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The M Word Symposium An Interdisciplinary Adventure

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The "M Word" Symposium: An Interdisciplinary Adventure

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Most importantly, I must acknowledge the constant love and support of my husband, David Faigman, without whom this conference would not have been possible, and my three daughters, Sarah, Amanda, and Hannah, whose confidence in me and willingness to be endlessly educated about all things hormonal never wavered. Their presence at the symposium brought home to me one of my greatest motivations for holding it, which was to educate and empower as many women as possible, and to fight for continuing robust research on these critical women's health issues. And lastly, some credit for both the symposium and this article must be given to the Vivelle Dot estradiol patch. This may come across as glib, but in all sincerity, neither would have come to fruition without it.

I. INTRODUCTION

I am honored to write this Article to introduce the *Hastings Women's Law Journal* Winter 2011 Symposium Issue. This issue includes just a small sampling of written submissions from participants in our February 2011 symposium, entitled "Frontiers in Women's Health: The Role of Hormones in Aging and Disease," which was jointly sponsored by the HWLJ and the UCSF/UCHastings Consortium on Law, Science and Health Policy.[1] Included herein are Dr. Marianne Legato's keynote address, *From Gender to Genomics: Achievements and Challenges in Sex Specific Science*, and Dr. Cynthia Stuenkel's article, *Hormone Therapy for Postmenopausal Women: A Brief History of Time*, which touch on just a few of the many topics explored and debated at this dynamic conference. Additionally, symposium panel moderator Professor Jamie King has contributed a personal piece, entitled *Living ART.*

In this article I aim to summarize the issues that provided the impetus for the symposium. The title of my contribution is an homage to the original, tongue-in-cheek title I gave to the proposal for the conference when it was just a seed of an idea. Even as the idea was bubbling to the surface, I admit that I wondered whether proposing a symposium organized around the topic of menopausal hormone therapy ("MHT") was either (1) a wise career move or (2) worth my energy to develop, given what I assumed might be people's reactions. My running joke was that if one wanted to make people uncomfortable, one might speak openly in polite company about "female troubles," but if one wanted to send people (men *and* women) fleeing to hide under the bed in the fetal position, the topic of menopause[2] would do the trick. While our society has "come a long way, baby," in our willingness to have mature discussions regarding previously mentioned-only-in-whispers subjects like breast cancer or PMS,[3]

1. The UCSF/UC Hastings Consortium on Law, Science & Health Policy is dedicated to improving interdisciplinary communication and collaboration between the law and the health sciences. For more information, please see http://www.ucsf-hastingsconsortium.org/. The event was livestreamed, and archival video is available at http://www.livestream .com/uchastings.

2. Menopause is the permanent end of menstruation and fertility, and is usually defined as occurring twelve months after a woman's last menstrual period. *See Menopause: Definition*, MAYO CLINIC (July 23, 2011), http://www.mayoclinic.com/health/menopause /DS00119.

3. "PMS" is the commonly used acronym for premenstrual syndrome, which can cause a wide variety of physical or emotional symptoms, including abdominal bloating, headache, fatigue and irritability that typically occur about five to eleven days before the onset of menstruation. *See* A.D.A.M. Med. Encyclopedia, *Premenstrual Syndrome*, PUBMED HEALTH, http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002474/ (last reviewed Nov. 16, 2011). While PMS seems to be discussed more openly in American society today than in the past, at least among women, a recent humorous advertising campaign touting the benefits of milk in reducing the severity of symptoms caused such a furor that it was discontinued shortly after it began airing. *See* Juliet Williams, *Got PMS? New Campaign Says Milk Can Help With That*, ASSOCIATED PRESS, July 13, 2011, *available at*

menopause remains a hugely uncomfortable and mysterious issue in most arenas. Perhaps this is because it combines two such fraught and touchy areas, namely women's cycles and the dread and denial surrounding aging.

So, how does an untenured law faculty member decide to pursue and attempt to organize a conference around this topic, bringing together academics and researchers from different fields, some of whom literally do not speak the same professional language? And why do the students on an academic law journal board embrace that idea, even though at first glance one might imagine the topic not feeling "relevant" to the median law student age group? I can answer the first question honestly, and refer the reader to the journal's foreword for the answer to the second.

