institute May 2006

Sponsors and Collaborators: **Kronos Longevity Research Institute**
Albert Einstein College of Medicine
Brigham and Women's Hospital
Columbia Presbyterian Medical Center
Mayo Clinic
University of California, San Francisco
University of Utah
University of Washington
Yale University

Information provided by: Kronos Longevity Research Institute

ClinicalTrials.gov Identifier: NCT00154180

Purpose

The study will examine the effects of estrogen and progesterone on the development of atherosclerosis in menopausal women when hormone treatment is initiated within 3 years of the menopausal transition.

Condition	Intervention	Phase
Menopause Arteriosclerosis	Drug: Conjugated equine estrogens 0.45 mg/day Drug: Transdermal estradiol, 50 mcg/day Drug: Micronized progesterone, 200 mg/day x 12 d/month	Phase IV

MedlinePlus related topics: Vascular Diseases
Genetics Home Reference related topics: Vascular Diseases

Study Type: Interventional
Study Design: Prevention, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study

Official Title: Effects of Estrogen Replacement on Atherosclerosis Progression in Recently Menopausal Women

Further study details as provided by Kronos Longevity Research Institute:
Primary Outcomes: Rate of change of carotid intimal medial thickness by ultrasound
Secondary Outcomes: Change in coronary calcium score by X-ray tomography; Plasma lipid profiles; Blood clotting factors; Serum inflammatory factors; Hormone levels; Cognitive and Affective scores on standard psychometric tests; Quality of life
Expected Total Enrollment: 720

Study start: September 2005; Expected completion: June 2010

The KEEPS is designed to explore the hypothesis that early initiation of hormone therapy, in women who are at the inception of their menopause, will decrease the rate of accumulation of atherosclerotic plaque, indicating a likely delay in the onset of clinical cardiovascular disease. The study is designed as a multicenter, 4 year randomized clinical trial. It will evaluate the effectiveness of of 0.45 mg/day of oral conjugated equine estrogens or 50 mcg/day of transdermal estradiol via skin patch changed weekly (each in combination with cyclic oral, micronized progesterone, 200 mg daily for 12 days per month), versus placebo in preventing progression of carotid intimal medial thickness by sonogram and the accrual of coronary calcium in women aged 42-58 who are within 36 months of their final menstrual period at initiation of treatment. A number of secondary endpoints including biochemical and genetic risk factors for cardiovascular and thrombotic disease, and effects on cognition will also be studied. The study will enroll a total of 720 women in 2005-6, with an anticipated completion of the trial in 2010.

Eligibility

Ages Eligible for Study: 42 Years - 58 Years, Genders Eligible for Study: Female

Accepts Healthy Volunteers

Criteria

Inclusion Criteria:

- menses absent for at least 6 months and no more than 36 months
- good general health
- plasma FSH level greater than or equal to 35 mIU/ml
- estradiol levels < 40 pg/ml
- normal mammogram within 1 year of randomization

Exclusion Criteria:

- use of hormone replacement or supplement within 3 months of randomization
- endometrial thickness >5 mm by vaginal ultrasound
- in utero exposure to diethylstilbestrol (DES)
- current smoking > 10 cigarettes/day
- obesity-body mass index > 35
- history of clinical cardiovascular disease
- history of cerebrovascular disease
- history of thromboembolic disease
- coronary calcium score ≥ 50 units
- dyslipidemia-LDL cholesterol >190 mg/dl
- hypertriglyceridemia-triglycerides >400 mg/dl
- lipid lowering medication (statin, fibrate,or > 500 mg/day of niacin)
- nut allergy (Prometrium includes peanut oil)
- uncontrolled hypertension-systolic BP >150 and/or diastolic BP > 95
- hysterectomy
- history of, or prevalent, chronic diseases including any cancer (other than basal cell skin cancers), renal failure, cirrhosis, diabetes mellitus, and endocrinopathies other than adequately treated thyroid disease

- known HIV infection and/or medications for HIV infection
- results of any safety laboratory test chemistries, (TSH, CBC, U/A) more than 20% abnormal

Location and Contact Information

Please refer to this study by ClinicalTrials.gov identifier NCT00154180

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More Information

Information on hormone treatment and KEEPS rationale

Information on sponsoring institution

Publications

Harman SM, Naftolin F, Brinton EA, Judelson DR. Is the Estrogen Controversy Over? Deconstructing the Women's Health Initiative Study: A Critical Evaluation of the Evidence. Ann N Y Acad Sci. 2005 Jun;1052:43-56.

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Health Authority: United States: Institutional Review Board
ClinicalTrials.gov processed this record on 2007-03-29

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XVI. Pharmacy Licensure Requirements

State	Number of Pharmacy License Categories*	Must Nonresident Pharmacies be Licensed/ Registered?	Initial Licensure/ Registration Fee	Renewal Fee	Renewal Schedule	Must Nonresident Pharmacists be Licensed?
Alabama	2	Yes	$500	$400	2 years	No U
Alaska	3	Yes A	$300 EE, FF	$300 FF	2 years	No U
Arizona	3	Yes	$400	$400	2 years	No
Arkansas	4	Yes	$300	$300	2 years	Yes E
California	6	Yes	$340	$175	1 year	No
Colorado	1	Yes A	$250	$240	2 years	No
Connecticut	5	Yes A, B	$600	$150	1 year	No
Delaware	1	Yes D	Varies	$200	2 years	No
District of Columbia	4	No	$150	$150	1 year	—
Florida	16	Yes A	$250	$250	2 years	No
Georgia	9	No	$100	$95	2 years	No
Guam	1	No	$50	$30	1 year	No
Hawaii	2	Yes	G, I	$220/$270 T	2 years	No
Idaho	6	Yes	$100 J	$100 J	1 year	No
Illinois	6	Yes	$100	$200	2 years	No
Indiana	6	Yes	$100	$200	2 years	No
Iowa	4	Yes A	$150	$150	1 year	No K
Kansas	1	Yes	$140	$125	1 year	No
Kentucky	3	Yes	$100	$100	1 year	Yes GG
Louisiana	6	Yes	$150	$125	1 year	Yes L
Maine	3	Yes B	$200	$200	1 year	No
Maryland	3	Yes	$300	$250	1 year	No
Massachusetts	5	No	$351 AA	$351 AA	2 years	No
Michigan	1	Yes	$180	$260	2 years	No
Minnesota	6	Yes	$165	$165	1 year	No
Mississippi	4	Yes	$300	$300	2 years	No
Missouri	11	Yes	$250	$400	2 years	No U
Montana	4	Yes	$200	$100	1 year	No U
Nebraska	1	Yes	$255	$255	1 year	Yes Q
Nevada	2	Yes	$500	$500 I	2 years	No
New Hampshire	1	Yes	$500 C	$250 C	1 year	No U, CC
New Jersey	2	Yes	$275	$175	1 year	No
New Mexico	3	Yes	$400	$400	2 years	No
New York	1	Yes	$345	$260	3 years	No
North Carolina	3	Yes	$500	$200	1 year	No
North Dakota	11	Yes	$175	$175	1 year	No
Ohio	11	Yes	$150	$150	1 year	No
Oklahoma	4	Yes A	$250	$150	1 year	No U
Oregon	4	Yes	$175	$175	1 year	Yes CC
Pennsylvania	1	No	$100	$100	2 years	No
Puerto Rico	1	R	R	$3	1 year	—
Rhode Island	4	Yes A	$125	$62.50	1 year	No
South Carolina	1	Yes	$300	$200	1 year	No
South Dakota	2	Yes	$200 N, O	$200 N, O	1 year	No
Tennessee	7	Yes	$168	$168	2 years	Yes F
Texas	5	Yes A	$356	$353	2 years	No
Utah	5	Yes A	$200	$103	2 years G	No
Vermont	4	Yes	$270	$70	2 years	No
Virginia	1	Yes	$270	$270	1 year	No
Washington	1	Yes	$365	$240	1 year	No
West Virginia	1	Yes A	$150	$100	1 year	No
Wisconsin	1	No	$53	$56	2 years	—
Wyoming	2	Yes	$150 resident $300 nonresident	$150 resident $300 nonresident	1 year	No

* See "Footnotes (*)" on pages 49-50 for categories of pharmacy licenses for those states that issue more than one category. Contact the state board of pharmacy for specific information about these licenses.

