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The Rise and Fall of Estrogen Therapy:

The History of HRT

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Abstract: This paper explores the history of hormone replacement therapy ("HRT"). It focuses on the development and marketing of HRT drugs, the regulation of HRT by the Food and Drug Administration ("FDA"), and the effect medical studies have had on the development, marketing, and regulation of HRT over the years. First, a discussion of the difficulty of defining menopause is explored. Second, the early history, treatments, and attitudes towards menopause are described. Next, the discovery, manufacture, and FDA approval of estrogen are detailed. The subsequent section examines how the pharmaceutical industry created a perception of menopause as a disease in all midlife women. Then, the cost-benefit analysis of HRT is explored through medical studies' connection of HRT to various diseases. Finally, the aftermath of the landmark Women's Health Initiative study is discussed, followed by a few concluding thoughts on what we can learn from the history of HRT.

Introduction

Apparently, in the year 2005, women are still a mystery, even to themselves. Presently, millions of American women near, at, or beyond menopause are confused over estrogen, the female hormone – or, more specifically, estrogen as hormone replacement therapy ("HRT"). Estrogen products were first approved by the Food and Drug Administration (the "FDA") in 1941 for the direct symptoms of menopause: hot flashes and night sweats, vaginal dryness and atrophy. In the following decades, estrogen (either alone or combined with progesterone) had acquired a reputation as an antidote to many of the illnesses and afflictions of aging, and even as a preventative drug for such diseases as osteoporosis, heart disease, and Alzheimer's. Scores of observational and case studies supported the overwhelmingly positive view of hormone replacement therapy, and naturally drug makers and their advertising agencies enthusiastically embraced estrogen as well. After all, this was a billion dollar business.

This is not to say that hormone replacement therapy didn't have its share of ups and downs in the 60-plus years since it was FDA-approved. It did: links to uterine cancer led to a course-correction – the addition of progesterone to help mediate some of the complications for women who still had a uterus (*i.e.* no hysterectomy). And later, more links to other cancers presented themselves. But not until the Women's Health Initiative study was abruptly halted in 2002 were many of the long-heralded benefits of hormone replacement therapy seriously questioned. Ever since the premature stop of the WHI study, estrogen has been thrown back into the world of the unknown. The benefits of temporary use of estrogen for which it was initially-approved in 1941 have not been heavily challenged; rather, the major criticism of HRT today focuses on the risks and effects of long-term use for menopausal symptoms as well as for diseases and purposes other than menopause. The current question is how women should weigh the risks and benefits of using estrogen, because the advice and scientific findings are uncertain at best. An analysis of this question is beyond the scope of this paper (and the knowledge of this author); rather this paper focuses on the history of hormone replacement therapy.

What is menopause?

Since hormones, up until recently, have been promoted as a cure-all for the symptoms of menopause, a good starting question is what is menopause, and what are the symptoms of menopause? If we believe that taking hormones can eliminate a whole range of real or potential problems, then a long regimen of hormones may seem very attractive. But if hormone therapy can only deal with a more limited range of symptoms, the wisdom of taking hormones for years may not be as salient.

Menopause, in its most simple definition, is the time in every woman's life when her period stops, and a woman has technically "reached" menopause when she has not had a period for 12 months in a row.[1] *Meno* is derived from the Greek word for month, and *pause* is derived from the Greek work *pauses*, or halt.[2] It is a normal part of aging for women, and it occurs generally between the ages of forty-two and fifty-eight years old, with the median age at 51.[3] During menopause, a woman slowly produces less of the hormones estrogen and progesterone.[4] Although not every woman going through menopause experiences a noticeable change as a result of the decreased estrogen and progesterone levels other than cessation of menses, many women do experience various symptoms, and varied degrees of symptoms.[5] This is why menopause is often referred to as "the change" or "the change in life."[6] But one of the problems of referring to menopause as a "change," other than simply referring to having a monthly period and then not having one, is that many people (including the medical profession) conflate aging with menopause. Menopause is not synonymous with a woman's midlife; rather it is an event of her midlife.

As a result, many well-respected medical organizations have lists of symptoms that vary wildly and include many symptoms that are best viewed as part of aging instead of specific to menopausal women.[7] There are a few symptoms that everyone can agree on, though. These symptoms may include one or more of the following, both as a woman approaches menopause, and also continuing through menopause:[8]

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[1] U.S. Food and Drug Administration, *Menopause & Hormones Fact Sheet*, *at* http://www.fda.gov/womens/menopause/mht-FS.html (Sept. 2003) [hereinafter *Menopause & Hormones Fact Sheet*].

[2] Sandra Coney, The Menopause Industry: How the Medical Establishment Exploits Women 83 (1^{st} U.S. ed. rev., Hunter House, Inc. 1994) (1991).

[3] Karen J. Carlson et al., The New Harvard Guide to Women's Health 375 (2004).

[4] *Id.*

[5] *Id.*

[6] *Id.* at 374.

[7] Linda Gannon, *Endocrinology of Menopause, in* The Meanings of Menopause: Historical, Medical and Clinical Perspectives 179, 186 (Ruth Formanek ed., 1990).

[8] *See, e.g., Menopause & Hormones Fact Sheet*, *supra* note 1.

♣

Changes in the menstrual cycle, such as a difference between the time between periods or a different flow.

♣

Hot flashes (also known as "hot flushes), which includes getting warm in the face, neck and chest.

♣ Night sweats. (Both hot flashes and night sweats are also referred to as vasomotor symptoms).

♣

Vaginal changes, also referred to as vulvar and vaginal atrophy, when there is dryness, itching, burning, or thinning of the vagina; these changes are also associated with sex becoming painful.

Women who experience significant problems from these symptoms are about 5-15% of the menopausal population.[9] Most of the other supposed mental and physical symptoms of menopause, such as depression, irritability, and sleeplessness are either equally as applicable to midlife men as they are women, or the peak of their occurrence in women preceded menopause and are the result of chronological age or premenstrual syndrome.[10]

[9] CARLSON, *supra* note 3, at 376.

[10] *See, e.g.* G. Bungay et al., *Study of Symptoms in Middle Life with Special Reference to the Menopause*, 281 BRITISH MEDICAL JOURNAL 181, 181-84 (1980); *see generally* National Institutes of Health, *National Institutes of Health State-of-the-Science Conference Statement: Management of Menopause-Related Symptoms March 21-23, 2005* (March 23, 2005 draft) *available at* http://consensus.nih.gov/ta/025/ $025 Menopause INTRO postconf.htm [hereinafter NIH State-of-the-Science Conference Statement]$.

The loss of estrogen at menopause has also been highlighted as the major cause for osteoporosis, or thinning of the bones, and thus osteoporosis has been listed by the FDA as a symptom of menopause.[11] But osteoporosis, which may lead to loss of height and bone breaks, is as much due to old age as it is to a decrease in estrogen, and as such, can be conflated as a symptom that is specific only to menopause.[12]

The Early History of Menopause and its Treatments

One of the earliest known references to menopause is from an Egyptian medical text dated 2000 B.C.: "If a menopausal woman has pain or makes trouble, pound her hard on the jaw."[13] Today's woman going through menopause would almost certainly object, not only to the violence but also to the mere temporary distraction from a sometimes painful, long experience with menopause! Present treatments for difficult menopausal symptoms do not involve a good hard smack, but rather are more likely to be a mixture of diet, exercise, herbal remedies, and prescription remedies.[14] A medical textbook from the era of Renaissance Europe, almost 500 hundred years ago, reflects a similar treatment to today's standards, recommending an herbal remedy with exercise.[15] Specifically, the medical text recommended a "decoction of myrrh and apples" for women who were experiencing problems with menopause, and if that did not work, "a cure may sometimes also be affected by pouring some of this same substance into her sandals, and urging the patient to walk."[16]

[11] *Menopause & Hormones Fact Sheet*, *supra* note 1.
[12] National Women's Health Network, The Truth About Hormone Replacement Therapy: How to Break Free from the Medical Myths of Menopause 160-161 (2002).
[13] Barbara Seaman, The Greatest Experiment Ever Performed on Women: Exploding the Estrogen Myth 7 (2003).
[14] *See generally NIH State-of-the-Science Conference Statement*, *supra* note 10.
[15] *See* Seaman, *supra* note 13, at 7.
[16] *Id.*

In the 1899 Merck Manual Diagnosis & Therapy, a coarse brown powder named Ovariin was prescribed for "climacterica," which is another name for menopause, and other ovaries-related problems.[17] Ovariin was an oral medicine derived from the dried and pulverized ovaries of a cow, and though a primitive attempt at medicating menopausal symptoms, the director of the NIH Women's Health Initiative, Dr. Jacques Rossouw, believes that it may have had some estrogenic effect.[18] The 1899 Merck Manual also contained an additional twenty-eight treatments for woman's climacteric.[19]

One of the conclusions from this observation is that menopause is not necessarily a phenomenon of the modern age, as doctors, pharmaceutical companies and writers might suggest. One school of thought argues that as a result of the considerable increase in average life expectancy in the past 100 years, women have "outlived their ovaries," and thus menopause is simply an artifact of an unexpected recent increase in life span beyond reproductive age.[20] However, there is a fair amount of credible research countering such assertions. For example, an article by Thomas Perls and Ruth Fretts in the *Annals of Human Biology* suggests that just because the average life span has increased over the years, it does not mean that there were not plenty of adults living into what we would consider "old age," and in fact, the mitigating factors of increased death at childbirth a hundred years ago had a skewing effect on the average life expectancy.[21] The article goes on to refute the "outliving one's ovaries" explanation by arguing:

[17] Merck & Co., Merck Manual Diagnosis & Therapy 54 (1899); *see* Seaman, *supra* note 13, at 8.
[18] Seaman, *supra* note 13, at 8.
[19] *See* Merck & Co., *supra* note 17; *id.* at 8.
[20] Thomas T. Perls and Ruth C. Fretts, *The Evolution of Menopause and Life Span*, 28(3) Annals of Human Biology 239, 242 (2001).
[21] *Id.*

> Firstly, though average life expectancy has increased markedly in just the past century, the **human life span has been significantly longer than the age of menopause, probably since the time menopause evolved**. There is no evidence to indicate that we have done something special as a species in even the past millennium that would facilitate a doubling or tripling of the human life span. Certainly there is evidence from Ancient Greece indicative of elder statesmen living well into their 80s and early 90s. Secondly, if menopause was simply an artefact, we would not expect, over the course of evolution, a natural selection for genes that influence when menopause occurs. Contrary to this supposition, genetics does appear to play a role in the timing of menopause; and finally, the nonadaptive hypothesis begs the question of why would the reproductive system fail long before other systems, such as the cardiovascular system?[22]

As such, since menopause is not necessarily a new phenomenon, rather just a more noticeable increase in the incidence of menopause, it is not surprising when books from more than a century ago discuss menopause at length. Some books from more than a century ago viewed menopause as a period of adjustment rather than a disease, and they also wrote about the "change" in validating terms.[23] For example, in George Napheys' 1869 book The Physical Life of Women: Advice to the Maiden, Wife, and Mother, he wrote that:

> after a certain number of years, a woman lays aside those functions with which she has been endowed for the perpetuation of the species, and resumes once more that exclusively individual life which has been hers when a child. The evening of her days approaches, and if she has observed the precepts of wisdom, she may look forward to a long and placid period of rest, blessed with health, honored and loves with a purer flame than any which she inspired in the bloom of youth and beauty.[24]

French physicians of the same time also viewed menopause in a positive light, seeing it as a return to more carefree days, and referring to this period as *le retour d'age*, meaning a return to youth before the time of fertility.[25] In this same spirit, some doctors of the time were urging their female patients to "view menopause as an opportunity to reclaim their lives and to avoid harsh medicines, as hot flashes were natural and not an illness."[26] And in a interesting view that seems to fit nicely in with contemporary recommendations by the FDA and women's health organizations, Thomas Graham wrote in his 1837 book, The Diseases of Females,

[23] *See* SEAMAN, *supra* note 13, at 9.
[25] SEAMAN, *supra* note 13, at 9-10.
[26] *Id.* at 10.

that with the exception for attention to diet and exercise, "little or nothing is required for the management of ordinary cases."[27]

Though these books do exist, and some doctors viewed menopause in a positive light, for the most part, this attitude really was an exception to the rule; through the late 1960s and the beginning of the women's movement, overall attitude of menopause was that people didn't discuss it and it was generally an embarrassing problem.[28] Women, prior to the women's movement in the 1970s, were thought to be ruled by their hormones and thus were inferior to men, making menopause a shameful secret.[29] Women were embarrassed to admit they were going through menopause, and thus did not seek advice for menopausal symptoms, because it would signal the end of their active life.[30]

The Discovery and Manufacture of Estrogen

The modern treatment of menopausal symptoms can be traced back to the pharmaceutical company Merck & Co., Inc., because Merck was the leader in the field of capitalizing on the use of animal glands in medicine.[31] Through the time of World War II, however, drug companies were small-time concerns, making patent medicines that people could buy over the counter at pharmacies, while doctors were likely to use pills and potions made to their own recipe.[32] The pharmaceutical revolution changed this around the time of

[27] Thomas Graham, The Diseases of Females (1837); *see generally NIH State-of-the-Science Conference Statement*, *supra* note 10.

[28] National Women's Health Network, *supra* note 12, at 38-39.
[29] *Id.*
[30] *Id.* at 39.
[31] Seaman, *supra* note 13, at 10-11.
[32] Coney, *supra* note 2, at.183.