I came to commonly refer to myself, during the months we spent preparing for the symposium, as the "poster child for menopause," acutely aware that I would be the median age of menopause, fifty-one, on the date we chose to hold the event. But aside from the coincidence of my age matching that statistical median age, my interest in, and exhaustive research on, menopause and MHT was borne out of my personal struggles to cope with bewildering, frightening, and frankly infuriating symptoms.

During the spring law school semester in 2010, I experienced uncharacteristic distractibility, forgetfulness, fatigue, and what seemed to be a diminished ability to take in and remember "new" material I was reading, in addition to a general outlook that felt more negative than what had been my normal baseline. I was suffering from insomnia, often coupled with nighttime "hot flashes," which is in my opinion an awfully mild phrase to describe a sensation akin to a coal-fired furnace raging out of control and taking over one's internal thermostat. All of this was terribly inconvenient and distressing, due to a particularly intellectually demanding teaching schedule.[4] I felt like I was barely keeping up, working longer and longer hours on my background reading and class preparation, and needing to read new material more than once in order to recall information. While lecturing, I noticed an increase, subtle but real, in the following: (1) instances of what I would characterize as "verbal memory" deficits, basically a general lack of fluidity in my thought processes and their translation into words (for example, forgetting, mid-sentence, a case name that was quite familiar to me, or finding myself almost at a loss for words when trying to answer a student's question), (2) loss of my "train of thought," (again, sometimes mid-sentence), and (3) "tip of the tongue"

http://www.businessweek.com/ap/financialnews/D9OEDRFO1.htm; Shelby Knox, *Victory! Got Milk Ends Sexist PMS Ad Campaign Early Amid Public Outcry*, CHANGE.ORG (July 22, 2011), http://news.change.org/stories/victory-got-milk-ends-sexist-pms-ad-campaign-early-amid-public-outcry.

4. I was teaching, in addition to a seminar I had taught before, a new course entitled "Science in Law," which was quite demanding due to the wide range of topics I was covering, in addition to brushing up on scientific methods and statistics, which comprised the early framework of the course.

phenomenon, the sense that the ideas and words were *there* but just out of reach and inaccessible in the moment.[5] These symptoms came and went unpredictably and, for a person in the early stages of a mid-life career shift to academia, were becoming a handicap and were downright scary. I tried to explain it to my husband and daughters, but had difficulty doing so. (I usually resorted to the highly scientifically sophisticated sentence: "I feel like I'm getting stupider.") While they were supportive and patient, I know they felt helpless in the face of my growing alarm.

The only explanation I could think of, aside from premature dementia caused by some as-yet-undetected terrifying illness or tumor, was that this was just part of the normal aging process. Maybe fifty was not, in fact, the "new thirty," but instead was the era of the "Incredible Shrinking Brain." In retrospect, I should have suspected hormonal causes. With an undergraduate degree in biology and a lifelong obsession with all things medically related, I should have been able to self-diagnose with ease. But I didn't. In retrospect, I still cannot fathom why the pieces did not come together. Perhaps denial about my march toward middle age, combined with a vague knowledge that my own mother had experienced "late" menopause, contributed to my thinking that menopause and its symptoms were still far off in the future. Or perhaps it was simply that I was struggling, running faster and faster to meet my own standards in my teaching and in my role as a wife and mother, and I couldn't spare the time or the brain cells to stop the treadmill long enough to either figure it out on my own or enlist a doctor's help to do so. I was still having regular, if shorter, cycles, so menopause wasn't really on my radar screen, and instead I lay awake worrying about early-onset Alzheimer's disease and full-blown clinical depression, as my negative outlook crowded out other aspects of my character and personality.

I limped my way through the semester and gratefully collapsed after the last day of classes. I turned to some unanswered emails, and found one from my oldest daughter, sending me a link to a *New York Times Magazine* feature article entitled, *The Estrogen Dilemma*, by Cynthia Gorney, a UC Berkeley journalism professor and freelance writer.[6] As I had had little time for reading outside of class materials and background research for my new course for several months, I was looking forward to reading something "non-work-related," so I printed the article and set it on my bedside table. As I started reading the article that night, what felt like a thousand light bulbs came on over my head, and I felt a profound rush of emotion and

5. I did not know it then, but these are common complaints of women in the years leading up to menopause and after, and there is scientific evidence that explains the possible biological mechanisms of how fluctuations and reductions in circulating estrogen levels can cause these symptoms.