XVI. Pharmacy Licensure Requirements (cont.)

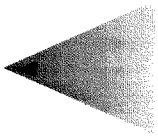
State	Initial Controlled Substance Fee	Controlled Substance Renewal Fee	Controlled Substance Renewal Schedule	Is There a Separate Licensing Category for Online/Internet Pharmacies?
Alabama	$300	$300	2 years	No
Alaska	None	None	—	No W
Arizona	None	None	—	No V
Arkansas	None	None	—	No
California	None	None	—	No
Colorado	None	None	—	No
Connecticut	None	None	—	No
Delaware	$40	$40	2 years	No
District of Columbia	$50	$50	1 year	No
Florida	None	None	—	Yes
Georgia	None	None	—	—
Guam	$150	$120	1 year	—
Hawaii	$60	$60	1 year H	Yes*
Idaho	$60	$60	1 year	No Y
Illinois	$5	$5	2 years	No
Indiana	$100	$100	2 years	No X
Iowa	$100*	$100*	2 years*	No Z
Kansas	None	None	—	No
Kentucky	M	M	M	No
Louisiana	$25	$25	1 year	No W
Maine	None	None	—	No
Maryland	$60	$60	2 years	BB
Massachusetts	$151	$151	2 years	No
Michigan	$85	$150	2 years	No
Minnesota	None	None	—	No
Mississippi	$50	$50	2 years I	No
Missouri	None DD	None DD	DD	No
Montana	$35	$35	1 year	No
Nebraska	None	None	—	No
Nevada	$80	$80	2 years I	No
New Hampshire	None	None	—	Yes
New Jersey	$20	$20	1 year	No
New Mexico	$60	$60	1 year	No
New York	None	None	—	No
North Carolina	None	None	—	No
North Dakota	None	None	—	No
Ohio	—	—	—	No
Oklahoma	M	M	M	No
Oregon	$25	$25	1 year	No
Pennsylvania	None	None	—	No
Puerto Rico	$200 S	$200 S	1 year	—
Rhode Island	$50	$50	1 year	No
South Carolina	$125	$125	1 year	No
South Dakota	M	M	3 years M	No
Tennessee	$40	$40	2 years	No
Texas	$25	$25	1 year P	No
Utah	$90	$68	2 years	No
Vermont	None	None	—	No
Virginia	None	None	—	No
Washington	$80	$58	1 year	No
West Virginia	$25	$25	1 year	No
Wisconsin	None	None	—	No
Wyoming	$40	$40	1 year	No

* See "Footnotes (*)" on pages 49-50.

XVI. Pharmacy Licensure Requirements (cont.)

LEGEND

A — If pharmacy ships, mails, delivers, dispenses, and/or provides prescription drugs and/or devices to state residents. (TX – If pharmacy routinely provides such services. WV – If more than 10% of prescription volume is dispensed by mail.)
B — Registered, not licensed.
C — $150 for nonresident pharmacies.
D — Prorated initial licensing fee; renewal fee varies.
E — One licensed AR pharmacist required as pharmacist-in-charge (PIC) for AR permit.
F — If acting as PIC of a licensed out-of-state pharmacy.
G — Odd years. (HI – $295.)
H — State Department of Public Safety, Narcotics Enforcement Division.
I — Even years. (HI – $185.)
J — Mail Order Annual Fee – $250; Mail Order Initial Fee – $500.
K — Unless they enter state to provide pharmacy services.
L — One licensed LA pharmacist required as PIC for LA permit.
M — Not handled by the Board of Pharmacy.
N — $200, community pharmacy and institutional full-time pharmacy.
O — $160, institutional part-time pharmacy.
P — Issued by Texas Department of Public Safety.
Q — NE-licensed pharmacist must be employed by the pharmacy.
R — Not addressed in pharmacy act or Board regulations.
S — Required by the local Controlled Substances Act.
T — $220 – odd years; $270 – even years for pharmacy renewal.
U — Not by this state, but by the state in which the pharmacy is located.
V — They are considered to be "limited service."
W — All out-of-state pharmacies in same category.
X — Registers these entities as nonresident pharmacists.
Y — They would be considered mail service if we licensed them.
Z — Pharmacies would be licensed in the same manner as a "brick-and-mortar" pharmacy based on location.
AA — Plus Controlled Substance fee of $151.
BB — No separate category. A full service pharmacy in MD may have an online/Internet component or a pharmacy may receive a waiver to perform only this service. Nonresident pharmacist (out-of-state) must comply with general nonresident regulations.
CC — Licensure of nonresident pharmacists is required when performing remote entry activities, but does not dispense prescriptions into the state (telemedicine).
DD — Controlled substances registration is handled by another state agency, not the Board of Pharmacy.
EE — Plus one-time application fee of $50.
FF — $600 for out-of-state pharmacies.
GG — If pharmacy is shipping 25 or more prescriptions per month into KY, must have KY pharmacy permit and a KY licensed pharmacist as a pharmacist-in-charge.



Licensing*law*

Footnotes (*)

AK — Retail, institutional, drug room, out-of-state.
AR — Hospital, institutional, retail, charitable clinic.
AZ — Community, hospital, limited service.
CA — Community pharmacy, hospital pharmacy, exempt hospital, out-of-state, licensed correctional facility, sterile compounding facility.
CT — Commnnity, nuclear, long-term care, infusion specialty.
DC — Retail, institutional, nuclear, special, or limited use.
FL — Class I institutional (nursing home), Class II institutional (hospital), Modified Class IIA, Modified Class IIB, Modified Class IIC, community, special parenteral/enteral, special nonresident, special closed system, special end stage renal disease, animal shelter, nuclear. Special parenteral/enteral extended scope. Special assisted living facility. Internet, nonresident.
GA — Retail, hospital, nuclear, prison, pharmacy school, pharmacy clinic, pharmacy benefits manager, researcher, opioid treatment center.
HI — Pharmacy license and miscellaneous permit for out-of-state pharmacies.
IA — General, hospital, limited use, nonresident. Controlled substance registration not required for nonresident pharmacies.
ID — Retail drug outlet, institutional drug outlet, parenteral, non-pharmacy drug outlet, limited service, out-of-state mail service pharmacy.
IL — Retail; off-site hospital, nursing home pharmacies; on-site hospital, nursing home pharmacies; Nuclear; ambulatory care facility pharmacies and hospital or nursing home pharmacies providing services to the general public.
IN — Based on type of business conducted.
KS — Resident and nonresident.
LA — Community, hospital, institutional, nuclear, charitable, out-of-state.
MA — Retail and nuclear restricted.
MD — Full service pharmacy permit; various waiver permits. Nonresident pharmacy permit.
ME — Retail, rural health center, mail order.