World War II, with the discovery and large-scale production of sulfanilamide, and subsequently penicillin, streptomycin, and an explosion of antibiotic products.[33]

At first, it was not research by pharmaceutical companies, but rather research by scientists, such as Dr. Charles Edouard Brown-Sequard, Dr. Edgar Allen, and Dr. Edward Doisy, that led to the current formulation of estrogen.[34] Dr. Brown-Sequard's announcement in 1889 that he had "rejuvenated himself" by injecting "sensitive parts of his body" with a mixture of guinea pig and dog testicle extracts, led to a flurry of research during the 1890s into the field of sex gland extracts as a fountain of youth.[35]

In particular, Dr. Allen and Dr. Doisy teamed up to unlock the key of estrogen research.[36] From 1923 through 1938, they established the existence of estrogen and described its effects, as well as identified all of the female hormones and the relations among them.[37] By the end of their research, the field of hormone research was hot for scientists as well as pharmaceutical companies develop new drugs they could market.[38] The drug manufacturers saw the hormone research as having the potential for curing a wide range of ills, but also having major benefits for those who were not suffering from any problems in the first place.[39] The drugs had the potential for use for menopause, menstruation, beautiful unwrinkled skin, thicker hair, more passionate sex, curing infertility, and birth control, just to name a few.[40]

Drug manufacturers believed that their profits would skyrocket as a result of these drugs, and went out

[33] *Id.*
[34] *See* Seaman, *supra* note 13, at 10-14.
[35] *Id.* at 11-12.
[36] *Id.* at 12; *see* Robert Meyers, D.E.S.: The Bitter Pill 39 (1983).
[37] Seaman, *supra* note 13, at 12.
[38] *Id.* at 13.
[39] *Id.*
[40] *See* i*d.*

courting scientists, especially biochemists such as Dr. James Bertrand Collip.[41] Dr. Collip, co-discoverer of insulin in 1922, was courted by W.J. McKenna of Ayerst[42] Laboratories in 1929, and in 1930 the partnership of Collip and Ayerst Labs produced its first product.[43] The product, called Emmenin, was derived from the late-pregnancy urine of Canadian women, and was introduced in 1930 as the "first orally effective estrogen."[44] However, Ayerst labs almost immediately looked for a new source, because "low activity, high cost, and problems of taste and odor lessened the chances for long-term survival of the product."[45]

Stallions were the next source tried, because they were said to have the most potent estrogen in their urine of any living animal, despite the fact that stallions are male; however, the stallions frequently kicked over their collection buckets, making them an economically unsound source for sustained collection.[46] Mares, in contrast, proved to be a much better collection source, and their urine was "at least two and one half times the potency of human urine."[47] Ayerst dubbed the product Premarin, which is just a contraction of the drug's description: PREgnant MARes's urINe.[48]

In Germany at the same time, a rival team financed by the well-established and wealthy pharmaceutical drug

[41] *Id.*

[42] Ayerst Labs was acquired by American Home Products in 1943, who already had bought Wyeth Labs in 1931. In an effort to "reflect its role as a global research-driven pharmaceutical company committed to solving the world's health problems through leading-edge biotechnology," American Home Products changed its name to Wyeth in March 2002. *See* Wyeth, *Wyeth Timeline*, *at* http://www.wyeth.com/about/

timeline.asp (last visited April 18, 2005); Melody Petersen, *American Home Products is Changing Its Name to Wyeth*, N.Y. Times, March 11, 2002, at C14.

[43] Seaman, *supra* note 13, at 18-20.

[44] *Id.* at 20.

[45] *Id.*

[46] *Id.*

[47] *Id.*

[48] *See* P. Clark, *Canada's Foals*, ASPCA Animal Watch, Fall 1997, at 26-27. Interestingly enough, the most visible opponents of HRT at first were not women's health groups, but animal rights activists who have exposed the cruelty to mares involved in the production of Premarin. An estimated 75,000 pregnant mares are use to produce Premarin and related products. The constantly pregnant mares are kept in small stalls, and their slaughtered foals have become a $9 million per year industry as a delicacy in Belgium, France, and Japan. Animal rights groups estimate that Wyeth-Ayerst will use one less pregnant mare for every 150 women who decide not to take Premarin. *Id.*

company Schering was also working on formulations for the treatment of menopausal symptoms.[49] Adolph Butenandt, a scientist backed by Schering, also used human pregnancy urine to derive the raw materials for a product called Progynon.[50] Progynon, which was essentially the same product as Ayerst's Emmenin, was marketed to German women for the treatment of night sweats and hot flashes.[51] Similar to the Ayerst story, Schering gave up on the human pregnancy urine as a source, and soon switched to a mare's urine product called Progynon 2.[52] Based on Butenandt's work, by 1938, Schering scientists Hans Inhoffen and Walter Hohlweg synthesized ethinyl estradiol, which remains the most popular estrogen used in birth control to this day.[53]

In order to prevent Schering from obtaining a patent on estrogen (and as an effect of their countries' World War II rivalry), a team of English chemists, including Charles Dodds, developed a formula for a cheap[54] yet powerful synthetic, nonsteroidal estrogen and released the formula to the public in the British magazine *Nature* on February 5, 1938.[55] This estrogen, diethylstilbestrol ("DES"), had the same effects as estrogens derived from animals and plants, but was three times more powerful; additionally, anyone could make it because Dodds had relinquished his own patent rights when he published the formula.[56] In publishing his formula, Dodds was conforming to the British custom at the time (and his own opinion) that scientific work was done by scientists working for the public good; thus such discoveries should be made available to the public without having to pay high prices to proprietary pharmaceutical companies.[57] From the

[49] SEAMAN, *supra* note 13, at 22.
[50] *Id.*
[51] *Id.*
[52] *Id.*
[53] *Id.* at 27.
[54] *See* MEYERS, *supra* note 36, at 41. In 1938, the synthetic version of estrogen cost around $2 per gram, while the natural version of estrogen (ethinyl estradiol) cost around $300 per gram. *Id.*
[55] SEAMAN, *supra* note 13, at 35; *see* MEYERS, *supra* note 36, at 41.
[56] SEAMAN, *supra* note 13, at 36. Diethylstilbestrol came to be known as DES in the United States and stilbestrol in England. *Id.*; *see* MEYERS, *supra* note 36 at 41-2.
[57] *See* MEYERS, *supra* note 36, at 41-2.

beginning, though, Dodds was concerned about the cancer-causing potential of DES, as well as any harmful noncancerous effects of introducing a foreign substance into the complex female reproductive cycle.[58]

Other scientists confirmed Dodds' suspicions. Even as early as 1932, data suggested that estrogens induced mammary cancer in mice,[59] and throughout the 1930s, there were already numerous warnings published in prestigious journals about Butenandt's estrogens.[60] In December 1939, the *Journal of the American Medical Association* published editorials urging a thorough investigation of DES prior to approval by the Food and Drug Administration ("FDA"), after the journal caught wind of rumors that many requests to market DES were being filed at the FDA, because of the possibility of carcinogenesis and the risk of putting it on the market due to the unknown long-term effects.[61] One of the editorials, "Estrogen Therapy – A Warning," remarked:

> Regarding conflicting reports about DES... apparently **a thorough investigation of this compound is in order before it can be prescribed for routine therapy**... **The possibility of carcinoma induced by estrogens cannot be ignored**... it appears likely that the medical profession may be importuned to prescribe to patients large doses of high potency estrogens, such as [DES], because of the ease of administration of these [products].[62]

A second editorial in the same issue of *JAMA* was written by the Council on Pharmacy and Chemistry that discussed negative side effects of DES.[63] In observing DES in menopausal use, various side effects,

[58] *Id.* at 42.

[59] *See* MEYERS, *supra* note 36, at 54. The French scientist A. Lacassagne reported incidence of mammary cancer in mice after treatment with estrogens in 1932. *Id.*

[60] SEAMAN, *supra* note 13, at 38, 44; *see* MEYERS, *supra* note 36, at 42, 54. Dodds himself published a study in the *British Medical Journal* on September 10, 1938, only a few months after publishing the formula for the synthesis of DES, that showed DES caused miscarriages in rate and rabbits. Also, in 1939, Dr. Charles Geschickter reported in *Radiology* that mammary cancer has been produced in rats known to have no history of spontaneously developing cancer by injecting them with DES as well as with other estrogens. Also, in 1939 and 1940, faculty from the Northwestern University Medical School published a numbers of articles showing changes to the genitalia of animal fetuses when exposed to DES and other estrogens. MEYERS, s*upra.*

[61] *See* SEAMAN, *supra* note 13, at 44; MEYERS, *supra* note 36, at 77 (quoting from *JAMA* December 23, 1939 articles by MacBryde et al., Buxton & Engle, and Shorr et al.)

[63] *Id.* The Council on Pharmacy and Chemistry (an advisory group of physicians and scholars) included George N. Papanico-

such as "nausea, vomiting, abdominal stress, anorexia, and diarrhea... associated with the gastrointestinal tract... [and] were frequent enough to alarm not only the patients but also the investigators."[64] In conclusion, the Council warned that:

> because the product is so potent and because the possibility of harm must be recognized, the Council is of the opinion that it **should not be recognized for general use... at the present time**... and that **its use by the general medical profession should not be undertaken until further studies** have led to a better understanding of the functions of the drug.[65]

Another editorial in *JAMA* four months later commented on the use of small doses of estrogens to treat patients in order to avoid toxic side effects.[66] The editorial stated: "It would be unwise to consider that there is safety in using small doses of estrogens, since it is quite possible that the same harm may be obtained through the use of small doses of estrogen if they are maintained over a long period."[67]

Regardless of such warnings in scientific journals, thirteen drug companies had applied to the FDA to market DES by 1940.[68] After all, DES was cheap, effective in oral form, an excellent copy of natural estrogens and containing all the same powers, and best of all, unpatented![69] Thus, DES was available for anyone who wanted it without charge (*i.e.* no licensing fees or royalties) and limited research costs.[70] There was huge potential for high profit margins because most traditional overhead costs were eliminated, even though the

laou, originator of the Pap smear, and Ephraim Shorr, who as an FDA adviser, several years later recommended against federal approval of DES. *See* MEYERS, *supra* note 36, at 77.

[64] *Id.*

[66] MEYERS, *supra* note 36, at 77 *(*quoting *JAMA* April 20, 1940 article).

[67] *Id.* Interestingly enough, this statement foreshadowed the FDA's stance more than 60 years later. *See infra* p. 65 and note 373.

[68] *Id.* at 78. The companies were Abbott Laboratories, Ayerst, McKenna & Company, George A. Breon & Company, Charles E. Frosst & Company, Eli Lilly, Merck, William S. Merrell Company, Sharp & Dohme, Inc., E.R. Squibb & Sons, Upjohn, Winthrop Chemical, and Wyeth Laboratories. *Id.*

[69] *Id.* at 76.

[70] *Id.*

companies would still have to incur marketing and production costs.[71]

The FDA, however, put the drug companies in a catch-22. The FDA let the companies know that it would turn down any application, but that the companies had the right to protest.[72] A protest by the companies was not really a good option, because the warnings about cancer that were published in scientific journals were not yet widely known by the public; once the media caught wind of the cancer warnings, it would almost certainly be brought to the public's attention, backfire in the companies' collective face, and shut the door to DES marketing permanently.[73]

The other option was for the companies to quietly withdraw their applications, regroup, and make another attempt to get approval later; this is exactly what the companies did on December 30, 1940, and the withdrawal was approved the by the FDA on January 17, 1941.[74] Instead of individually fighting the FDA in the public domain, the drug manufacturers held a meeting and decided the best course would be to withdraw all of their applications from the FDA and wage a targeted campaign as a group.[75] This group was to become the precursor to the formation of the official pharmaceutical lobbying group in 1951, Big Pharma, the powerful industry lobby.[76] The companies agreed that pooling their resources was essential in order to gather a master file on DES and work towards winning government approval the next time around.[77] Four companies – Eli Lilly, Winthrop, Upjohn, and Squibb – led the effort and were known as the "Small Committee" and would do the bulk of the work on behalf of all of the companies.[78]

[71] *Id.*
[72] SEAMAN, *supra* note 13, at 44.
[73] *Id.*
[74] MEYERS, *supra* note 36, at 79.
[75] SEAMAN, *supra* note 13, at 44.
[76] *Id.*
[77] MEYERS, *supra* note 36, at 79.
[78] *Id.*; SEAMAN, *supra* note 13, at 44.

J.A. Morrell of Squibb himself collected 257 articles on DES showing the drug's use in clinical situations.[79] By gathering articles showing the clinical use (*i.e.* how doctors would use the drugs with their human patients), rather than articles solely about laboratory tests on animals, the committee wanted to emphasize to the FDA that DES would be safe for specified uses in humans.[80] Also, by stressing the clinical (*i.e.* human) impact of DES, the Small Committee wanted to keep attention away from the theoretical concerns and published animal studies showing that DES was well-known for causing cancer.[81]

The doctors of these (and other) pharmaceutical companies were only one part of the DES campaign. The other part involved Carson Frailey, the Washington lobbyist-publicist who was the executive vice president of the trade group the American Drug Manufacturers Association and had been an industry official since the 1920s.[82] Frailey knew all the right people in the middle levels of government – the civil servants and bureaucrats who would be around long after their politically-appointed bosses and the presidents who appointed them were gone.[83]

Frailey started out by organizing a meeting on January 28, 1941.[84] The meeting's purpose was to gather doctors from across the country so that they would write to the FDA in favor of DES approval; fifty-four doctors agreed to write to the FDA, describing their clinical experiences with a total of more than 5,000 patients.[85] Only four doctors felt that DES should not be approved.[86] After five months, the lobbying campaign seemed to be having the desired effect, because on May 12, 1941, Frailey sent letters to the Small Committee members saying: "The time now seems propitious to suggest that you re-file [your] new

[79] MEYERS, *supra* note 36, at 81.
[80] *Id.*
[81] *Id.*
[82] *Id.* at *79;* SEAMAN, *supra* note 13, at 44.
[83] MEYERS, *supra* note 36, at 79.
[84] SEAMAN, *supra* note 13, at 45.
[85] *Id.*
[86] *Id.*

drug application for [DES]. I am making no commitments that the application will be permitted to become effective, but the suggestion offered has official background."[87]

The FDA officially approved DES for use in four types of treatments on September 19, 1941, including menopausal symptoms.[88] Once DES was approved for a few limited uses, the law permits DES to be used by physicians for off-label purposes in an experimental capacity; the FDA does not interfere with a doctor's right to practice medicine, even though the doctor might be using a legal drug for purposes other than which it had been approved by the FDA.[89] Thus, immediately after the FDA's initial approval of DES for use with menopausal women, pharmaceutical companies and physicians became more interested in using DES to prevent miscarriages, and began using it for this purpose.[90] Even though the doctors were legally permitted to use DES in this off-label capacity, in 1947, the FDA officially approved DES for use in preventing miscarriages – which later proved to be the most controversial and harmful use of DES.[91]

Dr. Allen and other scientists, meanwhile, had been continuing to research, focusing on the role of estrogens in female cancers.[92] In April 1941, just as the FDA was reexamining applications from Eli Lilly, Squibb, and several other drug companies to approve estrogen products for the treatment of menopause, Allen published an article in the journal *Cancer Research* on the propensity of estrogens to cause cervical cancer in animals, and concluded that estrogen was a carcinogen: "The high incidence of cervical cancer in these experimental groups emphasizes that estrogen is a very important factor, not merely an incidental one, in