6. Cynthia Gorney, *The Estrogen Dilemma*, N.Y. TIMES, Apr. 18, 2010, (Magazine) at MM52, *available at* http://www.nytimes.com/2010/04/18/magazine/18estrogen-t.html?pagewanted=all. Cynthia Gorney was one of the panelists at the conference.

insight. It was the first time in months that I did not feel like I was losing my mind. Ms. Gorney's open and honest description of her own struggles with perimenopausal[7] and menopausal symptoms, as well as those of other women she interviewed, felt so familiar to me. I literally sobbed with relief as I recognized my own symptoms being described, explained, and logically attributed to decreases and wild fluctuations in estrogen levels.

The relief and odd joy I felt as it dawned on me what was probably causing my symptoms were followed by confusion, shock, and then anger, as I read the rest of the article. Like every woman "over a certain age" who wasn't living under a rock in July of 2002, when the Women's Health Initiative ("WHI")[8] hormone trial findings were splashed across the front page of every newspaper,[9] I had read the articles. What I had gleaned from them back in 2002 was that decades of conventional wisdom was turned on its head. Contrary to the large body of previous evidence that hormone use in menopause could be protective of the cardiovascular system and brain, as well as protecting against bone loss, the WHI trials reportedly showed that hormone therapy actually *increased* a woman's risk of heart disease, dementia, and breast cancer.

The study results, presented as they were in a distilled-down, simplified popular media analysis, had landed like a neutron bomb on hormone therapy. At the time, I was in my early forties and not yet suffering any symptoms of perimenopause, but I had a vague memory that my mother had experienced difficulty in menopause, and I knew that my sister, thirteen years older than I, had severe symptoms and credited PREMPRO[10]

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7. "Perimenopause, also called the menopausal transition, is the interval in which a woman's body makes a natural shift from more-or-less regular cycles of ovulation and menstruation toward permanent infertility, or menopause." *Perimenopause: Definition*, MAYO CLINIC (Sept. 16, 2010), http://www.mayoclinic.com/health/perimenopause/DS0055. The perimenopause period is marked by erratic and dramatic fluctuations in reproductive hormone levels. *See, e.g.*, Edtya J. Frackiewicz & Neal R. Cutler, *Women's Health Care During the Perimenopause*, 40 J. AM. PHARMACISTS ASS'N 800 (2000).

8. *Background and Overview of the Women's Health Initiative*, WOMEN'S HEALTH INITIATIVE, *available for download at* http://www.nhlbi.nih.gov/whi/mediakit12-14-05.pdf.

9. The story was widely published across the U.S. *See*, News Release, National Institutes of Health, NHBLI Stops Trial of Estrogen Plus Progestin Due to Increased Breast Cancer Risk, Lack of Overall Benefit (July 9, 2002), *available at* http://www.nhlbi.nih.gov/new/press/02-07-09.htm.

10. PREMPRO is the commercial name for the combination MHT pill that contains both conjugated equine estrogens, derived from the urine of pregnant mares, and a manufactured form of progestin, Medroxyprogesterone Acetate. *See*, PREMPRO, http://www.PREMPRO.com/index.aspx?source=google&HBX_PK=s_PREMPRO&HBX_OU=50&o=47364519|223603789|0&skwid=43000000330517390 (last visited Oct. 31, 2011). In women with a uterus, it is necessary to add a progestin to estrogen therapy for menopausal symptoms, to prevent and overgrowth of cells in the uterus, which can increase risk for uterine cancer. Wyeth Pharmaceuticals was the original manufacturer of PREMPRO, but Wyeth was bought out by Pfizer in 2009. PREMPRO was the medication used in the E+P arm of the WHI hormone trials, and was provided free by Wyeth. It was a logical choice to use PREMPRO, since most of the women in the observational trials had used this medication for MHT. *See* Writing Grp. for the Women's Health Initiative

with saving her sanity and her marriage. Because it was my understanding that menopause symptoms can "run" in families, I had been assuming that I, too, would probably want to avail myself of hormone therapy once menopausal symptoms arose, if indeed they did. After I read the popular media accounts of the WHI findings, however, I figured that I would have to forgo hormone therapy because of these new data. Yet it became clear as I read Gorney's article that everything I thought I "knew" about hormone therapy in menopause was far from clear and might in fact be exactly wrong.