Footnotes continue on page 50.

Footnotes (*) — cont.

MN — Community/retail, hospital, parenteral-enteral/home health care, long-term care, nuclear, nonresident.

MO — Community ambulatory, hospital outpatient, long-term care, nonsterile compounding, radiopharmaceutical, renal dialysis, medical gas, sterile product compounding, consultant services, shared services, and Internet. Controlled substances registration is handled by another state agency, not the Board of Pharmacy.

MS — Community, institutional, limited closed door, nonresident.

NC — Pharmacy permits, limited service permits, out-of-state permits.

ND — Outpatient, home health care, nuclear, out-of-state, research, hospital, long-term care, mail order, governmental agency, office practice, telepharmacy.

NJ — Retail, hospital/institutional. Specialized permits where applicable.

NV — Retail, institutional.

OH — Retail, hospital, long-term care, fluid therapy/home health care, clinic, HMO, mail order, nuclear, specialty, durable medical equipment, charitable.

OK — Retail, hospital, nonresident, charitable.

OR — Pharmacy categories include "retail with controlled substances," "retail without controlled substances," "institutional without controlled substances," and "institutional with controlled substances."

PR — Board issues licenses to pharmacies (community and institutional), wholesalers, manufacturers, non-pharmacy over-the-counter drug outlets, and drug deposits.

RI — Retail (includes community, parenteral, nuclear), institutional (includes hospital, HMO, university, other settings).

SD — Full time, part time.

TN — Community, hospital, nursing home, home health care, nuclear, other.

TX — Community, nuclear, institutional, clinic, nonresident.

UT — Class A: Retail; Class B: Institutional; Class C: Wholesaler (in-state); Class D: Out-of-State Mail Order; Class E: Other.

VT — Retail, institutional, research and investigation, manufacturer, wholesalers, and nonresident pharmacies.

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4/5/07

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Stages of Atherosclerosis

		Lipid lowering (e.g. Statins)	Estrogens e.g. Premarin, Estradiol
Young adult	**Initiation** (endothelium, fatty streaks)		
	↓	↓	↓
Middle age	**Progression** (raised lesions)		
	↓	↓	→
Older ages	**Complicated lesions** (erosion or rupture of unstable plaque)		
	↓	↓	↑
	Heart Attack/Stroke		

Conclusions

- Age is a powerful risk factor for atherosclerosis
- Prevention is aimed at slowing transition to more severe stages of age-related atherosclerosis
- Lipid lowering achieves this at each stage, no known long term harm, represent a good strategy for long term prevention
- Estrogen appears to have favorable effects at earlier stages only, harm at later stages (and has other long term risks), not a good long term prevention strategy
- No apparent differences between estradiol and conjugated equine estrogen effects on atherosclerosis

Hormone Therapy Circa 1995

- Proven uses
  - Treatment of hot flashes, night sweats, vaginal atrophy
  - Prevention of osteoporosis
- Recommended (but unproven)
  - Prevention of heart disease
  - Based on observational studies of association
    - Do hormones reduce risk?
    - Or are hormone users healthier to start with?
    - Likely overestimate benefit, if any
- Other uses
  - Correcting a presumed “hormone deficiency” to remain “forever young”

Women's Health Initiative
Trials of Hormone Therapy

Main study question: does hormone therapy prevent heart attacks?

- More than 27,000 women age 50-79
- Women with risk factors and previous heart disease included
- Planned duration 8 years
- Tested the hormones thought to be associated with reduced risk of heart attacks (observational studies)

  Estrogen = Conjugated equine estrogen (women without uterus)

  plus

  Progestin = medroxyprogesterone acetate (women with uterus)

Women's Health Initiative

Main Results

- Trial of Estrogen plus Progestin
  - Ended early after 5+ years
  - Increased breast cancer, heart disease, stroke, blood clots, dementia
  - Reduced fractures, colorectal cancer
- Trial of Estrogen-only
  - Ended early after 7 years
  - Increased stroke, blood clots, dementia
  - No effect on heart disease, cancer
  - Reduced fractures

Hormone Therapy after WHI

- Change in recommendations to “Do not use hormone therapy to prevent heart disease”
- Black box warning on package insert
- Large drop in hormone prescriptions
  - Approx. 21 million women given prescriptions in 2001
  - Approx. 6 million women in 2006
- Proven uses
  - Treatment of hot flashes, night sweats, vaginal atrophy (low dose, short time, prefer local)
  - Prevention of osteoporosis (prefer other therapies)

Post-WHI: Additional Issues

- Are hormone effects different if started immediately after menopause?
  - Secondary analyses of combined WHI Trials
    - Women starting hormones close to the menopause may have fewer heart attacks and deaths compared to the increases in women distant from the menopause
    - Stroke and breast cancer increased irrespective of years since menopause
    - Provides some reassurance that younger women using hormones for the short term for relief of hot flashes and night sweats are not at increased risk of heart disease
    - Older women with hot flashes and night sweats are at high risk if they start hormone therapy
  - Ongoing surrogate outcome trials (imaging studies of coronary and brain arteries) in younger women
  - Findings should not be taken to imply that any early benefit for coronary disease will persist into older ages
- Would estradiol have had a different effect?
- Role of route of administration (transdermal versus oral)

Statement
of the
American Pharmacists Association

On Bioidentical Hormones: Sound Science or Bad Medicine?

Before the Special Committee on Aging United States Senate

April 19, 2007

APhA

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Statement of the American Pharmacists Association
To the Senate Special Committee on Aging

On "On Bioidentical Hormones: Sound Science or Bad Medicine?"

April 17, 2007

The American Pharmacists Association (APhA) welcomes the opportunity to present the pharmacist's perspective on pharmacy compounding and bio-identical hormones. As the medication experts on the health care team, and the front-line health professionals dedicated to partnering with patients to improve medication use, pharmacists have a unique perspective on ensuring that patients have access to safe and effective medications. APhA, founded in 1852 as the American Pharmaceutical Association, represents more than 60,000 pharmacist practitioners, pharmaceutical scientists, student pharmacists, pharmacy technicians, and others interested in improving medication use and advancing patient care. APhA members provide care in all practice settings, including community pharmacies, hospitals, long-term care facilities, managed care organizations, hospice settings, and the military.

APhA supports the Committee's goal that patients receive safe and effective medications. Pharmacists rely upon quality products as the first step in their work to help patients make the best use of their medications. However, when a prescriber writes a prescription for a product that is not commercially available, pharmacists use their scientific training and education to compound the medication. Compounding involves tailoring a medication to meet an individual patient's needs.

Compounding medications is an important component of pharmacy practice. Virtually all practicing pharmacists will be involved with compounding activities at some point during their career—and most practitioners engage in some element of compounding in each week of practice. Because pharmacist compounding activities are a critical component of the American health care system — allowing physicians to prescribe medication therapy to best meet the needs of their patients — APhA has a compelling interest in helping pharmacists, in collaboration with practicing physicians, compound drug formulations to meet the needs of patients.

Our comments provide a brief history of pharmacist compounding, describe the important role pharmacy compounding plays in our health care system, discuss how to distinguish between compounding and manufacturing and the current regulatory system, and describe efforts to improve the quality of the practice of compounding.