[87] MEYERS, *supra* note 36, at 81-82.
[88] *Id.* at 82. The officially approved treatments were: (1) menopausal symptoms (including hot flashes); (2) senile vaginitis (in postmenopausal women this inflammation can lead to an ulcertation of the vaginal cells); (3) gonorrheal vaginitis (a vaginal infection that can lead to serious complications); and (4) to prevent lactation in women who had recently given birth. *Id.*
[89] *See* Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration: Notice of Proposed Rule Making, 37 Fed. Reg. 16503 (August 15, 1972).
[90] MEYERS, *supra* note 36, at 82.
[91] *Id.*
[92] SEAMAN, *supra* note 13, at 14.

cervical carcinogenesis."[93] Allen went on to point out that one reason why in other studies the incidence of cervical cancer in mice had been low is that "mammary cancer appears at an earlier age than does cervical cancer, and consequently animals may die of the former; *i.e.*, many of them do not live long enough fro the cervical cancer to develop."[94]

Thus, by the time the FDA was considering approval of estrogen products, it should have been aware that there were multiple well-run animal studies going on at major research centers showing the ability of DES to cause cancer as well as interfere with the normal development of the sexual and reproductive systems of offspring born to pregnant animals treated with DES.[95] Despite this knowledge, the FDA approved, in 1941, the use of DES for the treatment of menopausal symptoms and menstrual disorders.[96] DES and other estrogen products were approved for use under the newly revised Food, Drug and Cosmetic Act, which in 1938 underwent a major change in its standard of approval before companies could sell the product to the public.[97] The new standard now required that the drugs up for approval met certain showings of purity, strength, consistency, and safety (though, not of effectiveness).[98] In fact, DES was the first drug that was not life-saving to be tested under the new standard.[99] The new standards were not necessarily a bad thing for the pharmaceutical industry; in fact, with the government's seal of approval giving "ethical backing" to new drugs, it helped to increase the sales of drugs.[100]

Menopause as a "disease"

[93] *See id.;* MEYERS, *supra* note 36, at 55.
[94] *See* MEYERS, *supra* note 36, at 55.
[95] *Id.*
[96] *See supra* p. 16 and note 88; MEYERS, *supra* note 36, at 62; Premarin, made of conjugated equine estrogens, was approved by the FDA on May 8, 1942. SEAMAN, *supra* note 13, at 48.
[97] MEYERS, *supra* note 36, at 74, 87.
[98] *See* Food, Drug, and Cosmetic Act, 75 P.L. 717, 75 Cong. Ch. 675, 52 Stat. 1040 (1938); *id.*
[99] MEYERS, *supra* note 36, at 74, 87.
[100] *Id.* at 75.

Prior to the synthesis of estrogen and its use as a medical treatment, the medical profession was rather uninterested in middle-aged women.[101] Any complaint that middle-aged women brought to their doctors was seen as part of the transition from youth to old age and could be blamed on menopause.[102] But for the most part, doctors did not have any miracle cure for the symptoms of menopause, nor any label to define what women were experiencing.[103]

In modern medicine, however, the medical industry has "discovered" the middle-aged woman and her disease.[104] As Ivan Illich describes in his book, Limits to Medicine:

> In the detection of sickness, medicine does two things: it "discovers" new disorders, and it ascribes these disorders to concrete individuals. To discover a new category of disease is the pride of the medical scientist. To ascribe the pathology to some Tom, Dick, or Harry is the first task of the physician acting as a member of a consulting profession. Trained to "do something" and express his concern, he feels active useful, and effective when he can diagnose disease.[105]

For most of the last fifty-plus years since the estrogen has been an FDA-approved treatment for menopausal symptoms, the middle-aged woman was no longer ignored, but became a prime target for the treatment of her new disorder: estrogen deficiency syndrome.[106] Estrogen therapy was thus a useful tool help to replace a biological deficiency of estrogen that started at midlife.[107] Since all women aged 40-60 go through menopause, the number of patients afflicted with estrogen deficiency syndrome (at the time and in the future) was enormous – the ultimate discovery! And with the discovery of this new disease, the doctor would

[101] *See* Coney, *supra* note 2, at 19.
[102] *See id.* at 18.
[103] *See id.* at 18-19.
[104] *See, e.g., id.* at 18.
[106] *See* Coney, *supra* note 2, at 19.
[107] Susan E. Bell, *The Medicalization of Menopause, in* The Meanings of Menopause: Historical, Medical and Clinical Perspectives, *supra* note 7, at 43, 53.

feel "active, useful and effective" because every middle-aged woman who came through his office would be diagnosed and treated.

Therefore, during the second half of the twentieth century, the medical industry had determined that the middle-aged woman, in her normal state, was sick; the idea of normal aging in women had been collapsed into a definition of pathology.[108] The perception of menopause had changed from simply the end of menstruation or a life stage, to one of an illness that no woman can escape.[109] Menopause, like hypothyroidism and diabetes, was a deficiency disease and therefore it, too, could be treated with a replacement therapy.[110] As one physician said in late 1975, even in the face of a possible estrogen-cancer link, "I think of the menopause as a deficiency disease, like diabetes. Most women develop some symptoms, whether they are aware of them or not, so I prescribe estrogens for virtually all menopausal women for a indefinite period."[111]

This change in perception of menopause can be linked, as it is in many other new "disorders" like erectile dysfunction and irritable bowel syndrome, to a marketing phenomenon by pharmaceutical companies called "if you build it, they will come."[112] Because pharmaceutical companies have a profound influence on the ways people define and understand diseases, the "if you build it mentality" is often successful in creating a new disease class.[113] After all, pharmaceutical companies have tremendous resources to invent drugs where none existed before, design clinical research to position those drugs in the marketplace, fund patient and professional groups who speak through the popular media, and vigorously promote awareness of their medicines and the ailments they are designed to treat. [114]

[108] Coney, *supra* note 2, at 18-19.
[109] *Id.* at 19.
[110] Bell, *supra* note 107, at 54.
[111] Jane E. Brody, *Physicians' Views Unchanged on Use of Estrogen Therapy*, N.Y. Times, Dec. 5, 1975, at 45.
[112] *See* Katharine Greider, The Big Fix: How the pharmaceutical industry rips off American consumers 118 (2003).
[113] *Id.* at 117-118.
[114] *Id.* at 117.

An executive in drugs marketing noted that "it's not just about branding the drug; it's branding the condition and, by inference, a branding of the patient... What kind of patient does a blockbuster create? We're creating patient populations just as we're creating medicine, to make sure that products become blockbusters."[115] An article in the *British Medical Journal* agreed, and labeled the pharmaceutical companies' behavior "disease-mongering" because the companies are really selling drugs to essentially healthy people.[116] Drug companies campaign to raise awareness among doctors and consumers about a given disorder with the implicit understanding that there is a cure, and the cure is, of course, the pharmaceutical company's new drug.[117] Hormone replacement therapy is probably one of the best examples of the "if you build it, they will come" phenomenon, because vast numbers of women have taken it to prevent health problems associated with a "risk factor" that literally every woman will experience if she lives long enough: menopause.[118] As a result, the use of hormone replacement therapy was successfully marketed as not only a treatment for menopausal symptoms of estrogen deficiency, but also as a preventative therapy to stave off any adverse effects from estrogen deficiency that come with menopause.

Although estrogen therapy was approved for treatment of menopausal symptoms in 1941, the real takeoff for marketing and prescribing estrogen did not happen until more than two decades later.[119] The female population in the 1940s, 50s and 60s had been primed since birth to accept their proper role in society as a mother, caregiver, and housewife and were thus the perfect target for the marketing of estrogen.[120] The

[115] *Id.* at 118.
[116] *Id.* at 118-119.
[117] *Id.* at 119.
[118] *Id.* at 120.
[119] *See* CONEY, *supra* note 2, at 40-43.
[120] *See id.*

middle-aged woman during these decades had already fulfilled most of her major purposes by bearing and raising children, and only had the role of housewife left after her children were grown and left the house.[121] In the 1960s, the medical industry picked up on the opportunity to exploit the many housewives who suffered from what Betty Friedan dubbed "the problem that has no name," namely that of the emotional trauma over society's perception of her diminishing feminine role. [122] Since biologically these midlife women were going through menopause, any emotional or physical complaint would be seen as a symptom of menopause.[123]

Thus, during the 1960s, midlife women were targeted by a flurry of advertisements for tranquilizers and antidepressants promising a cure for the symptoms of menopause.[124] These advertisements created a stereotype of the menopausal woman as beset with psychological devils, anxious about her femininity and her waning attractiveness, and grieving over the loss of her ability to bear children.[125] By creating a medical condition, pharmaceutical companies had ingeniously diagnosed the menopausal woman as ill and in need of treatment.[126] The success of this campaign is evident from the numbers of drugs designed to treat the menopausal woman's mental condition: during this period, women were more likely than men to be using psychotropic drugs;[127] from 1966-1971, the use of tranquilizers such as Valium had increased 110% and antidepressants had increased by 320%;[128] and from 1966-1971, 17% of all women (compared to 8% of men) had been prescribed psychotropic drugs and the median age for women using them was 44 years.[129] The widespread prescription of tranquilizers and antidepressants to housewives eventually led to its practice being discredited, but not before the way had been paved for acceptance of the next category of drugs that would

[121] *Id.* at 40.
[122] *See* Betty Friedan, The Feminine Mystique (1965); Coney, *supra* note 2, at 66-68.
[123] *See* Coney, *supra* note 2, at 68.
[124] I*d.* at 66-67.
[125] *Id.* at 67.
[126] *Id.*
[127] Lawrence Linn & Milton Davis, *The Use of Psychotherapeutic Drugs by Middle-Aged Women*, 12(4) Journal of Health and Social Behavior 331-40 (1971).
[128] Coney, *supra* note 2, at 68-69.
[129] *Id.*

"treat" menopause.[130]

The prominent gynecologist Dr. Robert A. Wilson made it his personal crusade to continue the legacy of treating menopause as a disease that could respond to medical treatment.[131] Wilson wrote a book in 1966 called Feminine Forever that identified the previously unrecognized and widespread health threat of estrogen deficiency, and proposed a solution to this problem.[132] Wilson's work seems, by today's standards, transparently misogynistic.[133] He called menopause a state of "living decay," unabashedly touting estrogen as a way to make older women more attractive and "pleasant to live with."[134] Wilson wrote that the "tragedy of menopause" is that it "often destroys her character as well as her health."[135] Wilson wanted to save women from this horrible fate by having women use estrogen from "puberty to grave" in order to abolish menopause and keep women "feminine forever."[136] He was playing into the fantasy of a fountain of youth and was succeeding.

Wilson can also be viewed as a savvy entrepreneur and an evangelist.[137] There is no doubt that Wilson made money from the sale of his book (100,000 copies sold in the first seven months alone) and the thousands of patients that flocked to him to be treated (by 1966 he said he had treated 5,000 women with estrogen).[138] But Wilson's self-image – that of a medical saint – was likely what drove his desire to spread his message.[139] He

[130] *Id.*
[131] *Id.*
[132] Robert A. Wilson, Feminine Forever (1966).
[133] Greider, *supra* note 112, at 121.
[134] Wilson, *supra* note 132.
[135] *Id.*
[136] *Id.*
[137] Coney, *supra* note 2, at 69.
[138] *Id.* at 70.
[139] *Id.*

had founded a private trust in 1963, the Robert Wilson Research Foundation, for the purpose of promoting estrogens.[140] Wilson recruited the makers of hormones to support not only his book but also his foundation and his many public appearances.[141] Three such drug manufacturers contributed to his foundation in 1964: $17,000 from Searle, since Wilson was trying to show that their oral contraceptive, Enovid, was a way to prevent menopause if indefinitely used; $8,700 from Ayerst, the maker of the estrogen Premarin; and $5,600 from the Upjohn Corporation, whose progestin drug Provera Wilson was testing for use in menopause.[142] And 1964 was not the only good fundraising year: the Wilson Foundation received funding totaling more than $1.3 million from the pharmaceutical industry.[143]

In November 1966, Wilson received a slap on the wrist from the FDA, who pronounced Wilson "unacceptable as an investigator for drugs in the menopause" because he was disseminating promotional material claiming hormones has been shown to be effective to "'prevent aging,' a condition for which they had never been proved to work."[144] Despite FDA's disapproval of Wilson, his theory on menopause was not easily quashed. Feminine Forever was widely excerpted in such popular women's magazines as *Vogue*, and during the late 1960s and early 1970s more than 300 articles promoting Wilson's message on estrogen use appeared in women's magazines.[145]

Drugmakers, too, ran with Wilson's message through various means. Ayerst Laboratories helped to fund

[140] *Id.*
[141] Greider, *supra* note 112, at 120.
[142] Seaman, *supra* note 13, at 52.
[143] Coney, *supra* note 2, at 70.
[144] Seaman, *supra* note 13, at 51.
[145] Coney, *supra* note 2, at 70.

the writing of Feminine Forever, provided Wilson with editorial assistance, and even surreptitiously bought enough copies at retail to push it onto the best-seller lists.[146] Ayerst then kept the buzz going around the tantalizing title and Wilson's promise of staying young and sexy well after the book was out of print.[147] Ayerst and other pharmaceutical companies wove Wilson's message throughout advertisements, confirming the menopausal woman as anxious about aging and emotionally unstable, both of which can be corrected with estrogen therapy.[148] A 1972 promotional film said: "The physical alterations that are associated with the menopause may induce emotional changes. When a woman develops hot flashes, sweats, wrinkles on her face, she is quite concerned that she is losing her youth – that she may indeed be losing her husband."[149] From just a small sample of print ads for estrogen therapy, Wilson's message comes across loud and clear:[150]

♣

The menopausal woman in the 1950s and 1960s ads is sad, anxious, and emotionally out of control. Typical of such images is a 1960 ad by Hoffman-La Roche Laboratories for the drug Marplan showing a sad woman in a barren, dreary city with the caption: "When 'change of life' seems the end of life. With the advancing years, woman's vulnerability to depression often becomes intense. The future looms insecure: menopausal symptoms spark somatic concern. And as she faces losing a symbol her femininity, even suicidal panic may supervene." An Ayerst ad also displays three very depressed looking women with the caption: "The Estrogen Deficient Woman: The Needless Martyr."