It seemed that the WHI hormone trials had raised more questions than they answered, and that more and better research was critically necessary. But it also seemed that the National Institutes of Health ("NIH") was not interested in funding this additional research. Wait just a minute, I thought—hormone therapy to treat sometimes debilitating symptoms of menopause *used to be* thought to be protective of the heart and brain, as well as bones, based upon decades of observational data and high quality animal and *in vitro* studies.[11] Then, several hundreds of millions of dollars were spent on randomized clinical trials,[12] which some researchers claimed showed that hormone therapy *increases* cardiovascular disease and dementia risk. But, after further analysis, it is now clear that there are substantial limitations in said expensively gathered trial data[13] and that the data do not come close to answering all the questions.

Investigators, *Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results from the Women's Health Initiative Randomized Controlled Trial*, 288 JAMA 321 (2002).

11. *See* discussion *infra* Parts II.B.

12. The original budget for the entire Women's Health Initiative was $625 million. *See* COMM. TO REVIEW THE NIH WOMEN'S HEALTH INITIATIVE, INST. OF MED., AN ASSESSMENT OF THE NIH WOMEN'S HEALTH INITIATIVE 19 (Susan Thaul & Dana Hotra, eds., 1993). The total cost of all the studies in WHI has been cited as $725 million, including $415 million for the dietary modification studies. National Heart, Lung, and Blood Institute, National Institutes of Health, Telebriefing on Women's Health Initiative (Feb. 7, 2006), *transcript available for download at* http://public.nhlbi.nih.gov/newsroom/home/DocDownload.aspx?ObjectType=Downloadable&id=236.

13. Indeed, there is an argument that the money might have been much better spent on several smaller trials, as mentioned below, rather than just two trials including, respectively, over sixteen thousand (E+P) and ten thousand (estrogen-only) women subjects each. Such staggeringly high numbers of trial subjects are not necessary for valid and reliable results (as long as scrupulous care is taken with randomization and stratification, if relevant), and potential confounds and biases are successfully predicted and controlled for as well as is possible. Increasing the number of trial subjects beyond what is necessary to obtain statistically significant results, while reducing the chances for random deviation from "ground truth" in the data, cannot reduce the risk that data is compromised by bias or confounds—*only proper study design and execution can accomplish that goal.* It is common for scientists to discover flaws in study design only after data are collected, which then normally leads to a new study design and one or more follow-up studies. One of the biggest limitations of the WHI hormone trials is that they did not include enough women in the population most relevant to MHT, namely women in their early fifties, to obtain powerful and statistically significant results, since the effects on this smaller subgroup were

And now the government has decided it does not want to, or it cannot,[14] spend any more money to seek those answers? This seemed illogical, given that menopause, with its dramatic decreases in circulating estrogen levels, affects all women who reach their fifties and younger women who have their ovaries surgically removed or experience early menopause for some other reason. Since women are overwhelmingly likely to die of some effect of cardiovascular disease, more likely than any other cause of death (including all forms of cancer)[15] and since women make up approximately 65% of Alzheimer's disease diagnoses,[16] shutting off the research funding pipeline prematurely made no sense to me. For decades, women were systematically excluded from all clinical trial research, and assumptions about women's health were made based on the idea that "women are just 'small men,' so we don't need to devote resources to studying women's health."[17] Finally, in 1991, the WHI was mandated by Congress.[18] But if funding does not continue at a robust level after the initial research reveals more critical questions to be answered, then what was really accomplished by the WHI? Was it simply a pat on the head, one act of throwing money at a previously neglected group (women—*half the population*), in the hopes that once the women got their research initiative, perhaps they would shut up and stop being so demanding?