Compounding: A Traditional Component of Pharmacy Practice
Compounding is a traditional component of pharmacy practice; only the drugs, dosage forms, and equipment or techniques have changed as pharmacy practice has advanced. As noted in the *Chronicles of Pharmacy*[1], "[p]harmacy, or the art of selecting, extracting, preparing and compounding medicines from vegetable, animal, and mineral substances, is an acquirement that must have been almost as ancient as man himself on earth."

The early practice of pharmacy required the compounding of virtually all medications, because there were few, if any, commercially available products. The need for compounded products has diminished with the founding of pharmaceutical companies, although the need for this practice still exists today. Because the preparation of an extemporaneous pharmaceutical dosage form is not a trivial exercise, we believe that when an FDA-approved, commercially available product

[1] Wootton, A. C. Chronicles of pharmacy. Boston: Milford House, 1971

can meet a patient's needs, it should be employed as the preferred course of action. However, when a patient's particular situation obviates the use of commercial products, the knowledge and skills of a compounding pharmacist can be extremely valuable, even lifesaving.

It is a fundamental responsibility of the pharmacy profession to extemporaneously compound quality prescription products for patients who have unique medication needs. Through their education and licensure, pharmacists assume an ethical obligation to the public to maximize the intended benefits of drug therapy while minimizing the unintended side effects and adverse reactions. Compounding enables pharmacists to use their unique knowledge and expertise of medication use to produce individualized, patient-specific medications that meet patient needs and improve health outcomes. Without compounding, pharmacists and physicians would be limited to a "one size fits all" strategy, which would have a direct, immediate, negative impact on the ability of health care providers to provide care to patients.

Compounding: Meeting Otherwise Unmet Health Care Needs
Compounding allows pharmacists and physicians to address the health care needs of patients who do not fall within the range of commercially available dosage strengths and formulations. Patient needs vary from extremely small doses and specific combinations of drugs, to preservative-free products, to liquid dosage forms, to delivery systems that are not commercially available. Without compounding, many patients would not have access to the correct combination of ingredients, the appropriate dose and dosage form, or the route of delivery that best meets their medical needs.

Compounding involves different activities in different pharmacy practice settings. It may mean the preparation of oral liquids, topicals, or suppositories; the conversion of one dose or dosage form into another; the preparation of specific dosage forms from bulk chemicals; the preparation of intravenous admixtures, parenteral nutrition solutions, or pediatric dosage forms from adult dosage forms; the preparation of radioactive isotopes; or the preparation of cassettes, syringes, and other devices with drugs for administration in the home setting. Examples of some of the most commonly compounded products include lotions, ointments, creams, gels, suppositories, intravenously administered fluids and medications, total parenteral nutrition products, and oral suspensions.

In addition to unique patient needs, manufacturing and market limitations may require medications to be compounded. While in many cases it may not be cost-effective for a large-scale manufacturer to tailor-make a medication, in other situations the qualities of a product prohibits its production through manufacturing. For example medications such as radioactive drugs used to diagnose or treat cancers or other diseases must be compounded because they do not have sufficient "shelf life" to withstand the commercial distribution process and therefore need to be prepared at the time of dispensing. Additionally, many manufactured "finished pharmaceutical" products are only "finished" in the sense of being ready to ship and then store in the pharmacy. These products must still be compounded, or in some cases merely reconstituted, by the pharmacist to provide a dosage form suitable for a patient's treatment.

Although compounding may be required in any pharmacy practice setting and for any type of disease, there are concentrations of compounding practice. For example, due to the nature of the care they provide, hospital pharmacies have historically had a strong compounding component to their practice. However, due to the new, more vigorous requirements for sterile compounding, some hospitals are outsourcing their sterile compounding to pharmacies in the community. Therefore, while use of sterile compounding will likely remain concentrated in hospitals, the production of such products is moving to other settings. Finally, due to the nature of the disease

and/or the patient size or age, compounding frequently occurs for patients with cancer, for pediatric care, and for hospice care.

Hospitals
Compounding in the hospital setting is a vital service that addresses the unique needs of patients requiring highly individualized medications. The primary compounding activity in hospitals is the preparation of intravenous admixtures ranging from simple fluid replacement to the delivery of complicated, individualized chemotherapy regimens. Because daily intravenous therapy is provided through compounding of medications, nearly every person who has ever been admitted to a hospital –and those who will be admitted today and likely in the future– has received a compounded medication. In fact, the immediate availability of extemporaneous compounding by a pharmacist provides the hospital physician with literally any form or strength of medication needed for a patient's specific needs.

Cancer and Pediatric Patients
Cancer patients frequently benefit from compounding pharmacists' knowledge and skills. Almost all chemotherapy involves drugs and drug combinations that are compounded, or at least reconstituted, by pharmacists. It is imperative that a patient receive the correct drug dosage based upon the patient's body size, the type of cancer, the size and type of tumor, and the clinical condition of the patient including their kidney and liver function. This can often only be accomplished by using compounded, patient-specific medication preparations.

The compounding of pediatric dosage forms has also been an area of extensive activity, because many drugs used to treat children are only available in adult dosage forms. Finding the right drug, dose and dosage form to treat sick children is a complicated task. Congress has made great strides in establishing incentives to improve the utility of manufactured products in treating children. And this year's discussions of reauthorizing the Prescription Drug User Fee Act (PDUFA) have highlighted the continued need to enhance this area of research and development. Despite these efforts, compounding is frequently the only available avenue to achieve the desired clinical outcomes for pediatric patients. Absent a pediatric formulation, commercially manufactured products for adult use must be modified and compounded for use in children. It has been estimated that more than 40% of doses given in pediatric hospitals require compounding to prepare a suitable dosage form[2]. Clearly, utilization of compounded medications is essential for the provision of medical care to hospitalized children.

Hospice Patients
As the Committee is aware, hospice programs provide care for patients near the end of their lives who can no longer benefit from curative treatment and generally have a life expectancy of six (6) months or less. Patients suffering from incurable cancer have very special needs. Relief of pain near the end of life is an important element of maintaining the dignity and comfort of a dying patient and their loved ones. Hospice patients often need medications to alleviate pain and to control nausea and vomiting for patients in the hospice setting. Unfortunately for many hospice patients, pain medications are often not manufactured in the required dosages. Additionally, some patients are not physically capable of swallowing the number of commercially manufactured tablets or capsules required or cannot take medications orally. If commercial products that provide the precise dose(s) required are not available, the hospice pharmacist can often remedy the situation by extemporaneously preparing an individualized product. A pharmacist can address these issues by either compounding a stronger product, by transforming tablets or

[2] Pain Palliat Care Pharmacother, 16(4): 71-78, 2002

capsules into a liquid, or by creating a preparation that can be applied topically or delivered rectally.

BHRT
APhA's position on pharmacy compounding stands, regardless of the specific medication. In fact, APhA does not take positions on specific medications or categories of medications. That being said, the Committee is holding this hearing to address, at least in part, the issue of bio-identical hormone replacement therapy (BHRT). To provide the Committee some perspective, we asked a small group of our members to share their experience with BHRT. Every pharmacist who responded had worked with physicians to manage women's health and BHRT had provided these women relief from symptoms that either commercially available products were unable to address or that commercially products created. However, once again, APhA does not have a position on BHRT. As long as a product is compounded based upon a valid prescription from a "triad" relationship in which the patient's physician has decided that the compounded product is necessary to meet the patient's individual health care needs, and the product is not commercially available, then the compounding is appropriate. There are risks with all medication, whether manufactured or compounded. It is the responsibility of prescribers, working with patients and pharmacists, to determine whether the benefits of a medication outweigh the risks.