♣

[146] SEAMAN, *supra* note 13, at 56.
[147] *See id.* at 56.
[148] *See* CONEY, *infra* note 150 and accompanying text.
[149] GREIDER, *supra* note 112, at 121.
[150] *See* CONEY, *supra* note 2, at insert between 246-247. The examples of the ads in the following bullet points are chosen from a section in Coney's book where copies of ads from this time are displayed. *Id.*

The "treated" menopausal woman in other ads is a happy, trouble-free wife standing proudly next to her husband, because otherwise she would have emotional and physical problems and be a burden to those around her. An ad for Hoffman-La Roche's Menrium says: "His wife has a lot of different menopausal symptoms, but only a few really irritate him. Her hot flashes, her vertigo, her palpitations – that's *her* problem. What really bothers him is her nervousness, her irritability, and her excessive anxiety, often expressed by endless "book-shuffling, chain-smoking, reading-lamp" insomnia!. . . [Menrium] takes care of the vasomotor symptoms as well as the emotional symptoms. That means the symptoms that bother his wife the most. And the symptoms that irritate him the most. So, to help them both get through menopause, remember Menrium."

♣

In ads from the 1950s-1970s, women who have been treated with estrogen therapy have happy, smiling faces. All of these women have been "cured" by hormones, giving women a "sense of well-being" or "joie de vivre," and making women "feel better." For example, one ad notes: "Her days and evenings are full. It's a busy, involved, normal life."

The ads were quite effective: doctors were willing to jump on the estrogen bandwagon, absorb the messages and prescribe the menopausal woman with drugs for her condition. This was despite the fact that estrogen had been approved for menopausal symptoms before the 1962 amendments to the Food, Drug, and Cosmetics Act required a stronger show of safety.[151] The successful public marketing of many tenuous benefits of estrogen had also preceded the 1962 requirements for contraindications, side effects and effectiveness, or any restrictions on what companies could claim in ads.[152] Doctors have always been able to prescribe

[151] *See supra* p. 18 and note 97.
[152] *See* MEYERS, *supra* note 36, at 74, 87.

FDA-approved medications for off-label uses as they see fit, and for whichever patients and conditions they choose.[153] Neither the FDA nor states (who license doctors) have ever had any authority over doctor's decisions.[154] Thus, doctors could be convinced of estrogen's off-label benefits through ads, or samples sent by pharmaceutical companies, or expensive dinners and "consulting fees" paid for by the drug makers.[155]

The well-run marketing campaigns by pharmaceutical companies had created a general accepted characterization of menopausal women as estrogen deficient, and thus there were many doctors who prescribed estrogen therapy for long-term replacement of estrogen.[156] In 1976, two researchers, who the previous year had linked estrogen to uterine cancer, commented on this practice:

> The 'estrogen forever' philosophy has fortunately not dictated the standard of therapy of the menopause [in the Medical Center where the researchers works]... Yet well-meaning **physicians frequently prescribe these hormones, giving some patients estrogen even before the menopause and continuing it in some for the duration of their lives**. Adverse effects may become... manifested only after years of exposure... By then many patients have become psychologically addicted to estrogen and... object to its discontinuance. These chronically exposed women are uniquely jeopardized.[157]

Also worthy of note is that although every middle-aged woman could be diagnosed as being estrogen-deficient, it was the middle-class Caucasian women who were the particular objects of interest to the pharmaceutical companies.[158] This subset of women was health-conscious and likely to see a doctor regularly.[159] They also had more disposable income at midlife than any other stage and could afford to pay for medical services.[160]

[153] *See supra* p. 16 and note 89.
[154] *Id.*
[155] *See* Jay S. Cohen, Overdose: The Case Against the Drug Companies: Prescription Drugs, Side Effects and Your Health 11 (2001); Meyers, *supra* note 36, at 74, 87.
[156] *See* Cohen, *supra* note 155, at 76-79.
[158] Coney, *supra* note 2, at 20.
[159] *Id.*
[160] *Id.* at 21.

Finally, middle-class Caucasian women placed high value on their physical attractiveness.[161] Their health and attractiveness were regarded as assets, important to their social status and sexual marketability because, in society's eyes, when women reach middle-age their worth is unavoidably declining.[162] The harsh societal view of aging women, and specifically middle-class Caucasian women, was ripe for exploitation by the medical industry. Thus a middle-aged, middle-class Caucasian woman was, and still is, especially susceptible to messages that target those fears and promise prevention of illness or everlasting youthful femininity.[163]

Not surprisingly, advertisements were not the only method used to reach the pharmaceutical companies' target audience. *The* outstanding New York public relations woman, Sandra Gorney, was hired by Ayerst Labs and did quite a spectacular job of legitimizing and iconizing the philosophy of Feminine Forever for a decade after its publication.[164] Ayerst Labs provided a "service for media" through the Information Center on the Mature Woman – which Sandra Gorney was hired to direct.[165] Magazine and newspaper editors frequently published features on current menopause questions and controversies supplied by Gorney, whose style was breezy and readable but authoritative.[166] Gorney's free newsletters and background papers were attributed, if at all, to the Information Center on the Mature Woman, even though, to Gorney's credit, her mailings to the media did acknowledge the Ayerst support.[167] According to some calculations, the sales of Premarin, Ayerst's hormone replacement drug, doubled or even tripled in the wake of Feminine Forever and

[161] *Id.*
[162] *Id.*
[163] *Id.* at 22. Although middle-aged Caucasian women were a good marketing target, they were also a good test subject. Since marketing was successful in targeting this group, they were the most prevalent users of estrogen therapy; because they were overall more likely to be healthy, this subsequently helped drug companies when good medical study results (with these women as the majority of test subjects) came out in favor of preventative use of estrogen. *See infra* pp. 35, 50 and notes 198, 294.
[164] SEAMAN, *supra* note 13, at 58-59.
[165] *Id.* at 59.
[166] *Id.*
[167] *Id.*

the PR of Sondra Gorney and stayed at record-breaking levels until the mid 1970s.[168] By 1975, Wyeth's product, Premarin, had become the fifth leading prescription drug in the United States.[169]

Celebrity endorsements by Lauren Hutton and Patti LaBelle were another way to capture public attention and legitimize the treatment of menopausal symptoms with hormone replacement therapy: in the 1980s, these women appealed to health-conscious concerns about disease prevention and women's determination to remain vital beyond middle age.[170] They endorsed the idea that HRT would not only help women get past the hot flashes and other symptoms of menopause (including, Hutton broadly hinted to *Parade Magazine,* looking older and feeling cranky) but, used long-term, it would also protect them from Alzheimer's, heart disease, stroke, osteoporosis, and colon cancer.[171] From these endorsements, the message came across loud and clear: it was admirable to take HRT, and it was questionable *not* to take it.[172]

The pharmaceutical companies had (and still have) another way of reaching the public: medical experts who appear on morning shows and give interviews to magazines and newspapers.[173] This was a sneaky way of promoting the benefits of hormone therapy without having to identify any connection to the drug company, and needless to say, a successful route under the cloak of legitimate, independent, professional opinion.[174] The public goes unaware of such connections, of course.

[168] *Id.* at 58.
[169] Gina Kolata & Melody Petersen, *Hormone Replacement Study A Shock to the Medical System,* N.Y. Times, July 10, 2002, at A1.
[170] Greider, *supra* note 112, at 122.
[171] *See* J. Tarshis, *Celebrities Reveal Their Secrets*, Parade, March 14, 2000, at 10-15; *id*.
[172] *See* Greider, *supra* note 112, at 122.
[173] *See* Seaman, *supra* note 13, at 60.
[174] *See id.*

But on November 20, 2002, reporter Sharyl Attkisson "outed" two of the most widely quoted menopause experts, Dr. Lila Nachtigall and Dr. Wulf Utian on the *CBS Evening News*, making them publicly acknowledge their receipt of financial support from the makers of Premarin and other hormones.[175] Both Nachtigall and Utian signed a disclosure statement a few weeks earlier, in connection with a speaking appearance at a workshop on menopausal hormone therapy at the NIH, that required them to declare whether they had any financial ties to drug companies.[176] Neither doctor acknowledged any such connections on this disclosure statement.[177] However, as Attkisson reported:

> The selling of HRT was a coup... but a lot of the claims weren't backed by serious science... **women never knew the same doctors promoting the wonders of HRT often had a vested interest in the drug's success**. Much of the information that got into print was bolstered by quotes from respected experts such as Dr. Nachtigall... Readers weren't told that Nachtigall is also a paid speaker for at least eleven drug companies including Wyeth[178] – the biggest maker of HRT drugs....Dr. Utian, another widely quoted specialist who is Director of the North American Menopause Society, has, as it turns out, gotten large grants and support from Wyeth.[179]

Although both doctors denied that financial support meant they were biased, Dr. Utian even commented that "when you see a magazine article and see a quotation from an expert, I think it's almost impossible to know whether there's a conflict of interest or not.[180] This is not to say that every medical expert cannot be trusted to be unbiased, or completely free from ties to pharmaceutical companies, but rather that their advice should be questioned in the first place to see if it is biased.

But because the public is generally unaware that pharmaceutical companies have such success shaping public opinion, the huge marketing efforts by pharmaceutical companies like Ayerst paid off – the rhetoric

[175] *Id.*
[176] *Id.*
[177] *Id.*
[180] *Id.*

of a panacea for a whole host of female concerns from aging to diseases was accepted by a medical profession and public that were willing to buy into the drug-company-created fantasy: Premarin became the number one prescribed in the United States in 1992, and 1997 it became the first Wyeth product to reach $1 Billion in sales – even with the ups and downs after 1975, Premarin remained in the top 50 prescribed drugs from 1966 until 2002.[181]

The Tumultuous Cost-Benefit Analysis of HRT

"For the midlife woman, [the medical treatment for menopause is a] paradox, for it contains both potential benefit and potential harm. The trick is to gain the first, while avoiding the second." – Sandra Coney, author of The Menopause Industry[182]

The ability of women to competently parse out information about their new "disorder" has been nearly impossible. The complexity of the issues and risks of hormone replacement therapy has made a decision regarding its use a daunting task to tackle alone. Thus women have had to rely on the mediating influence of their physicians, or alternatively, the simplified versions of medical wisdom in the mass media. The estrogen story was such a nice fairytale that it is almost too bad that at present, the story is falling apart piece by piece. Pharmaceutical companies made a miraculous fountain-of-youth drug, physicians were happy to pass along the dream to their willing and "needy" patients, and women were buying into the dream of youth and attractiveness.

1975: Estrogen linked to increased uterine cancer

[181] Wyeth, *supra* note 42; Coney, *supra* note 2, at 5.
[182] Coney, *supra* note 2, at 20.

DES, one of the estrogens used (either in combination with progesterone or alone) in hormone therapy for menopausal women, took a big hit in 1971: studies connecting women's DES use to prevent miscarriages during pregnancy with vaginal cancer in their daughters were published in the *New England Journal of Medicine*.[183] Four years later, the FDA withdrew its approval of the use of DES during pregnancy.[184] Cancer experts saw at once that the significance of the 1971 study, and subsequent studies by the same doctors, went far beyond the conclusions relating to DES in pregnancy; these studies had shown that estrogen could be "seed" as well as "fertilizer" to cancer in humans, meaning that it could cause cancer as well as help it to grow.[185]

As a result, scientists at the National Institutes of Health held a conference in 1971 to talk about the basis for the use of estrogen as a therapy for menopausal women.[186] The conference deplored the lack of data on menopause and noted the uncertainty of benefits from estrogen therapy, but also concluded that "...the association of abnormal and elevated estrogens and abnormalities of the endometrium (the lining of the uterus) is very suggestive..."[187] In 1973, *Medical Letter*, the *Consumer Reports* of prescription drugs, cautioned:

[183] A.L. Herbst et al., *Adenocarcinoma of the Vagina: Association of Maternal Stilbestrol Therapy with Tumor Appearance in Young Women,* 284 New England Journal of Medicine 878-881 (1971).

[184] Barbara Seaman & Gideon Seaman, Women and the Crisis in Sex Hormones, at ix (Bantam Books 1978) (1977). Interestingly, even when presented with a clear link in 1971, the FDA didn't take action against DES until 1973, when it issued a tardy warning against the use of hormones for diagnostic pregnancy tests or preventing miscarriages. Finally in 1975, the FDA withdrew approval of any use of hormones during pregnancy. *Id.*

[185] Herbst, *supra* note 183; *see* Seaman & Seaman, *supra* note 184, at 338.

[186] National Institutes of Health, K. Ryan and D. Gibson, eds., *Menopause and aging. Summary report and selected papers from a research conference on menopause and aging, May 22-23, 1971, Hot Springs, Arkansas* (1971).

[187] *Id.*

> The manufacturer's advice to 'Keep Her on Premarin' seems unwise... References frequently cited in promotions of estrogens... present personal opinion... or poorly controlled studies... or no criteria for defining such vaguely characterized states as melancholy, diminished sense of well-being, and decreased vitality... The *Medical Letter* **advises against the routine prescribing of estrogens during and after the menopause because there is no adequate evidence that such treatment is beneficial, and because... estrogens may promote or aggravate cancer in some women**.[188]

Then, in 1975, just before the completion and publication at the end of the year of conclusive studies showing the link between estrogen replacement therapy and endometrial cancer, Novak's Textbook of Gynecology came to conclusions that previewed the result of the studies:

> ...**estrogens can be of importance in the development of cancer in** those organs and tissues which are normally estrogen dependent, e.g. **the genital tract and breasts**... Any gynecologist who spends time in the pathology laboratory can be impressed the large number of postmenopausal endometria in which extreme degrees of hyperplasia and even endometrial adenocarcinoma are observed in women who have a history of prolonged estrogen therapy.[189]

Finally, in December of 1975, the *New England Journal of Medicine* published a series of articles comparing the risks of developing endometrial cancer between menopausal women who used estrogen for hormone replacement therapy and those who did not use estrogen.[190] The difference in risk of developing endometrial cancer between the two groups was dramatic: those who used estrogen therapy for five years or less were 5 times more at risk than non-users, and the risk kept increasing as the duration of the therapy increased, so that those who used estrogen for more than seven years were at 14 times the risk of non-users![191]

[190] Harry K. Ziel & William D. Finkle, *Increased risk of endometrial carcinomas among users of conjugated estrogens*, 293(23) New England Journal of Medicine 1167-1170 (1975); D.C. Smith et al., *Association of exogenous estrogen and endometrial carcinoma,* 293(23) New England Journal of Medicine 1164-1167 (1975).