The morning after I read the article I did two things that I believe altered the course of my life for the better: (1) I made an appointment with my doctor, which led to my using an estrogen patch and, shortly thereafter, resolution of my symptoms (it sounds dramatic to say that I felt as if I was given my life and my brain back, but I did), and (2) I started gathering and reading every published scientific article I could find on the subject of hormone therapy and the action of estrogen in the brain and body, which led to the idea for this symposium and the opportunity to meet and exchange ideas and information with some of the finest scientists and medical and legal scholars in the country.

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masked by the larger group of older women. *See* Orkun Tan et al., *What Can We Learn from Design Fault in the Women's Health Initiative Randomized Clinical Trial?*, 67 BULL. N.Y.U. HOSP. JOINT DISEASES 226 (2009).

14. One apparent reason for the reluctance to generously fund denial of funding for follow-up studies is, ironically, that the WHI data show that hormone use in menopause is more harmful than helpful, which raises obvious ethical concerns about the safety of trial subjects. This creates a "Catch-22" situation, where it may become impossible to prove the flaws and lack of external validity of most of the WHI hormone data because the WHI hormone data are used to deny future funding.

15. *See, e.g.*, Melonie Heron, *Deaths: Leading Causes for 2007*, NAT'L VITAL STAT. REP., Aug. 2011, at 1, 9, *available at* http://www.cdc.gov/nchs/data/nvsr/nvsr59/nvsr59_08.pdf.

16. *See, e.g.*, Alzheimer's Assoc., *2011 Alzheimer's Disease Facts and Figures*, 7 ALZHEIMER'S & DEMENTIA, no. 2, 2011 at 1, 12, *available at* http://www.alz.org/downloads/Facts_Figures_2011.pdf.

17. *See generally* MARIANNE J. LEGATO, EVE'S RIB: THE NEW SCIENCE OF GENDER-SPECIFIC MEDICINE AND HOW IT CAN SAVE YOUR LIFE (2002).

18. *Background and Overview of the Women's Health Initiative*, *supra* note 8.

What I found in my thorough literature review was that, taken as a whole, the body of research paints a much more complex picture than was presented by either the popular media accounts of the results of the WHI hormone trials or the original scientific publication of the data and interpretation thereof.[19] Indeed, the scientific evidence and data from the many modes of research, including the observational trials, animal studies, and *in vitro* experiments and observations, seem to converge most plausibly toward the conclusion, or at least the well-grounded hypothesis, that the overall results of the WHI hormone trials cannot and should not be generalized to women who elect to begin hormone therapy before or around the time of menopause. Further, there is a biologically plausible hypothesis, sometimes referred to as the "timing hypothesis,"[20] that might explain why this is the case, and why the results in the WHI trials were different than had been expected, given the observational data gathered on the effects of hormone therapy over the previous decades.

Over the course of weeks of research, I came to the personal decision to remain on the estrogen patch, to which I will eventually add a two week course of progesterone every few months.[21] I made this personal decision, first, because my distressing and almost debilitating symptoms are controlled and relieved with the addition of the estrogen. My quality of life is markedly better. Second, I believe, based upon the entire body of research to date, that my use of the patch will probably *reduce* my risk of cardiovascular disease and dementia, in addition to protecting me from bone loss and osteoporosis, among other benefits.[22] The additional lifetime

19. Writing Grp. For the Women's Health Initiative Investigators, *supra* note 10. *See also* Tara Parker-Pope, *How NIH Misread Hormone Study in 2002*, WALL ST. J., July 9, 2007, at B1, *available at* http://online.wsj.com/article/SB118394176612760522.html.

20. This is the idea that differences in age or time elapsed since menopause when MHT is initiated may account for differences in outcomes, including coronary heart disease and dementia. Under the timing hypothesis, the initially puzzling contradictions and even seemingly opposite effects of menopausal hormone treatment seen between the prior accumulated evidence on MHT and the data from the WHI hormone trials is logically explained, with compelling biological plausibility. *See, e.g.*, S. Mitchell Harman et al., *Timing and Duration of Menopausal Hormone Treatment May Affect Cardiovascular Outcomes*, 124 AM. J. MED. 199 (2011); V.M. Miller et al., *Using Basic Science to Design and Clinical Trial: Baseline Characteristics of Women Enrolled in the Kronos Early Estrogen Prevention Study (KEEPS)*, 2 J. CARDIOVASCULAR TRANSLATIONAL RES. 228 (2009).