Compounding vs. Manufacturing
One question that continues to plague the profession and our regulators—the state boards of pharmacy—is how to distinguish between compounding and manufacturing; with one practice regulated by state boards of pharmacy and the other process, by the Food and Drug Administration (FDA).

Compounding has traditionally been characterized by the triad relationship of the physician, pharmacist and patient working together to individualize care for maximum patient benefit. Pharmacy compounding is performed in response to a prescription from a licensed prescriber, or in preparation for a reasonably anticipated prescription, based upon prior experience and expected needs of individual patients.

APhA supports the National Association of Boards of Pharmacy's[3] (NABP) definition of compounding, which states:

> "Compounding" means the preparation of components into a drug product (1) as the result of a practitioner's prescription drug order or initiative based on the practitioner/patient/pharmacist relationship in the course of professional practice, or (2) for the purpose of, or as an incident to, research, teaching, or chemical analysis and not for sale or dispensing. Compounding includes the preparation of drugs or devices in anticipation of receiving prescription drug orders based on routine, regularly observed prescribing patterns.

The profession's definition of compounding does not encompass the preparation of massive amounts of a drug product with the contemplation of distribution to a mass market of unknown users in unknown venues. Rather, the definition supports our assertion that the purpose of pharmacist compounding is to prepare an individualized drug treatment for a patient based on an order from a licensed prescriber.

Manufacturing, on the other hand, is defined by NABP as follows:

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[3] NABP's Model State Pharmacy Act and Rules (August 2006)

> "Manufacturing" means the production, preparation, propagation, conversion, or processing of a drug or device, either directly or indirectly, by extraction from substances of natural origin or independently by means of chemical or biological synthesis. Manufacturing includes the packaging or repackaging of a drug or device or the labeling or relabeling of the container of a drug or device for resale by pharmacies, practitioners, or other persons.

As clear as this difference may seem to the profession of pharmacy, it has been a difficult distinction to implement because of the complexity and range of legitimate compounding activities. In public comments, even the FDA has suggested that the difference between compounding and manufacturing is better represented by the intersection of two jagged jigsaw puzzle pieces rather than a straight line.

The fundamental difference between compounding and manufacturing, and the key element in making any such distinction, is the existence of a pharmacist/prescriber/patient "triad" relationship. This triad should control the preparation of a drug product. Furthermore, compounded drugs are not for resale, but rather, are personal and responsive to a patient's immediate needs. Conversely, drug manufacturers produce batches consisting of millions of tablets or capsules at a time for resale, while utilizing many personnel and large scale manufacturing equipment, without knowledge of the specific patient who will ultimately consume them. And finally, compounding should not occur when a commercially available product is available.

The Current Regulatory System
A strong regulatory system exists for pharmacy compounding. State Boards of Pharmacy take the lead in regulating pharmacy compounding while the Food and Drug Administration plays a role when compounding crosses the line into manufacturing.

State Boards of Pharmacy
Pharmacists and pharmacies are licensed by States Boards of Pharmacy. Every state has a Pharmacy Practice Act and Board of Pharmacy Regulations that are used to regulate the profession. After sections of the Food and Drug Administration Modernization Act (FDAMA) were struck down, there was a flurry of activity by State Boards of Pharmacy to further clarify what is meant by pharmacy compounding and to explore legislative and regulatory changes to more clearly articulate the boundaries of practice for pharmacists in their jurisdiction.

Food and Drug Administration
As stated above, the FDA, which primarily regulates manufacturers, also plays a role in regulating compounding. Pharmacists rely on the FDA for strong, consistent regulation of pharmaceutical manufacturing and on the FDA to assure that these processes yield a safe and effective product.

The current regulatory system reflects the strengths of each agency and ensures patient access to medications that would otherwise be unavailable.

In the Courts
In addition to the statutory authority provided in the Food and Drug Administration Modernization Act of 1997 (21 U.S.C. § 353a), strong case law exists for exempting compounded medications from the FDA new drug approval process. In *Tommy G. Thompson, Secretary of Health and Human Services, et al., Petitioners v. Western States Medical Center et al.* in 2002, the United States Supreme Court ruled that "The Government argues that eliminating the practice

of compounding drugs for individuals would be undesirable because compounding is sometimes critical to the care of patients with drug allergies, patients who cannot tolerate particular drug delivery systems, and patients requiring special drug dosages. Preserving the effectiveness and integrity of the FDCA's new drug approval process is clearly an important governmental interest, and the Government has every reason to want as many drugs as possible to be subject to that approval process. The Government also has an important interest, however, in permitting the continuation of the practice of compounding so that patients with particular needs may obtain medications suited to those needs. And it would not make sense to require compounded drugs created to meet the unique needs of individual patients to undergo the testing required for the new drug approval process. Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so requiring such testing would force pharmacists to stop providing compounded drugs." (122 S.Ct 1497)

More recently, federal district court Judge Robert Junell ruled in *Medical Center Pharmacy v. Gonzales* in 2006, "Public policy supports exempting compounded drugs from the new drug definitions. If compounded drugs were required to undergo the new drug approval process, the result would be that patients needing individually tailored prescriptions would not be able to receive the necessary medication due to the cost and time associated with obtaining approval. When a licensed practitioner writes a prescription for a compounded drug for a patient, the medication is normally needed soon thereafter. It is not feasible, economically or time-wise for the needed medications to be subjected to the FDA approval process. It is in the best interest of public health to recognize an exemption for compounded drugs that are created based on a prescription written for an individual patient by a licensed practitioner. [...] Compounded drugs, when created for an individual patient pursuant to a prescription from a licensed practitioner, are implicitly exempt from the new drug definitions." (451 F.Supp 2d 854)

All compounding in response to a specific patient prescription remains within the realm of pharmacy practice; and because pharmacy practice is regulated by State Boards of Pharmacy, Boards are the primary enforcers of pharmacy compounding. It, through its own investigative process, a State Board of Pharmacy determines that a pharmacy is manufacturing, then it is appropriate for the FDA to get involved. The FDA's current inspection and enforcement authority over pharmacy compounding is sufficient.

Continuous Quality Improvement

As professionals, pharmacists continually strive to provide the best patient care possible, including continuous review of practices and taking steps to improve medication use and advance patient care. Pharmacy compounding conforming to the highest possible professional standards is essential to optimal patient care. Maintaining quality and advancing practice requires the profession to be vigilant, and continually improve our professional standards and regulatory efforts. Two organizations supplement the state legislative and regulatory efforts described above. The Pharmacy Compounding Accreditation Board (PCAB) and the USP are central to ensuring that patients receive safe and effective compounded products.

Pharmacy Compounding Accreditation Board

One of the more recent steps the profession has taken to advance compounding practice as part of our ongoing commitment to providing safe and effective pharmaceutical care to patients was the creation of the Pharmacy Compounding Accreditation Board (PCAB). Founding members of PCAB include the American College of Apothecaries, the American Pharmacists Association, the International Academy of Compounding Pharmacists, the National Association of Boards of Pharmacy, the National Home Infusion Association, and the United States Pharmacopeia.

These groups saw the value of voluntary programs to improve compounding activity. The initial work of PCAB included the development of compounding principles that must be followed by pharmacies that choose to be PCAB accredited. The PCAB principles are as follows:

- Compounding is the preparation of components into a drug product either as the result of a practitioner's prescription drug order based on a valid practitioner/patient/pharmacist relationship in the course of professional practice, or for the purpose of, or as an incident to, research, teaching, or chemical analysis that are not for sale or dispensing. Compounding is a part of the practice of pharmacy subject to regulation and oversight from the state boards of pharmacy. Compounded medication may be dispensed to prescribers for office use, where applicable state law permits. Office use does not include prescribers reselling compounded medications.