[191] *Id.* This refers to risks found in the Ziel and Finkle study where the control was non-estrogen users. The second study, by Smith et al, used as controls other cancer patients, but had similar results: The risk of estrogen users developing endometrial cancer was 4.5 times the risk those who did not use estrogen. *Id.*

Ayerst Labs, however, less than two weeks after the publication of these studies, was bold enough to send out a "Dear Doctor" letter to physicians arguing that the articles were "weak studies," and reassuring them that the link between estrogen therapy and cancer was not firmly established.[192] Some doctors did not need to be reassured by Ayerst because they were already dismissing the studies as not showing a direct link of estrogens to cancer. [193]

> Those doctors who have been liberal in their prescription of estrogens, giving them to virtually all menopausal women for indefinite periods, said that in their views the benefits of hormones still outweigh the risks. The doctors who traditionally have been more conservative in prescribing estrogens, restricting them to women with severe menopausal symptoms, for a period of one to four years, said that the drug is clearly useful for such women even if it may increase their risk of developing cancer of the endometrium.[194]

Despite any flaws in the endometrial cancer studies' design, the increase in cancer risk was "too high to be explained away by even major methodological flaws."[195] The FDA seemed to agree, because on December 16 and 17, 1975, it convened a hearing in front of its advisory committee on obstetrics and gynecology to discuss the recent evidence linking endometrial cancer with estrogen use by menopausal women.[196] A third study was presented to the committee, concluding that "among postmenopausal women who took estrogen the risk of developing endometrial cancer was greater than their combined risk of developing cancers of the breast, lung, ovary and colon."[197] Additionally, the panel heard a report showing the incidence of endometrial cancer in the San Francisco bay Area had increased by 50 percent from 1969 to 1979, after restricting the study to women over 50; the results were most obvious in upper socio-economic groups, where use of estrogens is most prevalent.[198] It was also reported at the conference that other cancer registries showed similar increases in

[192] Seaman & Seaman, *supra* note 184, at 355-356.
[193] Brody, *supra* note 111.
[195] Patricia Kaufert & Sonja McKinlay, *Estrogen-replacement Therapy: The Production of Medical Knowledge and the Emergence of Policy, in* Women, Health and Healing, 113-38 (Ellen Lewin and Virginia Olesen, eds. 1985).
[196] *FDA Panel Gets Data on Estrogen: Additional Evidence Link Drug to Cancer is Heard - Ruling Due This Week*, N.Y. Times, December 17, 1975, at 19.
[197] *Id.*
[198] *Id.*

endometrial cancer rates.[199]

On January 8, 1976, the FDA announced that it would release new warning labels for estrogen products used to treat menopausal and post-menopausal women, which would "emphasize the newly reported increased risk of cancer of the uterus associated with prolonged use of estrogen products, particularly in post-menopausal women."[200] And that same day, after Ralph Nader's Health Research Group had brought the Ayerst letter to the attention of the FDA, the agency released an announcement reprimanding Ayerst and calling the letter it sent to doctors "misleading in view of the recent and widely publicized discussion regarding estrogen therapy in women." [201]

The FDA also required in 1976 that that each package of estrogen contain an insert warning of the risks of estrogen.[202] If the doctors disliked the attention they were getting before from the link to uterine cancer, the action by the FDA was certain to annoy doctors. The studies' conclusion that the apparently beneficial drug that had been given to well women could cause cancer naturally led to the inference that their doctors could not necessarily be trusted: doctors had given their healthy female patients assurances that the estrogen was safe, but this evidently was not the case.[203] The American College of Obstetrics and Gynecology worried that the inserts in estrogen packages would further cause a rift in the doctor-patient relationship, because the information in the inserts about risks circumvented the normal process where doctors decided how much information to give to patients.[204]

[199] *Id.*
[200] *Letter on a Drug Assailed by FDA*, N.Y. Times, January 9, 1976, at 28.
[201] *Id.*
[202] Kaufert & McKinlay, *supra* note 195.
[203] Coney, *supra* note 2, at 198.
[204] *Id.*

By 1975, it was estimated that about 25 million prescriptions for estrogen therapy were written by doctors,[205] quadruple the amount prescribed in 1972.[206] Needless to say, the increased risk of cancer had the potential for widespread consequences.

Additionally, in 1974, there had been a report that had linked estrogen with gallbladder disease; the relative risk of estrogen users was two and a half times that of non-users.[207] The decline in hormone therapy prescriptions was evidence of the growing accumulation of evidence against estrogen: From 1975-9176, estrogen use declined by 18% from 1975-1976, and another 10% from 1976-1977.[208] By 1980, the number of annual estrogen prescriptions had fallen by 50%[209] Also, under pressure from grassroots activists as well as the FDA, Ayerst altered the Premarin advertising claims to include only menopausal symptoms such as hot flashes, night sweats, and vaginal dryness as indications of the drug.[210]

After the uterine cancer scare in 1975, scientists concluded that although estrogen is the major hormone player in menopause, since its use in treating menopausal symptoms like hot flashes and vaginal dryness have been quite effective, there had to be a way to mediate its effect on the uterus.[211] Estrogen is the hormone that allows the lining of the uterus to build up in preparation for pregnancy.[212] If estrogen were the only hormone available, the lining of the uterus would continue to build up, which would put women at greater risk for endometrial cancer.[213] Progesterone is the hormone that causes the lining to shed when no

[205] *Estrogen is Linked to Uterine Cancer*, N.Y. Times, December 4, 1975, at 1, 55.
[206] Brody, *supra* note 111.
[207] Boston Collaborative Drug Surveillance Program, *Surgically Confirmed Gallbaladder Disease, Venous Thromboembolism and Breast Tumors in Relation to Postmenopausal Estrogen Therapy*, 290(1) New England Journal of Medicine 15-19 (1974).
[208] Kaufert & McKinlay, *supra* note 195.
[209] Seaman, *supra* note 13, at 171.
[210] *Id.* at 170.
[211] *See* Carol Landau et al., The Complete Book of Menopause 139 (1994).
[212] *Id.*
[213] *Id.*

fertilization of the egg occurs.[214]

Pharmaceutical companies learned a few years later from preliminary epidemiology studies that they could add progesterone to the estrogen therapy drugs to offset the risks of endometrial cancer.[215] The addition of progesterone to estrogen, known as "opposed therapy," induced a regular bleed, helping to avoid the dangerous buildup of the lining that occurred under influence and hopefully protecting the uterine lining from cancer.[216] Drug companies successfully campaigned physicians to use this new combined hormone replacement therapy in women who still had their uterus, and by 1988, a significant shift in prescriptions had taken place from unopposed estrogen to opposed therapy.[217]

The problem with adding progesterone to the estrogen was that although postmenopausal women continue to produce some estrogen, there is essentially no progesterone production post-menopause because the function of progesterone is no longer necessary.[218] Thus no one could predict exactly what adding progesterone would do to a postmenopausal woman, because it was essentially a foreign hormone to the woman at that point in her life.[219] The most noticeable effect was that progesterone caused 25% of women who used this opposed therapy to experience premenstrual syndrome, and many women also started to begin menstruating again.[220] The return of menstruation is the most common reason women give for discontinuing the use of HRT for those who have already stopped menstruation.[221]

[214] *Id.*
[215] *See, e.g.*, M. H. Thom et al., *Prevention and Treatment of Endomtrial Disease in Climacteric Women Receiving Estrogen Therapy*, 2 (8140) The Lancet 455-457 (1979).
[216] Landau, *supra* note 211.
[217] D.K. Wysowski et al., *Use of Menopausal Estrogens and Medroxyprogesterone in the United States, 1982-1992*, 85(1) Journal of Obstetrics and Gynecology 6-10 (1995).
[218] Coney, *supra* note 2, at 200.
[219] *Id.*
[220] *Id.*
[221] *Id.*

1976: Estrogen linked to breast cancer

In 1976, breast cancer was added to the growing lists of diseases that estrogen therapy caused in menopausal women.[222] The first report of a higher risk of breast cancer in estrogen patients was especially alarming, because of the higher incidence of breast cancer among women (especially older women), and the poor prognosis for even early-stage breast cancer.[223] Even a moderate increase of breast cancer among women using hormone replacement therapy could have an enormous effect, because breast cancer is the most common cancer among women.[224] Currently, the Susan G. Komen Breast Cancer foundation notes that the chance of getting breast cancer increases as women get older, from a 1/36 chance when a woman is 50, to a 1/23 chance when the woman is 70, to a 1/7 chance of ever getting breast cancer.[225] The biology of breast cancer is still not well understood, but many experts believe that estrogen stimulates the growth of cancer in cells in the breast and that progesterone might add to estrogen's effect, thus increasing the risk of breast cancer dramatically.[226]

The effects of estrogen and progesterone on breast cancer were unclear through the 1970s, when studies showed no elevation in risk, and through the 1980s when several studies showed small elevations in risk, especially for long-term users; only in the 1990s were doctors' suspicions about the increased risks of breast

[222] R. Hoover et al., *Menopausal Estrogens and Breast Cancer*, 295(8) New England Journal of Medicine.401-405 (1976); Coney, *supra* note 2, at 262.

[223] *Id.*

[224] Breastcancer.org, *Who Gets Breast Cancer?*, *at* http://www.breastcancer.org/cmn_who_idx.html (last visited April 4, 2005).

[225] The Susan G. Komen Breast Cancer Foundation, *Breast Cancer Risk Factors Fact Sheet*, *at* http://www.komen.org/stellent/groups/harvard_group/@dallas/documents/-komen_site_documents/rfapfactors.pdf

[226] *See, e.g.*, The Susan G. Komen Breast Cancer Foundation, *How Hormones Affect Breast Cancer Fact Sheet*, *at* http://www.komen.org/stellent/groups/harvard_group/@dallas/documents/-komen_site_documents/rfaphormones.pdf

cancer due to estrogen and progesterone more clearly borne out in studies.[227] For example, a 1989 Swedish study found that after nine years' use women using estrogen-only hormones had nearly twice the rate of breast cancer compared to women not using hormones, and the risk increased with the addition of progesterone so that women using a combination of estrogen and progesterone had four times the rate of breast cancer compared to nonusers.[228] On their follow-up of women in this study in 1992, the researchers again found that the risk they discovered in 1989 remained – the risk of combined estrogen-progesterone therapy had increased and in their opinion, was "more hazardous" in terms of breast cancer than estrogen alone.[229]

A meta-analysis of many small studies in 1991 by the Centers for Disease Control found that an increased risk of breast cancer among hormone replacement therapy users did not begin until after at least five years of use, and applied to women with both surgical and natural menopause.[230] After 15 years of use, a 30% increase in the risk of breast cancer was found for estrogen users, mostly among women who began using estrogen (with or without progesterone) prior to menopause – they were 2.2 times more likely to develop breast cancer than nonusers.[231] And those who had a family history of breast cancer had 3.4 times the risk.[232] The authors concluded that the added risk of hormone use to American women would be about 4,708 preventable cases of breast cancer every year and 1,468 preventable deaths.[233]

Although this study found a breast cancer link to long-term users of HRT, there were also studies that found

[227] *See* Coney, *supra* note 2, at 262-267.
[228] L. Berkvist et al., *The Risk of Breast Cancer after Estrogen and Estrogen-Progestin Replacement*, 321 New England Journal of Medicine 293-297 (1989).
[229] I. Persson et al., *Combined Oestrogen-Progestogen Replacement and Breast Cancer Risk*, 340 The Lancet 1044 (1992).
[230] Karen K. Steinberg et al., *A Meta-analysis of the Effect of Estrogen Replacement Therapy on the Risk of Breast Cancer*, 265 JAMA 1985-90 (1991).
[231] *Id.*
[232] *Id.*
[233] *Id.*

an increase for short-term and current users. In 1992, the American Nurses' Health Study, a prospective study with nearly half a million person-years of follow-up, showed a 33% increased risk of women currently using HRT, with a potentially greater risk in women using combined therapy.[234] In 1993, a meta-analysis study by some of the same authors confirmed the Nurses' Health Study results, showing a 40% increase in risk of breast cancer for current users of HRT, which was not related to the duration of therapy.[235]

Although the findings of the studies through the 1990s were somewhat contradictory, the overall wisdom seemed to be by this time that using HRT for more than a very short time could increase the risk of breast cancer dramatically.[236] While studies suggested that five years of hormone therapy use might be safe, there appeared to be a significant risk of breast cancer if the therapy was used for longer than five years.[237] Current users appeared to be most at risk, and possibly even short-term users, too.[238]

1980s Hormone therapy and its promise to prevent osteoporosis

By the 1980s, hormone replacement therapy was in deep trouble. With links to two cancers, and other various problems, women were increasingly disenchanted with hormone therapy.[239] Taking a possible carcinogen for hot flashes was not reason enough and sales of hormone drugs plummeted accordingly.[240] Fortunately for the makers of hormone therapy, in the early 1980s several studies showed that estrogen was effective

[234] Graham A. Colditz et al., *Type of postmenopausal hormone use and risk of breast cancer: 12-year follow-up from the Nurses' Health Study*, 3 Cancer Causes and Control 433-439 (1992).
[235] Graham A. Colditz et al., *Hormone Replacement Therapy and Risk of Breast Cancer: Results from Epidemiologic Studies*, 168(5) American Journal of Obstetrics & Gynecology 1473-80 (1993).
[236] National Women's Health Network, *supra* note 12, at 47-48.
[237] *Id.* at 48.
[238] *Id.*
[239] Coney, *supra* note 2, at 200.
[240] *Id.*

in slowing bone loss, starting with one that found a marked retention of bone loss on women who were undergoing surgical menopause (they had had their ovaries surgically removed in a procedure called an oophorectomy).[241] Normally, postmenopausal ovaries continue to produce some estrogen throughout life; thus after an oophorectomy, the absence of the ovaries often causes severe menopausal symptoms that do not respond to natural remedies.[242] Unfortunately, when the results of this study were publicized, the distinction was not made clear between women who had had oophorectomies and women who were undergoing natural menopause, and consequently, the findings were promoted as if estrogen were helpful to every menopausal woman.[243] Thus, an old theory on the ability of estrogen to stimulate bone formation and help prevent osteoporosis was successfully renewed, albeit on false pretenses.[244]

In 1984, a Consensus Conference on osteoporosis by the National Institutes of Health warned against widespread use of hormone replacement therapy because of the unknown risks but otherwise had stated that estrogen was the "most effective" way of preventing osteoporosis and recommended that bone-density measuring devices be made available for screening.[245] Osteoporosis, the condition where the bones in the skeleton progressively thin with age, is one risk factor for bone fractures.[246] The drug manufacturers of hormone therapy, however, capitalized on the positive results by this conference, and started a campaign to reorient women's perception of the benefits of estrogen by: (1) emphasizing the gravity of osteoporosis, (2) stressing that osteoporosis is a woman's disease, and (3) creating a perception that the cancer risk was trivial