21. Adding progesterone in addition to estrogen, as part of a hormone regimen, either daily or cyclically, is necessary for women who have not undergone a hysterectomy and still have a uterus, to prevent an abnormal buildup of the uterine lining, which can increase the risk of uterine cancer and can lead to breakthrough bleeding. *See, e.g.*, Elisabete Weiderpass et al., *Risk of Endometrial Cancer Following Estrogen Replacement With and Without Progestins*, 91 J. NAT'L CANCER INST. 1131 (1999).

22. This is absolutely not a medical recommendation for any other woman. Every woman should make her own decision, but it should be an informed decision, armed with the truth about the WHI trials and all the data available, not based on a personal anecdote like mine, but also, not based on inaccurate and sensationalistic interpretations of the science.

exposure to estrogen, which has been shown to be correlated with lifetime breast cancer risk, may increase my chances of developing breast cancer, but as discussed below, even this is more complicated than the initial WHI reports suggested.[23] My estrogen patch is simply one type of estrogen exposure that adds to my lifetime exposure from all sources.[24] In my personal situation, including an analysis of my known risk factors, my patch probably increases my breast cancer risk only slightly, rather than the dramatically increased risk sometimes hinted at in popular media reports about hormone therapy.[25]

My initial research, as well as anecdotal evidence I have gathered in the past two years, points to the increase in breast cancer risk as the most frightening possibility to women contemplating MHT in the post-WHI world. I believe that this fear, as opposed to the data regarding cardiovascular and dementia risk, is the major factor that has resulted in fewer women opting for MHT.

While it is true that, just like circulating estrogen from other sources in my body, the estrogen from my patch might cause any "estrogen-receptor positive" as-yet-undetected breast cancer tumor that I might develop to grow more aggressively than it otherwise would,[26] there is not yet any definitive proof that the estrogen component of hormone therapy treatment *causes* breast cancer, aside from the long-known *lifetime* estrogen exposure

23. There is evidence that the synthetic progestin in PREMPRO (Medroxyprogesterone Acetate, or "MPA") used in the WHI E + P trial arm may be the cause of the small, non-statistically significant increase in breast cancer seen in the trial treatment group. There is still much to be learned about the many and varied protocols available for hormone therapy, which differ depending on the type of estrogen, the type of progestin, and the administration method (i.e., oral pill form, skin patch or spray, vaginal suppository, etc.) *See* Agnes Fournier et al., *Unequal Risk for Breast Cancer Associated With Different Hormone Replacement Therapies: Results From the E3N Cohort Study*, 107 BREAST CANCER RES. & TREATMENT 103, 108 (2008).

24. MHT was found in pre-WHI observational studies and randomized clinical trials to increase age-adjusted incidence of breast cancer by about 20%, but to decrease breast cancer *mortality* by over 20%. *See, e.g.*, Leif Bergkvist et al., *The Risk of Breast Cancer After Estrogen and Estrogen-progestin Replacement*, 321 NEW ENG. J. MED. 293 (1989); Graham A. Colditz et al., *The Use of Estrogens and Progestins and the Risk of Breast Cancer in Postmenopausal Women*, 321 NEW ENG. J. MED. 1589 (1995); Francine Grodstein et al., *Postmenopausal Hormone Therapy and Mortality*, 336 NEW ENG. J. MED. 1769 (1997).

25. There are many factors that correlate with risk of breast cancer, not all of which have a clear causal explanation. In my case, I may have a lower risk of breast cancer because of several personal characteristics and life events, including: No personal history of breast cancer; No first degree relatives have been diagnosed with breast cancer; No exposure to high doses of chest radiation; No maternal exposure to DES; Late onset of menstruation; Had first child at the age of 23; Non-dense breasts; Not obese; Good amount of physical exercise; Low to moderate alcohol consumption; Never smoked cigarettes; Breast fed three children. *See generally Breast Cancer Risk Factors*, UCSF MEDICAL CENTER, http://www.ucsfhealth.org/education/breast_cancer_risk_factors/ (last updated Aug. 17, 2011).