- Compounding may be conducted in anticipation of receiving prescription orders when based on routine, regularly observed prescribing patterns. Anticipatory compounding is limited to reasonable quantities, based on such patterns.

- Compounding does not include the preparation of copies of commercially available drug products. Compounded preparations that produce, for the patient, a significant difference between the compounded drug and the comparable commercially available drug product or are determined, by the prescriber, as necessary for the medical best interest of the patient are not copies of commercially available products. "Significant" differences may include, for example, the removal of a dye for a medical reason (such as an allergic reaction), changes in strength, and changes in dosage form or delivery mechanism. Price differences are not a "significant" difference to justify compounding.

- Both the prescriber (via the prescription) and the patient (via the label) should be aware that a compounded preparation is dispensed.

- The pharmacy may advertise or otherwise promote that it provides prescription drug compounding services. Such advertising should include only those claims, assertions, or inference of professional superiority in the compounding of drug products that can be independently and scientifically substantiated.

United States Pharmacopeia
In addition to the collective effort represented by PCAB, individual organizations have pursued improvements in pharmacy compounding practice. The United States Pharmaceopeia (USP), the official drug standard setting body for our country, has a long history of addressing pharmacy compounding. The USP establishes standards for compounding medications. Recently, the USP has strengthened its USP Chapter <795> Nonsterile Compounding and USP Chapter <797> Sterile Compounding standards.

Conclusion
Through compounding, pharmacists fulfill a legitimate and essential need –providing patients with medications tailored to their needs. The professional education and training of pharmacists provides the unique knowledge and skills necessary to fulfill this health care need. By working together, prescribers and pharmacists help patients access otherwise unavailable therapies such as cream for breast cancer patients' radiation burns, or anticonvulsants in a suppository form when patients' veins are not accessible for injection. Without compounding, many physicians, pharmacists and patients would lose access to valuable treatments.

APhA Statement to the Senate Special Committee on Aging
April 19, 2007

APhA supports the Committee's efforts to discuss this important issue and appreciates the opportunity to share the perspective of pharmacists on this issue. While pharmacist compounding improves patients' lives every day, we must continually improve our practices to provide the best patient care. Improving our efforts to provide quality compounded products will require collaborative efforts of consumers, the profession, State Boards of Pharmacy, and the FDA. Each stakeholder has an expertise that is essential in assuring the continued availability of this practice with the quality patients deserve.

Consumers must play a role in all of these efforts, as we are pursuing this work for them. The profession must take the lead in guiding the regulatory agencies in how to draw the line between compounding and manufacturing, and in developing guidelines and voluntary accreditation or certification processes to demonstrate compliance with those guidelines. The State Boards of Pharmacy, responsible for regulating the profession, should maintain their primary regulatory role of pharmacy practice, including compounding. The FDA has a role in regulating manufacturers, as well as defining some broad guidance, such as the identification of substances that should not be used in manufacturing or compounding because the substances have been withdrawn from the market for safety and efficacy concerns.

All of these efforts require collaboration, coordination, and ongoing communication. To that end, pharmacists are ready to partner with stakeholders to develop effective strategies to improving the quality of compounding practices. Thank you for the opportunity to present the views of the nation's pharmacists. APhA looks forward to working with the Committee to ensure that patients are receiving quality compounded products.

Written Testimony of
Jane L. Murray, MD
Board Chair, Women in Balance

Before the Senate Special Aging Committee on April 19, 2007

I am a licensed physician and a founder of the national, non-profit organization Women in Balance which is comprised of thousands of women and health professionals dedicated to helping women achieve optimum health, wellness and hormone balance through providing education and promoting research. My experience as a physician has shown me that women need more not fewer options in health care, especially related to hormone balance. Compounded medications are an important option for many patients to meet their hormone needs as well as to treat other conditions. Subjecting compounding pharmacists and physicians to onerous federal oversight that duplicates well-established regulations already in place at the state level is both burdensome and unnecessary.

Natural or bioidentical hormones commonly used for perimenopausal and menopausal women include progesterone and the natural estrogens (estradiol, estrone, and estriol), DHEA, and testosterone. The hormones are compounded, to fill a prescription from a physician, in personalized doses and combinations and in unique delivery methods to meet the needs of each woman. Bioidentical hormones manufactured by pharmaceutical companies come in limited doses and delivery methods. Compounded bioidentical hormones are available from specialty compounding pharmacies and only with a prescription from a health care provider, and bioidentical progesterone creams are available over the counter. Over the past decade, millions of women have used bioidentical hormones with great success.

State boards of pharmacy regulate compounded medicines. In addition, every active ingredient used in bioidentical hormone treatment has a U.S. Pharmacopeia monograph. As a licensed physician, I must be able to prescribe freely for my patients to meet their unique needs and that may include prescribing bioidentical hormones.

Many of my patients and those of other doctors who prescribe compounded bioidentical hormones know first hand the relief that these hormones can provide and the importance to a women's overall health. There is a tremendous amount of grass roots support for continuing bioidentical hormones. In October of 2005, Wyeth filed a citizen's petition with the FDA that, if implemented, would severely restrict the hormone treatment options available to women. Over 50,000 women, physicians and pharmacists filed comments opposing the Wyeth petition and supporting the use of bioidentical hormones.

Thank you for the opportunity to submit testimony to the Committee.

Written Testimony of
Steven F. Hotze, MD

Before the Senate Special Aging Committee on April 19, 2007

Federal intervention into the practice of pharmacy, specifically compounding pharmacy, would prove detrimental to the health of many Americans. As a physician who has used compounded pharmacy medications for years and who currently owns a compounding pharmacy, I have a unique perspective on ensuring compounded drugs are readily available to the patients who need them. It is common for physicians to determine that manufactured off the shelf prescription drugs are inadequate to meet the medical needs of an individual patient. Compounding pharmacy helps ensure the individualized treatment that patients both need and demand.

Pharmacists who specialize in compounding prepare customized medications in accordance with a doctor's prescription. These medications, which are not produced by pharmaceutical companies, are prepared using FDA approved bulk products and are provided to meet specific patient needs. Through clinical experience, a physician may decide to use alternative delivery systems (e.g. suppositories, creams, gels, liquids or capsules) for a specific medication. Often compounded medications are not commercially available in the strength requested by the physician. In other cases, a patient may be allergic to the dyes, additives or excipients found in drugs produced by pharmaceutical manufacturers. In this situation, the solution is prepared without the allergy causing ingredients. Compounding pharmacy allows physicians to provide patients with alternative therapies otherwise not commercially available.

The Food, Drug, and Cosmetic Act (FDCA) of 1938 established the authority of the Food and Drug Administration (FDA) over the pharmaceutical manufacturing of drugs. Pharmacies were specifically exempted from FDA regulation and their governance was delegated to the State boards of pharmacy. At that time, all pharmacies practiced the compounding of medications. Pharmacies, including compounding pharmacies, should remain under the regulation of the States.

Most pharmacists, like others in business, realize that their self-interest is best served by operating their enterprises with the interests of their customers in mind. To do otherwise would result in a loss of business. State laws address the issue of fraudulent and dangerous business practices. State boards of pharmacy establish guidelines for safely conducting pharmacy practices and procedures.