[241] *See, e.g.*, Harry K. Genant et al., *Quantitative Computed Tomography of Vertebral Spongiosa: A Sensitive Method for Detecting Early Bone Loss after Oophorectomy*, 97 Annals of Internal Medicine 699-705 (1982).
[242] National Women's Health Network, *supra* note 12, at 41.
[243] Seaman, *supra* note 13, at 77.
[244] *See id.* at 75-77.
[245] National Institutes of Health, NIH *Consensus Development Statement on Osteoporosis*, *April 2-4 1984*, Volume 5, No.3; *see* Seaman, *supra* note 13, at 76.
[246] *See supra* p. 4 and notes 11, 12.

when measured against the benefits of estrogen.[247] As with menopause, the drug companies (and in this case, also the dairy industry) had a lot to gain by "disease-mongering."[248] By showing older women with so-called "dowager's humps," dubbing older women "little old ladies," and using wheelchairs and crutches as symbols for osteoporosis in advertisements, the drug companies scared women into worrying about the risks of developing such severe osteoporosis more than they were helping to "educate" women.[249] The ads played out the fear of osteoporosis to the fullest by telling women in advertisements to talk to their doctors "before it's too late" and offering free bone mineral density tests to see how much has been "lost."[250]

Osteoporosis was the perfect disease to market because there are no symptoms until a person develops fractures – the so-called "silent disease" – thus no postmenopausal women could be sure she was safe.[251] And the criteria were set so that one quarter of all women over 65, and more than half over 75, would be diagnosed with osteoporosis if had bone density tests; thus doctors and drug companies were promoting long-term preventative benefits for women, meaning long-term use of estrogen therapy.[252] Additionally, since only 23% of women had even heard of osteoporosis, a full-scale campaign could easily educate about the disease and promote drugs to help the disease at the same time.[253]

The interesting point here is that osteoporosis itself is not the problem; it is only one risk factor of bone fractures. The fractures themselves are what lead to disability and death.[254] But other risk factors (that

[247] *See* Coney, *supra* note 2, at 202.
[248] *See supra* p. 20-21 and note 116.
[249] National Women's Health Network, *supra* note 12, at 27.
[250] *Id.* at 145.
[251] John Abramson, Overdo$ed America 62 (2004).
[252] *Id.* at 62.
[253] Amanda Spake et al., *The Menopausal Marketplace*, 133(19) U.S. News & World Report 42-48 (2002).
[254] National Women's Health Network, *supra* note 12, at 153.

conveniently got lost in the advertisements) include race, ethnicity, body build, diet, smoking, and physical activity, all of which have a significant impact on a woman's risk of fracture in old age.[255] However, drug companies emphasized the connection between menopause, osteoporosis, fractures, and death.[256] By capitalizing on favorable numbers on osteoporosis and fractures, especially when looking at the combined number of fractures of wrists, vertebrae and hips, drug companies could claim that up to 50% of all fifty-year-old women will eventually experience a fracture.[257] These numbers were and still are misleading because a wrist fracture is not debilitating, and the study showing the largest percentage had counted multiple fractures for a single woman as if each fracture had happened to multiple women.[258]

The risk of hip fractures has specifically been used to market products to prevent osteoporosis.[259] These type of fractures are a perfect target for drug companies, since by age 85, thirty-three percent of women have suffered hip fractures, causing chronic pain, disability, and sometimes (with the additional factor of prolonged bed rest) complications that ultimately lead to death.[260] However, the complications that result from hip fractures are not simply caused by declining estrogen: Hip fracture rates are higher for women over the age of eighty, but they may often be a marker and not the cause of declining health and impending death; most patients who suffer a hip fracture have severe concomitant illness that accounts for much of the increased mortality after hip fracture.[261] Also, even though white women are most likely to have hip fractures, one study showed that they are the least likely to die afterward: the mortality rate for white women

[255] *Id.* at 152.
[256] *See id.* at 145-146.
[257] *Id.* at 148.
[258] *Id.* at 148-9; *see* E. A. Chrischilles et al., *A Model of Lifetime Osteoporosis Impact*, 151 Archives of Internal Medicine 2026-2032 (1991).
[259] National Women's Health Network, *supra* note 12, at 149.
[260] Cohen, *supra* note 155, at 76.
[261] Steven R. Cummings et al., *Should Prescription of Postmenopausal Hormone Therapy be Based on the Results of Bone Densiometry?*, 113(8) Annals of Internal Medicine 565-567 (1990).

(per thousand person months) was 17.2, compared with 22.9 for black women, 33.5 for black men, and 33.7 for white men.[262] Additionally, an increased propensity to fall with age and environmental factors, such as proportionately higher medication use among women, interact to put women at risk of hip fractures.[263]

The drug companies' campaign picked up momentum when it had generated enough support for a National Osteoporosis Week.[264] Then, in 1986, the National Osteoporosis Foundation was created with drug company support.[265] This was a smart move by the drug companies – a disease foundation, by its form, lends legitimacy to a cause because its message is not directly tainted by a profit-motive as a pharmaceutical companies' obviously is. It is alleged by the National Women's Health Network that this foundation consistently overstates the number of women who will experience the most debilitating effects of osteoporosis even though studies show that most women with the disease do not experience the severe problems that women fear.[266]

Regardless of the National Women's Health Network's assertion, the studies showing the slowing of bone loss, the positive NIH reports, and the marketing of osteoporosis awareness had paid off, because in 1986, the FDA announced that it approved estrogen as an effective treatment for postmenopausal osteoporosis.[267] This reversed the FDA's 1976 finding that there was no conclusive evidence of estrogen's effectiveness against osteoporosis.[268] Notably, though, the FDA also recommended that estrogen therapy should be accompanied by a high-calcium diet and exercise, suggesting that the agency acknowledged that it was not an estrogen

[262] S. J. Jacobsen et al., *Race and Sex Differences in Mortality Following Fracture of the Hip*, 82(8) American Journal of Public Health 1147-1150 (1992).
[263] Coney, *supra* note 2, at 147.
[264] Spake, *supra* note 253.
[265] National Women's Health Network, *supra* note 12, at 27.
[266] *Id.*
[267] Oral Estrogens for Postmenopausal Osteoporosis, 51 Fed. Reg. 12568 (April 11, 1986).
[268] *Id.*

deficiency alone that caused osteoporosis.[269]

The major complication to treatment of osteoporosis is how to define it and who to treat.[270] Bone mineral density tests are recommended as a way to determine which osteoporosis category a person fits into (normal, osteopenia, osteoporosis, or severe osteoporosis), based on how many standard deviations a person is above or below the bone density of a normal young adult of the same sex.[271] Despite this scoring method, there are presently no internationally accepted guidelines for the use of bone density in trying to assess risk for osteoporosis.[272] While bone density tests can show loss of bone mass, screening cannot predict how rapidly someone will lose bone, and most importantly, cannot predict whether someone will actually have fractures; bone loss is neither constant nor predictable.[273] Further, any margin of error of the instruments, seasonal variations in bone mass, and the comparison standard are all reasons to question the results of any bone density test.[274] Finally, bone density is only one component of bone health – bone density is not a substitute for bone quality, which cannot be quantitatively measured.[275]

Definitions of osteoporosis have gone through many changes, and will continue to do so, because the way the medical community establishes the contemporary definition is the result of a negotiated political process.[276] Current definitions of osteoporosis are agreed upon by a national consensus panel of medical experts – panels that are generally funded by government agencies, often with the help of drug companies.[277] Without

[269] *See id.*
[270] Seaman, *supra* note 13, at 171.
[271] National Women's Health Network, *supra* note 12, at 148.
[272] Seaman, *supra* note 13, at 171.
[273] National Women's Health Network, *supra* note 12, at 156.
[274] *See id.*
[275] Seaman, *supra* note 13, at 173.
[276] Susan Love, Dr. Susan Love's Hormone Book 97 (1997).
[277] *Id.*

a doubt, this is a conflict of interest – those who are setting the definitions of osteoporosis as a disease are also the ones profiting from it.[278]

Notably, ignored in most of the hype about osteoporosis prevention is the inverse relationship, also known as the "seesaw" phenomenon, between bone health and female cancers: namely, that women and other mammals get more breast cancer when their bones mass is good, and less if their bones are thinning.[279] Estrogen stimulates growth, perhaps in bone and cancer cells simultaneously.[280] But since deaths from cancer start to occur far earlier in life than deaths from hip fracture, it seems presumptuous to give women estrogen to prevent osteoporosis until doctors have figured out the relationship between the two.[281]

1985: Hormone therapy and its positive effect on heart disease risk

Just as the public was being educated on osteoporosis, and estrogen's promise to help with this disease, estrogen won another huge comeback battle in 1985: heart disease, the number one killer of postmenopausal women.[282] A lot of media attention surrounded a finding in the *New England Journal of Medicine* that the Nurses' Health Study[283] showed that registered nurses who were currently using estrogen had 70 percent

[278] SEAMAN, *supra* note 13, at 173.
[279] *Id.*
[280] *Id.*
[281] *Id.*
[282] *See* National Heart, Lung, and Blood Institute Women's Health Initiative, *Why WHI*, *at* http://www.nhlbi.nih.gov/whi/whywhi.htm (last visited April 13, 2005).
[283] The Nurses' Health Study was run out of the Harvard School of Public Health and it observed 32,300 postmenopausal women for more than three years. *See infra* note 284.

risk of developing coronary heart disease than women who had not used hormones.[284] In the same issue of the *NEJM*, the results of the Framingham Heart Study showed that women who had taken estrogen were 50 percent *more* likely to develop heart disease, but this was largely dismissed by the media; since the Framingham study results involved older women (who were thus at greater risk) and they had received higher doses of estrogen, the conclusions of the study were questioned by others.[285] Yet again, the medicalization of menopause and the definition of menopausal life as a state of estrogen deficiency had provided the context and platform for a skewed view of heart disease as a newly urgent problem for women, best treated by estrogen.[286]

Soon after, researchers were churning out positive studies about hormones preventing heart attacks, atherosclerosis, and bone loss, while not increasing cancer, stroke, or blood clots.[287] In fact, these observational studies showed that hormones reduced mortality from all causes – including accidents and homicides![288] By 1992, Premarin was the number one prescribed drug in the United States,[289] and sales were topping their 1975 peak: one out of five postmenopausal women in the United States were taking hormones; the use of hormones to prevent osteoporosis and heart disease had created enough renewed interest to override continuing concerns about the link to breast cancer, even though heart disease had not been approved as a listed indication on hormone products.[290] Major medical professional organizations were recommending long-term use of HRT: The American of College of Physicians issued guidelines to practicing physicians recommending

[284] M.J. Stampfer et al., *A Prospective Study of Postmenopausal Estrogen Therapy and Coronary Heart Disease*, 313(17) New England Journal of Medicine 1044-1049 (1985); *see* Abramson, *supra* note 251, at 63.
[285] P.W. Wilson et al., *Postmenopausal Estrogen Use, Cigarette Smoking, and Cardiovascular Morbidity in Women over 50*, 313(17) New England Journal of Medicine 1038-1043 (1985); *see* Abramson, *supra* note 251, at 63.
[286] H. Tunstall-Pedoe, *Myth and Paradox of Coronary Risk and the Menopause*, 351 The Lancet 1425-1427 (1998).
[287] Spake, *supra* note 253.
[288] *See, e.g., id.*
[289] Wyeth, *supra* note 42.
[290] *See* Abramson, *supra* note 251, at 63-64.

that "all women... should consider preventive hormone therapy," and that 10 to 20 years of therapy were recommended for "maximum benefit."[291] The American College of Obstetrics and Gynecology also recommended that all postmenopausal women, barring a medical contraindication like breast cancer, should take HRT for life.[292] Premarin sales increased another 40 percent over the next three years, in part because of such professional recommendations.[293]

But the flurry of positive reports on heart disease after 1985 seemed a little too good to be true to some doctors. As Elizabeth Barrett-Connor, a veteran hormone researcher, noted:

> I thought there were two or three very strong biases such that healthy women at low risk of heart disease were receiving the drugs and being studied. I knew all along that women taking estrogen were better educated, wealthier, and there was compliance bias – that is, people who are compliant in clinical trials, even with a placebo, have less disease. The research seemed even less reliable when... during many of the years covered in these studies, the standard Physicians' Desk Reference suggested estrogen should not be prescribed to women with heart disease, hypertension, or diabetes. **So women with heart risks were not receiving the drug. It's no surprise, then, that women taking the drugs had less heart disease**.[294]

In 1987, Barrett-Connor convinced the National Institutes of Health to begin a three-year clinical trial called the Postmenopausal Estrogen/Progestin Interventions Trial ("PEPI"), a study of the effects of hormones on key heart disease risk factors, such as lipids, blood clotting, and weight gain.[295] The results of PEPI, published in 1995, were clear: while HRT reduced some risks – such as LDL, or "bad cholesterol" – it increased others, such as fats called triglycerides.[296] PEPI also found that the most used type of progesterone interfered

[291] American College of Physicians, *Guidelines for Counseling Postmenopausal Women About Preventive Hormone Therapy*, 117 Annals of Internal Medicine 1038-1041 (1992).
[292] Abramson, *supra* note 251, at 63.
[293] *Id.* at 63-64.
[295] *Id.*
[296] The writing group for the PEPI trial, *Effects of Estrogen or Estrogen/Progestin Regimens on Heart Disease Risk Factors in Postmenopausal Women*, 273(3) JAMA 199-208 (1995).

with the beneficial effect estrogen had on cholesterol.[297]

After the bad news about breast cancer in 1989, Wyeth was eager to begin promoting Premarin for prevention of heart disease, and in June 1990 it asked the FDA to approve a label change Premarin for heart disease prevention in women without a uterus, based only on the observational studies.[298] The FDA Fertility and Maternal Health Drugs Advisory Committee approved the label change (with only one vote against), agreeing with Wyeth-sponsored researcher testimony that a clinical trial would be difficult and unnecessary to do so, since the women with heart disease were likely to benefit from hormones: "the cardiovascular benefits of Premarin may outweigh the risks depending on the individual patient's risk profile for various estrogen related diseases and conditions."[299]

No professional society opposed the label change, but Cynthia Pearson from the National Women's Health Network (a nonprofit, independent advocacy group) noted the sexist nature of the request, and the weak nature of the evidence: No drug had ever been approved for heart disease prevention (even aspirin for healthy men) unless it was verified by large randomized controlled clinical trials.[300] Although the FDA usually acts on the decisions of its advisory committees, apparently Pearson's argument for applying the same standard held weight with higher authority in the FDA, because the FDA never moved to enact the label change recommended by the committee, exercising what some might call a "pocket veto."[301] Whatever happened, almost a year later Bruce Burlington, then deputy director of the FDA's Office of Drug Evaluation, explained to a Senate committee why the label change had been withheld: "The studies that are available

[297] *Id.*
[298] Abramson, *supra* note 251, at 68.
[299] Cynthia Pearson, *FDA Waffles on Premarin Decision*, Network News, July/Aug 1990, at 1-7.
[300] Seaman, *supra* note 13, at 93, 149-150.
[301] *See* Seaman, *supra* note 13, at 150.