26. For a discussion of the four main types of breast tumors and the generally better prognosis for hormone-receptor positive tumors, see generally, Nancy Walsh, *Breast Cancer Risk Factors Vary by Tumor Subtype*, BREASTCANCER.ORG (May 22, 2009), http://www.breastcancer.org/risk/new_research/20090522.jsp.

correlation.[27] In fact, what was initially downplayed in the data from the estrogen-only arm of the WHI trials is that the data show that women in the estrogen-only hormone therapy group had a *reduced risk* of breast cancer as compared to the placebo group.[28] There is a biologically plausible hypothesis that the equine estrogen in Premarin, used in the estrogen-only trial (the same estrogen in PREMPRO) may lower breast cancer risk by binding to the estrogen receptors in the breast, thereby "blocking" other estrogens' access to breast cells, similar to the action of the "SERM" drugs[29] given to prevent breast cancer recurrence in patients. The estrogen in my patch, 17β-Estradiol, is biologically identical to the most prominent estrogen naturally produced by the human body, and therefore it may not act in the same way as Premarin.[30]

My personal calculus includes the facts that I have no family history of breast cancer, I do not have "dense" breast tissue,[31] I undergo annual mammography screening,[32] I have never smoked, and I am doing all that I can to minimize my other risk factors for breast cancer, such as exercising

27. "Since data on tumor doubling times in women suggest that a breast cancer requires at least 8 years from inception to achieve a clinically detectable size, this early increase in risk is consistent with accelerated growth of pre-existing lesions, rather than causality." R. D. Langer, *On the Need to Clarify and Disseminate Contemporary Knowledge of Hormone Therapy Initiated Near Menopause*, 13 CLIMACTERIC 303, 305 (2010) (citing D. von Fournier et al., *Growth Rate of 147 Mammary Carcinomas*, 45 CANCER 2198 (1980)). *See also*, Fournier et al., *supra* note 23, on synthetic progestin MPA as the probable problematic fraction of PREMPRO.

It is true that breast cancer diagnoses have declined since the number of women opting for MHT has declined, and many tout this as definitive proof of a causal link between MHT and breast cancer. But this is far from simple or definitive. The decline in diagnoses may be due to a decreased rate of mammography screening, or an epidemiological "glitch." There is some evidence that the rate of diagnosis is beginning to increase again. *See generally* Winnifred Cutler & Regula Burki, *A Public Health Paper on Breast Cancer Incidence that Does Not Withstand Scrutiny*, 13 CLIMACTERIC 607 (2010); Nancy Breen et al., *Was the Drop in Mammography Rates in 2005 Associated with the Drop in Hormone Therapy Use?*, CANCER, Aug. 22, 2011.

28. *See* Andrea Z. LaCroix et al., Women's Health Initiative, *Health Outcomes After Stopping Conjugated Equine Estrogens Among Postmenopausal Women with Prior Hysterectomy: A Randomized Controlled Trial*, 205 JAMA 1305, 1308 (2011). *See also,* Tara Parker-Pope, *Estrogen Lowers Breast Cancer and Heart Attack Risk in Some*, N.Y. TIMES, Apr. 6, 2011, at A1, *available at* http://well.blogs.nytimes.com/2011/04/05/estrogen-lowers-risk-of-heart-attack-and-breast-cancer-in-some/.

29. *See* discussion *infra* p. 37, for more about SERMs.

30. *See* Fournier et al., *supra* note 23. *See also* Montserrat Garcia-Closas et al., *Clarifying Breast Cancer Risks Associated With Menopausal Hormone Therapy*, 7 LANCET ONCOLOGY 885 (2010).

31. "Denser" breasts are associated with a higher risk of breast cancer, in addition to and independently of circulating hormone levels. *See* Rulla M. Tamimi et al., *Endogenous Hormone Levels, Mammographic Density, and Subsequent Risk of Breast Cancer in Postmenopausal Women*, 99 J. NAT'L CANCER INST. 1178, 1178 (2007).