The recent results of the Women's Health Initiative study demonstrate the danger of drug company, FDA-approved, counterfeit hormones. Compounding pharmacies are able to offer physicians a natural, safe and effective treatment for women in midlife. That treatment is biologically identical hormone therapy that provides women with the same hormones that their bodies used to produce or currently produce in less than adequate amounts. With the baby boomer population aging, there are millions upon millions of

women who would benefit from the replenishment of these hormones, enabling them to obtain and maintain health and wellness, naturally.

Compounding pharmacies are part of the solution in providing essential care to millions of patients. While regulation at the State level can be improved, we need not to lose sight of the fact that over regulation of the compounding pharmacy profession could result in the denial of the very care and well being of our citizens of which this committee is vitally interested.

In summary, pharmacies, including compounding pharmacies, should continue to be regulated by their State boards of pharmacy to ensure the continued access of patients to the medicines they want, including bioidentical hormones.

Thank you for giving me the privilege of presenting my written testimony.

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STATEMENT OF DAVID G. ADAMS

On Bioidentical Hormones: Sound Science or Bad Medicine?

Before the Special Committee on Aging United States Senate

April 19, 2007

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Statement of David G. Adams
To the Senate Special Committee on Aging

"On Bioidentical Hormones: Sound Science or Bad Medicine?"

April 19, 2007

One of the stated purposes of this hearing is to examine the regulatory challenges posed by pharmacy compounding of "bioidentical" hormones. A key issue in this context is the proper balance between federal and state oversight of compounding. While FDA's statutory authority and policies are relatively easy to identify, the myriad of state laws and regulations poses a greater challenge in understanding the role the states play in the regulatory scheme.

To assist the Committee on this subject, I submit with this statement a report that I co-authored with my associate, Todd Halpern, on our research regarding state laws and regulations governing pharmacy compounding. The report was prepared for Sepracor Inc. While the report does not address the compounding of "bioidentical" hormones specifically (Sepracor does not manufacture and has no interest in hormone products), it does provide general background on protections offered under state law to patients who receive compounded drugs.

Report on State Laws and Regulations Related to Pharmacy Compounding

David G. Adams and Todd H. Halpern[1]

While the states have the primary role in regulating pharmacy practice, Congress has since the enactment of the Federal Food, Drug, and Cosmetic Act (FDCA) in 1938 provided general federal oversight over the promotion, preparation, and dispensing of drug products by pharmacists. In the current debate over the appropriate role of the U.S. Food and Drug Administration (FDA) in regulating pharmacy compounding, opponents of FDA regulation argue that state regulation obviates the need for significant FDA oversight. They oppose FDA enforcement initiatives under the FDCA, as well as recently legislative proposals, intended to protect patients with regard to compounded drugs. The current and proposed protections under the FDCA that are at issue include, among other things, the following:

(1) ***Requirements that pharmacists disclose important information about compounded products to patients and physicians.*** Patients who are dispensed compounded drugs are generally not informed of the special risks posed by compounded drugs and are generally unaware that they are even receiving a compounded drug.

(2) ***Standards for active ingredients that may be used in compounded products.*** Some drugs are compounded from ingredients that have never been approved by FDA for any medical use or that fail to meet minimal reference standards.

(3) ***Documentation of medical necessity for compounded drugs.*** Many compounded drugs are essentially copies of FDA-approved drugs that appear to have no medical justification.

(4) ***Standards for compounding sterile products.*** Many compounded drugs must be sterile but fail to meet sterility standards for FDA-approved drugs, or even lesser pharmacopoeial standards.

(5) ***Restrictions on compounding of copies of commercially available products that are approved by FDA.*** Compounded drugs are not demonstrated safe and effective and substitution of compounded drugs for FDA-approved drugs may subject patients to greater risks.

It is reasonable to ask whether and how the states provide these and other protections to patients. The capacity of the states to protect patients with regard to compounded drugs is a function of legal authority (state laws and regulations) and, where there is legal authority, a function of enforcement policies and resources.

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[1] David Adams and Todd Halpern are attorneys at Venable LLP, Washington, D.C. This report was prepared for Sepracor Inc.

This report addresses the state laws and regulations related to the five protections set forth above.[2] As described more fully below, these laws and regulations do not provide the protections offered to patients under the current or proposed provisions of the FDCA.

FINDINGS

1. Disclosure that a Product Is Compounded

- ***Only six states require that a pharmacy disclose to the patient that the drug being dispensed is a compounded drug.***

In Arizona, pharmacists must include on the label: "a statement, symbol, designation, or abbreviation that the pharmaceutical product is a compounded pharmaceutical product." Ariz. Admin. Code § R4-23-410(I)(4) (2007). In Colorado, the pharmacist must include the following statement on the label of all compounded drugs: "This product was compounded by the pharmacy." 3 Colo. Code Regs. § 719-1 (2007). In Iowa, when a compounded product is to be dispensed in place of a commercially available product, the pharmacist must inform both the prescriber and the patient that the product will be compounded. *See* Iowa Admin. Code r. 657-20.3(1) (2007). In Oklahoma, the pharmacist must include on the label "an appropriate designation that this is a compounded prescription." Okla. Admin. Code § 535:16-10-9 (2007). In Alaska, the patient must be made aware that the compounded product will be prepared by the pharmacist. Alaska Division of Corporations, Business and Professional Licensing, Pharmacy Statutes and Regulations, at Appendix C (2007). In Washington, a compounded drug can be substituted for a commercially available drug only with the written authorization of both the patient and the prescriber. Wash. Admin. Code § 246-878-020(1).

2. Active Ingredients Used in Compounded Drugs

- ***The vast majority of states do not address the quality or types of active ingredients compounding pharmacists may use.***

- ***Of the fifteen states that address the issue, eleven permit the pharmacist to rely on "professional judgment."***

See, e.g., Alaska Division of Corporations, Business and Professional Licensure, Pharmacy Statutes and Regulations, at Appendix C (providing that "a pharmacist shall use the pharmacist's professional judgment to receive, store and use drug substances for compounding prescriptions not found in official compendia").

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[2] This report reflects research performed by examining state statutes and regulations relating to the practice of pharmacy. Our research included searches in various databases (including WESTLAW and LEXIS), as well as review of statutory codes, administrative codes and other compilations published by various states and available online.

- ***Only one state, Utah, requires that active ingredients be approved by FDA for some medical use.***

See Utah Admin. Code r. 156-17b-614(3)(d). Of the three remaining states, one requires that the ingredients meet or exceed USP/NF standards, see Nev. Admin. Code § 639.757, and two require that the chemical be procured from another entity registered by that state's board, *see* 3 Colo. Code Regs. § 719-1.00.24 and Mo. Code Regs. Ann. tit. 20, § 2220-2.400.

3. Determination of Medical Necessity.

- ***No state other than Arkansas requires documentation of medical necessity prior to dispensing a compounded product.***

In Arkansas, a pharmacist must obtain documentation of a "specific medical need" when the compounded product is "essentially a copy" of a commercially available FDA-approved drug product.[3]

4. Standards for Compounding Sterile Pharmaceutical Products

- ***Only four states require compliance with the United States Pharmacopoeia (USP) chapter on sterile compounding.***

The USP, a private entity recognized in the FDCA with regard to certain pharmaceutical standards, has provided a chapter containing standards for sterile compounding (USP <797>) that is intended to be mandatory. The USP standards are far less strict than FDA standards for approved drugs and provide patients with less protection. Although opponents of FDA oversight of sterile compounding point to the USP standards as an alternative to the higher FDA standards, compounding interests have opposed adoption by the states of the USP requirement and the states have generally failed to adopt the USP chapter as a requirement. Only four states have adopted the USP chapter. *See* Utah Admin. Code r.156-17b-19 (2007); N.M. Code R. § 16.19.6.11 (2007); 856 Ind. Admin. Code 1-30-1, *et seq.* (2007); 247 Mass. Code Regs. 9.01(3) (2007).