[on Premarin's cardiovascular effects] do not constitute randomized, prospective clinical trials that offer hard data."[302]

Since the FDA had effectively said that it would not approve a claim that HRT decreased a women's risk of heart disease until there was a large randomized controlled trial supporting that conclusion, Wyeth agreed to fund a study, confident that the results would come out in their favor.[303] Thus, in 1993, three thousand women with heart disease volunteered for four years to be randomized to either an estrogen/progesterone combination pill or a placebo in the Heart and Estrogen/Progestin Replacement Study ("HERS"); Wyeth not only hoped that HRT would be beneficial for these women who already had heart disease, but also that a positive finding would supply more evidence that HRT would prevent heart disease in healthy women.[304]

In 1998, the HERS study released results not in line with Wyeth's expectations: even though their cholesterol levels improved, the women taking the hormones were just as likely to have a heart attack or die from heart disease, if not slightly more so.[305] The findings were so clear that researchers recommended that women with preexisting cardiovascular disease should not begin using HRT, a recommendation later seconded by the American Heart Association.[306] The findings from the HERS study were confirmed by a smaller trial in 2000; neither estrogen nor combination estrogen/progestin stopped arteries from narrowing in women who already had atherosclerosis before the study.[307] Thus, though estrogen and combination estrogen/progestin improved

[302]Senate Labor and Human Resources/Aging Subcommittee Hearing, FDC report, Pink Sheet, April 29, 1991; Seaman, *supra* note 13, at 150.
[303]Abramson, *supra* note 251, at 68.
[304]S. Hulley et al., *Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women*, 280(7) JAMA 605-613 (1998); National Women's Health Network, *supra* note 12, at 181.
[305]Hulley, *supra* note 304; National Women's Health Network, *supra* note 12, at 184-185.
[306]Hulley, *supra* note 304; National Women's Health Network, *supra* note 12, at 185.
[307]DM Herrington, et al., *Effects of Estrogen Replacement on the Progression of coronary-artery atherosclerosis*, 343(8) New England Journal of Medicine 572-574 (2000).

cholesterol levels, neither lowered the risk of heart attack or other heart disease in women.[308] Proponents of estrogen argued that the HERS trial was stopped too soon, that it used the wrong combination of estrogen and progestin, and that even if the results were accurate, they didn't apply to healthy women.[309] However, these arguments ignore the fact that the most widely-used drug was tested in HERS and that there is no prevention drug known that helps healthy people but that is ineffective in those with the disease.[310]

1996: Hormone therapy linked to increased blood clots

Oral contraceptives had carried a warning of risk of blood clots since the 1970s.[311] Although hormone replacement therapy was thought not to carry the same risks of blood clots, in October 1996, *The Lancet* published a series of articles associating both estrogen and combined estrogen/progesterone with blood clots.[312] These studies found a higher incidence of venous thromboembolism (blood clots in veins that can travel to the lung and cause pulmonary embolism).[313] This risk was confirmed in the HERS study.[314] At this point, though it had not yet been proven, the increased in blood clots was also thought to have implications for an increase in strokes.[315]

[308] National Women's Health Network, *supra* note 12, at 185.
[309] *Id.* at 181.
[310] *Id.*
[311] *See* Seaman, *supra* note 13, at 148.
[312] *See*, *e.g.*, Edel Daly et al., *Risk of Venothromboembolism in Users of Hormone Replacement Therapy*, 348(9033) The Lancet 977-980 (1996).
[313] *Id.*
[314] *See* Deborah Grady et al., *Postmenopausal Hormone Therapy Increases Risk for Venous Thromboembolic Disease: The Heart and Estrogen/Progestin Replacement Study*, 132(9) Annals of Internal Medicine 689-696 (2000).
[315] National Women's Health Network, *supra* note 12, at 55.

2002: Women's Health Initiative shows increased risks and limited benefits

Around the time that Cynthia Pearson, Elizabeth Barrett-Connor, and others were trying to convince the FDA and the NIH to do further studies on HRT and heart disease, the NIH's new female director, cardiologist Bernadine Healy, had set her sights on bigger goals: a massive clinical trial on women's health covering heart disease, breast and colon cancer, bone fractures, and the role of hormone therapy, diet, vitamins, and calcium in preventing these diseases.[316] The study, called the Women's Health Initiative ("WHI"), was well overdue, because most of the research over the years about the benefits and risks of HRT had been conducted through observational or non-randomized studies, not the "grade A" quality, large, randomized, placebo-controlled studies.[317] Though the WHI was opposed by some members of Congress who thought it was too expensive, by epidemiologists who thought the design was too complicated, and by leading gynecologists who thought the heart disease benefit was so well proven that it was unethical to ask women to accept the possibility that they might be randomized to a placebo, the FDA's clear statement on the need for methodologically and statistically sound evidence before it approved heart disease protection convinced Congress to fund the landmark study.[318] WHI was conducted as a consortium effort led by the National Heart, Lung, and Blood Institute ("NHLBI") in cooperation with the Office of Research on Women's Health, the National Cancer Institute, and the National Institute of Arthritis and Musculoskeletal Diseases, involving multiple clinical trials, observational trials, and community health initiatives, involving a total of 161,000 women participants.[319]

[316] Spake, *supra* note 253.
[317] *See* Seaman, *supra* note 13, at 159.
[318] *See* National Women's Health Network, *supra* note 12, at 180-181; *id.* at 150-151.
[319] *See* Women's Health Initiative, *at* www.whi.org (last visited at April 5, 2005).

The two most important pieces of the WHI were the hormone therapy clinical trials assessing whether the long-term use of estrogen or estrogen-plus-progestin would reduce the risk of coronary heart disease and help prevent hip fractures, and whether those possible benefits were greater than the possible risks from breast cancer, colon cancer, endometrial (or uterine) cancer, strokes, and blood clots.[320] One arm of the study involved 16,608 healthy women aged 50-79, who were recruited from 1993-1998 and randomly assigned to receive either a daily intake of Prempro (a combination estrogen-progesterone: 0.625 mg of Premarin plus 2.5 mg of Provera) or a placebo.[321] The second arm of the study was involved 10,739 women who had had a hysterectomy; they were randomly assigned to receive either a daily intake of 0.625 mg Premarin (estrogen-only) or a placebo.[322] Both Premarin and Prempro were chosen because they were the most commonly prescribed forms of estrogen-alone and combined hormone therapy, respectively, and had appeared to benefit women's health in previous studies.[323]

The first signs of trouble occurred in 2000, and again in 2001, when the WHI investigators complied with a recommendation from the study's independent safety-monitoring committee and informed participants that women receiving the hormones in both arms of the hormone therapy trials were more likely to have heart attacks, strokes, or blood clots than the women taking placebos.[324] Despite this, the safety-monitoring committee recommended continuing the trial due to the still uncertain balance of risks and benefits; it had determined that the actual number of women having any one of these events was still small and it did not cross the statistical boundary established to ensure participant safety.[325] Then, at the committee's regularly

[320] National Heart, Lung, and Blood Institute, *Facts About Postmenopausal Hormone Therapy*, *at* http://www.nhlbi.nih.gov/health/women/pht_facts.htm#whi (October 2002).
[321] *Id.*
[322] *Id.*
[323] *Id.*
[324] News Release, National Institutes of Health, NHLBI Stops Trial of Estrogen Plus Progestin Due to Increased Breast Cancer Risk, Lack of Overall Benefit, *at* http://www.nhlbi.nih.gov/new/press/02-07-09.htm (July 9, 2002).
[325] *Id.*

scheduled meeting on May 31, 2002, the data review revealed for the first time that the number of cases of invasive breast cancer in the estrogen plus progestin group had crossed the boundary established as a signal of increased risk; thus, supported by additional evidence of overall health risks exceeding any benefits, the committee recommended that the NLBHI stop this part of the study.[326] Though the study was supposed to last until 2005, the WHI followed the committee's recommendation; on July 8, 2002, it stopped the Prempro arm of the study and sent participants a letter informing them about the results and telling them that they should stop study medications.[327]

The key adverse effects, after an average of 5.2 years of use, were an increase in cases of breast cancer, heart attacks, strokes, and blood clots.[328] The main benefits from the study were fewer hip and other fractures and cases of colorectal cancer.[329] Additionally, there was no increase in deaths or the risk of endometrial cancer.[330]

Looking further at the relative and absolute risks in the estrogen plus progestin arm of the WHI, the findings were as follows:[331]

♣

[326] *Id.*
[327] *Id.*
[328] Writing Group for the Women's Health Initiative Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial*, 288(3) JAMA 321, 321-333 (2002).
[329] *Id.*
[330] *Id.*
[331] *Id.* This citation applies to all six of the bullet points that follow this sentence.

Breast cancer: The increased risk of breast cancer appeared after 4 years of hormone use. After 5.2 years, estrogen plus progestin resulted in a 26 percent increase in the risk of breast cancer – or 8 more breast cancers each year for every 10,000 women. Women who had used estrogen plus progestin before entering the study were more likely to develop breast cancer than others, indicating that the therapy may have a cumulative effect.

♣ **Heart attack:** For heart attack, the risk began to increase in the first year of estrogen plus progestin use and became more pronounced in the second year. After 5.2 years, there were 29 percent more heart attacks in the estrogen plus progestin group than in the placebo group – or 7 more heart attacks each year for every 10,000 women. Unlike HERS, which involved women with heart disease, the increased risk from estrogen plus progestin did not go back down again.

♣

Stroke: For the first time, estrogen plus progestin was shown to cause more strokes in healthy women. By the end of the study, the estrogen plus progestin group had 41 percent more strokes than the placebo group – or 8 more strokes each year for every 10,000 women.

♣ **Blood clots:** The risk of total blood clots was greatest during the first two years of hormone use – four times higher than that of placebo users. By the end of the study, it had decreased to two times greater – or 18 more women with blood clots each year for every 10,000 women.

♣ **Fractures:** Estrogen plus progestin reduced hip fractures by 34 percent – or 5 fewer hip fractures each year for every 10,000 women. This was the first solid evidence from a clinical trial that hormone therapy, in helping to prevent bone loss and osteoporosis, protects women against fractures.

♣

Colorectal cancer: The therapy also lowered the risk of colorectal cancer by 37 percent – or 6 fewer colorectal cancers each year for every 10,000 women. This reduction appeared after 3 years of hormone use and became more significant thereafter. However, the number of cases of colorectal cancer was relatively small, and more research is needed to confirm the finding.

The WHI findings are important for several reasons: As a clinical trial, they establish a causal link between use of the particular hormone therapy and its effects on diseases.[332] Further, the findings finally offer some firm guidance to the millions of American women who have a uterus and may consider taking the drugs – 6 million women used a form of combination therapy in 2002.[333] Though, for example, the risks of developing breast cancer by a woman taking estrogen plus progestin for a year are only slightly increased – according to the WHI 0.08 percent – if you apply that increased risk to a large group of women and over several years, then the number of women affected becomes an important public health concern. If 6 million women are taking combination therapy, then that would result in an extra 4800 cases of breast cancer every year, and if all the women took it for 5 years it would mean an extra 24,000 cases of breast cancer! The results of the Prempro arm of the WHI also apply broadly – the study found no differences in risk by prior health status, age, or ethnicity.[334] An additional wrinkle to the study happened when the un-blinded participants were asked to guess whether they had been taking Prempro or a placebo; though most of those on hormones guessed correctly, about half of those on placebos also thought they were taking the active drug, which begs the question: Should menopausal women be taking placebos if it seems to work anyway?[335]

[332] National Heart, Lung, and Blood Institute, *supra* note 320.
[333] *Id.*
[334] *Id.*
[335] Seaman, *supra* note 13, at 82.

Needless to say, stopping a part of the WHI early was a bomb dropped on the American public. As Elias Zerhouni, the director of NIH, said about the hormone debate in 2002: "Often in science the reaction to a new finding is directly proportional to the strength of the dogma it overturns. People are still in denial of the theory of relativity, too."[336] Users of HRT and the medical community were confused about how after almost 60 years of touting the benefits of HRT, the negative results of the WHI could be true.[337] But WHI *was* a grade A quality study on hormone therapy, even if there were some dissenters who thought that there should have been a separate study for women who had not yet undergone menopause (because there might be more benefit if HRT was started before menopause), and others who thought that various (especially lower) doses should have been studied.[338]

Wyeth surprised many people when it announced on September 4, 2002, that it was voluntarily changing the prescribing recommendations for the Premarin family of products, preempting the FDA and moving to a more cautionary stance than the FDA was inclined to require.[339] One commentator noted that Wyeth, in the 60 years that Premarin had been on the market, had never given in on a new regulation before the FDA ordered it.[340] The new labels on the Premarin family of products now read: "when used solely for the prevention of postmenopausal osteoporosis, alternative treatments should be carefully considered."[341]

In March 2003, the WHI published a study not initially included in the June 2002 release of study findings: whether estrogen plus progestin improves postmenopausal women's quality of life.[342] Quality of life is a

[336] Spake, *supra* note 253.
[337] *See, e.g.*, Abramson, *supra* note 251, at 68-69.
[338] Spake, *supra* note 253; *see id.* at 65, 69.
[339] Seaman, *supra* note 13, at 83.
[340] *Id.*
[341] *Id.*
[342] Jennifer Hays, et al., *Effects of estrogen plus progestin on health-related quality of life*, 348(19) New England Journal of

measure of how someone's health affects perceived well-being and ability to function (physically, mentally and socially).[343] To assess quality of life, WHI participants answered questions (when they joined the study and after one year) about their general health, physical functioning, bodily pain, energy, social functioning, mental health, depression, sleep disturbances, sexual satisfaction, and symptoms associated with menopause; the researchers found no clear benefits for those taking estrogen plus progestin on any of the quality of life measures.[344] More notably, for those women aged 50-54 who reported night sweats and hot flashes – the most common reasons for women to seek estrogen treatment – the study also found no improvements in quality of life for these women except a small improvement (1 point on a 20-point scale) in sleep disturbance.[345]

In May 2003, an ancillary study of the WHI called the Women's Health Initiative Memory Study ("WHIMS") released more results.[346] WHIMS results showed that the combination of estrogen and progestin (Prempro) not only failed to prevent Alzheimer's disease, but actually doubled the risk of developing dementia (primarily Alzheimer's disease), causing about 1 additional case of dementia for every 100 women treated with HRT for five years.[347] Although it had previously been thought that HRT might decrease the incidence of Alzheimer's disease, the WHIMS' increase in Alzheimer's disease led the WHI and the FDA to recommend against using HRT to prevent Alzheimer's or other memory loss; the FDA also decided that manufacturers should include this information in the labeling for all HRT products.[348]

MEDICINE 1839-54 (2003).