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[3] The Arkansas rule provides:

> Compounding a drug product that is commercially available in the marketplace or that is essentially a copy of a commercially available FDA-approved drug product is generally prohibited. However, in special circumstances a pharmacist may compound an appropriate quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available *based on documentation provided by the prescribing physician of a patient specific medical need* (e.g. the physician requests an alternate product due to hypersensitivity to excipients or preservative in the FDA-approved product, or the physician requests an effective alternate dosage form) or if the drug product is not commercially available. The unavailability of such drug product must be documented prior to compounding. The recommended methodology for documenting unavailability is to print the screen of wholesalers showing back-ordered, discontinued, or out-of-stock items." *Id.* (emphasis added).

070-02-0001 Ark. Code R. (2007).

- ***Six states have no standards related to the compounding of sterile pharmaceutical products.***

- ***Eight states have standards that fail to address compounding of sterile inhalation solutions.***

Inhalation solutions must be sterile and are currently manufactured by compounding pharmacies on a massive scale. Eight states have addressed sterile compounding of injectable products without addressing inhalation solutions. *See* Ala. Admin. Code r. 680-x-2.19 (2007); Cal. Code Regs. tit. 16, § 1751.02, *et seq.* (2007); D.C. Mun. Regs. Tit. 22, § 1923 (2007); Idaho Admin. Code r. 27.01.01.178 (2007); Ill. Admin. Code tit. 68, § 1330.99 (2007); Kan. Admin. Regs. § 68-13-1 (2007); 201 Ky. Admin. Regs. 2:076 (2007); N.D. Admin. Code 61-06-01-01, *et seq.* (2007).

- ***Most states have no requirements specific to high-risk compounding.***

Many inhalation drugs, as well as other drugs that must be sterile, are being compounded from nonsterile ingredients. The USP defines such compounding as "high-risk" compounding. Because such compounding is very difficult and poses special risks for patients, the USP provides stricter standards for high-risk compounding in USP <797>. Most states that provide standards for sterile compounding fail to address the special concerns posed by high-risk compounding. *See* Ariz. Admin. Code § 4-23-670 (2007); Alaska Division of Corporations, Business and Professional Licensing, Alaska Pharmacy Statutes and Regulations (2007), at Appendix A and Appendix C; Iowa Admin Code r. 657-8.30 (2007); La. Admin. Code tit. 46, §§ 2535(2), 2537; 02-392-018 Me. Code R. § 1, *et seq.* (2007); Md. Code Regs. 10.34.19.01; Minn. R. 6800.8000 – 6800.8008 (2007); Mont. Admin. R. 24.174.1121 (2007); Nev. Admin. Code §§ 639.525(5), 639.684 (2007); N.H. Code R. Ph. 404.01, *et seq.* (2007); N.J. Admin. Code § 13:39-11.1, *et seq.* (2007); N.C. Admin. Code 46.2800, *et seq.* (2007); Okla. Admin. Code § 535:15-19-1, *et seq.* (2007); Or. Admin. R. 855-041-0063 (2007); 14-130-001 R.I. Code R. § 19 (2007); S.C. Code Ann. § 40-43-88 (2007); S.D. Admin. R. 20:51:26:01, *et seq.* (2007); Tenn. Comp. R. & Regs. 1140-7-.01, *et seq.*; 04-030-230 Vt. Code R., part G (2007); Wash. Admin. Code §§ 246-878-040(1), 246-878-050; W. Va. Code R. §§ 15-1-15.2.3, 15-1-16 (2007); Wis. Admin. Code Pharm. Examin. Bd., § 15.01, *et seq.* (2007); 024-059-013 Wyo. Code R. § 10 (2007). Only eight states with sterile compounding standards address high-risk compounding. *See* 070-02-0001 Ark. Code R. (2007); Ga. Comp. R. & Regs. 480-11-0.02, Ga. Comp. R. & Regs. 480-11-.04 (2007); 3 Colo. Code Regs. § 719-1 (2007); 10-522-001 Del. Code Regs. § X (2007); Fla. Admin. Code Ann. r. 64B16-28.820 (2007); Mo. Code Regs. Ann. tit. 20, §§ 2220-2.200, 2220-2.020 (H) (2007); Ohio Admin. Code 4729:19-04, 4729:9-25 (2007); 22 Tex. Admin. Code § 291.26 (2007); 18 Va. Admin. Code § 110-20-411, et seq. (2007).

5. Compounding Copies of FDA-Approved Drugs

- ***The vast majority of states impose no restriction on the compounding of copies of FDA-approved drugs.***

Only eight states impose limitations on substitution compounding. *See* Iowa Admin. Code r. 657-20.3(1) (requiring a "significant difference" from the FDA-approved product, which would include, for example, the removal of a dye for a medical reason such as an allergic reaction); La. Admin. Code tit. 46, § 2533 (2007) (excluding from the definition of compounding "the compounding of drug products that are essentially copies of a commercially available product"); N.M. Code R. § 16.19.30.9 (2007) (requiring that the commercial product not be reasonably available from normal distribution channels in a timely manner to meet patient's needs and that the prescribing practitioner request that the drug be compounded); 14-130-001 R.I. code R. § 1.19 (2007) (excluding from the definition of compounding "the routine preparation, mixing or assembling of drug products that are essentially copies of a commercially available product"); Utah Code Ann. § 58-17b-102(18)(b) (2007) (excluding from the definition of compounding "the preparation by a pharmacist or pharmacist intern of any prescription drug in a dosage form which is regularly and commonly available from a manufacturer in quantities and strengths prescribed by a practitioner"); 024-059-013 Wyo. Code R. § 3(a) (limiting to medications or dosage forms that are not commercially available in the marketplace); 07-02-0001 Ark. Code R. § 1 (requiring documentation provided by the prescriber of a patient specific medical need or the unavailability of the drug product in the marketplace); Wash. Admin. Code § 246-878-020(1) (requiring both the patient and the prescriber authorize in writing the use of the compounded product); Alaska Division of Corporations, Business and Professional Licensing, Pharmacy Laws and Regulations, at Appendix C (requiring the authorization of the prescribing practitioner).

- ***Two states expressly permit such substitution compounding.***

In Georgia and South Carolina, such compounding is specifically permitted when (1) based on the existence of a pharmacist/patient/prescriber relationship and the presentation of a valid prescription drug order; or (2) in anticipation of a prescription drug order based on routine, regularly observed prescribing patterns. *See* Ga. Comp. R. & Regs. 480-11-0.02 (2007); S.C. Code Ann. § 40-43-86 (2007).

CONCLUSION

Congress determined over 60 years ago when it enacted the FDCA that patients receiving compounded drugs, like patients receiving commercially available drugs, are entitled to protection under federal law as well as under state law. While opponents of FDA oversight of pharmacy compounding argue that state regulation is adequate and obviates the need for federal standards, it is clear that state laws and regulations fail to provide many of the basic protections offered to patients under the current provisions of the FDCA and under proposed revisions to the statute.

Dated: May 15, 2007

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