[343] *Id.*

[344] *Id.*

[345] *Id.*

[346] Sally A. Shumaker, et al., *Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial*, 289 (20) JAMA 2717-2719 (2003).

[347] *Id.*

[348] Women's Health Initiative, *Frequently Asked Questions about the Women's Health Initiative Memory Study (WHIMS)*, *at* http://www.whi.org/faq/faq_whims.php (May 2003); U.S. Food and Drug Administration, *Questions and Answers for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women (Updated)*, *at* http://www.fda.gov/cder/drug/infopage/estrogens_progestins/
Q&A.htm (Created: February 10, 2004, Updated: April 19, 2004) [hereinafter *Questions and Answers*].

In March 2004, the estrogen-only part of the WHI was also ended prematurely.[349] In late 2003, the safety-monitoring board had reviewed the estrogen-only data, which showed some benefits of estrogen alone but also some continued risks.[350] After the NIH also reviewed the data, it decided to stop the study after 7 years, citing an increased risk of stroke – similar to that found in the Prempro arm when it was stopped in 2002 – considered unacceptable in healthy women in a research study which also showed no benefit in preventing heart disease.[351] The results indicated that estrogen alone does not appear to affect the risk of heart disease or breast cancer, but it did increase the risk of stroke and decrease the risk of hip fracture.[352] Overall, though, no benefit to taking estrogen was found, leading the researchers to conclude that estrogen-only treatment "should not be recommended for chronic disease prevention in postmenopausal women."[353] The WHI also concluded that "although hormone therapy is effective for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis who cannot take non-estrogen medications."[354]

The Post-WHI World

The fallout from the WHI study for makers of HRT was severe. For example, Wyeth's Premarin and its family of HRT products had been consistently top-selling drugs and took a huge hit in sales; in fact, Wyeth's Premarin, the dominant estrogen product on the market, had consistently been among the top-selling drugs in the nation.[355] In 2001, more than 45 million prescriptions were written for Premarin, and an additional

[349] News Release, National Institutes of Health, NIH Asks Participants in Women's Health Initiative Estrogen-Alone Study to Stop Study Pills, Begin Follow-up Phase, *at* http://www.nhlbi.nih.gov/new/press/04-03-02.htm (March 2, 2004) [hereinafter Estrogen-Alone News Release].

[350] *Id.*

[351] *Id.*

[352] The Women's Health Initiative Steering Committee, *Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy: The Women's Health Initiative Randomized Controlled Trial*, 291(14) JAMA 1701-1712 (2004).

[353] *Id.*

[354] Estrogen-Alone News Release, *supra note 349.*

[355] Spake, *supra* note 253.

21.4 million were written for Prempro, the leading combination estrogen-plus-progestin pill and the drug used in the WHI study.[356] Sales of Premarin products alone generated some $2.04 billion in sales in 2001.[357] But after the early halt of the Prempro arm of the WHI in July 2002, over the next 12 months, hormone prescriptions that had once soared – overall to 91 million in 2001 – nose-dived.[358] Sales of hormones overall fell 38 percent while sales of Prempro, the popular mix of estrogen and progestin that was the subject of the study, fell 74 percent.[359] Other research commissioned by drug companies showed that 18.5 million women used hormone therapy in 2002, but use had dropped to 7.6 million by January 2004.[360]

Many of the users of HRT that were using the drug for anti-aging or other preventative reasons stopped using HRT according to the recommendations of the WHI study; however, those women who were using HRT for severe menopausal symptoms remained on the drugs or returned when they could not find good alternate sources of relief – resulting in a slow in the rate of decline of hormone prescriptions.[361] From June 2002 to October 2003, the average rate of decline for hormone therapy overall was 3 percent a month, while Prempro prescriptions dropped at an average monthly rate of 8 percent; from November 2003 to April 2004, both categories dropped at a rate of 1 percent a month on average.[362] Some market research analysts predict that while most women would avoid the long-term therapy that once drove sales, demand will grow at about the same rate that women turn 50, the average onset of menopause.[363]

Adding to manufacturer's suffering, in January 2003, the FDA ordered black box warnings to be placed on

[356] *Id.*
[357] *Id.*
[358] Leslie Berger, *Two Years After: On Hormone Therapy, the Dust is Still Settling*, N.Y. TIMES, June 6, 2004, at Section 15, p.1.
[359] *Id.*
[360] *Id.*.
[361] *Id.*
[362] *Id.*
[363] *Id.*

the labels of all drugs for menopausal symptoms that contain estrogen or estrogen and progestin, stating that the drugs may slightly increase the risk of heart attacks, strokes, blood clots and breast cancer.[364] The FDA reasoned that since the increase of those risks from Prempro were present in the WHI, it must be assumed that all other products containing estrogen, including patches, creams, and pills, have similar problems unless proved otherwise.[365] This was a significant move by the FDA, because though some companies were trying to distinguish their products from Prempro and Premarin, and doctors were also claiming that other products were safer, the generalization of the new labels to all estrogen products put those companies and doctors on notice, and signaled that there is no assumption of safety – promoting or prescribing a "safer" product requires the appropriate studies to prove that claim.[366]

The new boxed warning – the highest level of warning information in labeling – highlighted the increased risks for heart disease, heart attacks, strokes, and breast cancer, and emphasized that these products had not been approved for heart disease prevention or memory loss.[367] FDA also modified the approved indications for Premarin, Prempro, and Premphase to clarify that these drugs should only be used when the benefits clearly outweigh risks.[368] Additionally, of the three indications for use (vasomotor symptoms, vulvar/vaginal atrophy, and osteoporosis), two were revised to include consideration of other therapies such as topical vaginal creams (for atrophy) or non-estrogen products (for osteoporosis).[369] Although the FDA kept "prevention of postmenopausal osteoporosis" as an indication, it required that the new drug labels state that when the hormone is used only for prevention of osteoporosis, it should be restricted to women who are of the

[364] News Release, U.S. Food and Drug Administration, FDA Approves New Labels for Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women Following Review of Women's Health Initiative Data, *at* `http://www.fda.gov/bbs/topics/NEWS/2003/NEW00863.html` (January 8, 2003) [hereinafter New Labels News Release].

[365] *Id.* As mentioned previously, Wyeth products had noted the risks, but they were the only ones to do so, and were not "boxed." *See supra* pp. 59-60 and note 339.

[366] Gina Kolata, *FDA Orders Warning on All Estrogen Labels*, N.Y. Times, January 9, 2003, at A18.

[367] New Labels News Release, *supra* note 364.

[368] *Id.*

[369] *Id.*

highest risk and even then, other osteoporosis drugs that do not contain estrogen should be considered.[370] Finally, the FDA took the position (which it still maintains today) that to minimize the potential risks and to accomplish the desired treatment goals, the new labeling and advice to health care providers should be to prescribe estrogen and combined estrogen with progestin products "at the lowest dose and for the shortest duration for the individual woman."[371]

Likely in response to the FDA's recommendation for the "lowest dose and shortest time," drug manufacturers in 2003 applied for and received approval for new lower-dose versions of drugs they already had on the market.[372] The FDA, despite approving the lower-dose pills, still acknowledges that "it is not known at what dose there may be less risk of serious side effects."[373] In addition, the FDA asked that manufacturers of estrogen and progestin products state whether studies have been conducted to identify the lowest effective dose for their product.[374]

Then, in August 2003, the results of the biggest study of all time, the Million Women Study, were published in *The Lancet*.[375] One million women in the United Kingdom completed questionnaires about their personal health, sociodemographic information, whether they had reached menopause, and whether they had ever taken or were currently taking hormones; over the following four years, the local cancer registries reported when women participating in the study developed or died from breast cancer.[376] The results showed that women who were currently taking hormones had a 66 percent higher change of getting breast cancer (30

[370] *Id.*
[371] *Id.*
[372] *See, e.g.*, Wyeth, *supra* note 42; News Release, U.S. Food and Drug Administration, FDA Approves Lower Dose of Prempro, a Combination Estrogen and Progestin Drug for Postmenopausal Women, *at* http://www.fda.gov/bbs/topics/NEWS/2003/NEW00878.html (March 13, 2003) [hereinafter Lower Dose of Prempro News Release].
[373] Lower Dose of Prempro News Release, *supra* note 372; *Questions and Answers*, *supra* note 348.
[374] *Questions and Answers*, *supra* note 348.
[375] Emily Banks, et al., *Breast Cancer and Hormone-Replacement Therapy in the Million Women Study*, 362(9382) The Lancet 419-427 (2003).
[376] *Id.*

percent for those taking only estrogen, 100 percent for combined estrogen-progestin) than the women not taking hormones.[377] This would mean that there were about 20,000 extra cases of breast cancer caused by HRT in the U.K. over the previous ten years.[378] Comparing the data to the United States, which has a greater population and rate of hormone usage, this would translate into at least 94,000 extra cases of breast cancer in the United States as a result of HRT.[379]

The study also confirmed that for those women who took estrogen alone for 10 years and still had their uterus, the risk of uterine cancer increased (10 extra uterine cancers per 1000) and the risk of breast cancer also increased (5 extra cases per 1000 women), for a total of 15 extra cancers per 1000 women.[380] While adding progestin did eliminate the risk of uterine cancers, it caused an extra 19 breast cancers per 1000 women over 10 years.[381] Therefore, though adding progestin solved the increased risk of uterine cancer, at the same time it seemed to increase the overall risk of getting other types of cancer.[382] The one good piece of news from this study was that past use of HRT did not seem to have an effect on the current risk of developing breast cancer; in other words, this findings was in line with results from previous studies that had suggested that the effects of current use of HRT on the risk of breast cancer wore off largely, if not wholly, within 5 years of ceasing use of HRT.[383]

Recently, a National Institutes of Health State-of-the-Science Conference took place on March 21-23, 2005 to talk about menopause-related symptoms and therapies.[384] Conspicuously at the beginning of the conference report, there is a note that the report will refer to hormone replacement therapy as "menopause hormonal

[377] *Id.*
[378] *Id.*
[379] ABRAMSON, *supra* note 251, at 70.
[380] Banks, *supra* note 375.
[381] *Id.*
[382] *Id.*
[383] *Id.*
[384] *NIH State-of-the-Science Conference Statement*, *supra* note 10.

therapy"; this reflects an ideology shift, due to recent studies, away from viewing menopause as an estrogen-deficient state that can be cured by giving women estrogen, to one of relieving menopausal symptoms.[385] The focus of the panel was to talk about the natural history of menopause, its associated symptoms, and effective and safe therapies for treatment of menopausal symptoms; however, the panel noted that much more research needed to be done on all three fronts.[386] The panel tried to separate out menopausal symptoms from those due to aging, finding that hot flashes, night sweats, and vaginal dryness were the most linked to menopause.[387] But since the most effective therapies for these menopausal symptoms can have serious side effects, individual women need better information to help them make a decision on what is best for them; the panel of medical experts at the conference called for research on a variety of women and therapies.[388] The results of the conference were highly anticipated, and the question marks prominent in the statement by the panel are disappointing evidence that the state of HRT is still very uncertain, and an individual woman weighing her risks and benefits is no doubt frustrated with the lack of concrete answers.

The mixed message is even present in advertisements for HRT drugs – current advertisements sound more like an ad for why women shouldn't take estrogen then why they should. Although at the start of a recent Premarin commercial, night sweats and hot flashes are promoted as a reason to use estrogen, and the narrator notes that Premarin is approved to treat "[menopausal] symptoms and prevent bone loss," the rest of the commercial lists a litany of reasons why women shouldn't take estrogen, overwhelming the listener with the risks and drowning out the initial marketing message.[389] Though complying with the FDA's guidance on alternative therapies for HRT approved indications, the commercial starts sounding as if Coca-Cola introduced itself and then told you all the reasons why you should not drink soda.

[385] *See id.*
[386] *Id.*
[387] *Id.*
[388] *Id.*
[389] *Premarin commercial* (NBC television broadcast, April 1, 2005).

The FDA is not currently considering taking estrogens or estrogen-progestin drug products off the market, although it promises to evaluate the ongoing safety and effectiveness of the HRT drugs, as it always has.[390] Currently, the FDA seeks to minimize risks and maximize benefits of estrogen and estrogen with progestin drug products by ensuring that women and health care providers fully understand these risks and benefits.[391]

Conclusion

The final chapter on estrogen therapy has not yet been written. Though there still might be a place for HRT drugs to treat vasomotor symptoms such as hot flashes and night sweats, and a place for vaginal creams for vaginal atrophy, there seems to be limited hope for the use of estrogen to prevent osteoporosis in the face of great risks of using HRT. New approaches and new drugs to treat menopausal symptoms are constantly arriving on the scene, but each poses the challenge of translating information and dosages based on large studies and statistics into a treatment that is tailored to an individual woman's needs.[392]

What is most interesting about hormone replacement therapy are the lessons to be learned. First, claims for the use of a drug, whether approved or off-label, should be proven by large, randomized, long-term, placebo-controlled trials with participants from the target population before widely prescribing them for that use. Second, the consuming public should make an effort to be more informed about the drugs they are taking by doing independent research on the drugs – doctors and health organizations may have biases from pharmaceutical companies and thus their information should not necessarily be taken at face value. Finally, prescribing drugs for preventative means to healthy women should be done with the utmost of caution!

[390] *Questions and Answers*, *supra* note 348.
[391] *Id.*
[392] *See The "Today" Show* (NBC television broadcast, January 10, 2005), *available at* http://www.msnbc.msn.com/id/6799284.