32. In fact, there is good evidence that being on hormone therapy may lead women to be more compliant with recommendations for annual mammography screening, since it is required in order to renew a hormone prescription through a doctor. *See generally* Langer, *supra* note 27.

and keeping my weight down. I made my decision after exhaustive personal research and in consultation with a physician and nurse practitioner whom I trust and respect. Yet I know that my decision, like most medical decision-making, is an exercise in weighing risks and benefits. For me, the possible benefits of preserving my cognitive function and cardiovascular health, in addition to improving my quality of life by controlling my symptoms, prevailed over my own fears around breast cancer. To a certain extent, given the incomplete picture painted by the current state of the scientific knowledge, I am rolling the dice (well-informed, carefully considered dice though they may be) and hoping I am right.

I began to wonder about, as we like to say in the law, "similarly situated" women. Were there millions of other women like me, who had read the media reports about the WHI trials and assumed they should forego MHT? I kept thinking to myself that a woman should not have to have a Stanford biology degree and access to an extensive database of medical and scientific research articles to become educated about the true state of scientific knowledge about the risks and benefits of MHT. I knew that I was on the proactive end of the spectrum with regard to my own health-care decision-making, so if I was previously uninformed about the true significance of the WHI trials, then I suspected that a high percentage of women in the U.S. were similarly uninformed. This concern, combined with the apparent unwillingness of federal funding agencies to aggressively fund follow-up research to answer the remaining significant questions, raised a multitude of interesting issues that could be explored in an academic symposium.

I do note that, in the months since the symposium, there has been a slight but noticeable shift in media coverage of the issue of MHT. For example, in April 2011, a group of WHI investigators published follow-up findings on 7,645 of the women in the estrogen-only WHI trial, who had taken Premarin for a mean duration of 7.1 years before the trial was halted by the investigators in 2004.[33] The follow-up data showed that, in all age groups, the Premarin treatment subjects had a 23% lower risk of breast cancer than the placebo group. Further, the younger women in the treatment group (age fifty to fifty-nine, reflective of the population of women most likely to be prescribed MHT during perimenopause or menopause) had lower risk of coronary heart disease, heart attack, colon cancer, and death, as well as a lower global index of chronic disease.[34]

33. *See generally* LaCroix et al., *supra* note 28.
34. *Id.*

These findings were reported in the popular press and on the websites of breast cancer awareness groups.[35]

The biological mechanisms behind these lowered risks (and the increased risks in some outcomes seen in older subjects) are not yet well understood. Still, the dissemination of these findings, along with other analyses of the WHI data and other scientific findings, have tempered some of the shrill warnings that dominated in the years immediately following the trials' termination. Many prominent researchers and clinicians who had previously hewed to the post-WHI dogma that potential harms from MHT outweigh benefits have begun publicly calling for more research. They are espousing a much more nuanced position than before, affirming that the benefits and risks of MHT for a particular woman depend on her age, health status, the type of hormone(s) used, and the method of delivery (i.e., pills, creams, patches and/or suppositories).[36] Interestingly, this position aligns closely with that of the scientists who have developed and are testing the timing hypothesis.

After developing the ideas and issues to be explored at the symposium, and enlisting the sponsorship of the *Hastings Women's Law Journal* and the UCSF/UC Hastings Consortium, we sought scientists, physicians and legal scholars with direct and related expertise to serve as panelists. It is common for established academics my age to have developed a scholarly focus over more than two decades. They therefore tend to propose and host conferences in subject areas in which they've been writing for many years, inviting colleagues in the same field whose work is well known to them, and who will undoubtedly recognize the name of the host professor. In contrast, I was a law professor reaching out to scientists and medical professionals who did not know me, and who almost certainly would never have imagined attending a law school symposium or cross-pollinating with legal scholars. I was struck by the openness and generosity with which my inquiries were met. Many panelists gave of their time to correspond with me and lead me to others at the cutting edge of women's health research, and one after another enthusiastically agreed to participate in the symposium. I was especially gratified on the day of the conference when more than one panelist commented on the quality of the assembled experts. It seemed that we had amassed a veritable "Who's Who" in the area of women's health and hormones, as well as some of the most interesting and prominent legal scholars in the areas of informed consent, shared medical decision making, and sex differences, and their significance in the law. We

35. *See, e.g.*, Parker-Pope, *supra* note 28; John Gever, *New WHI Estrogen Analysis Shows Lower Breast Cancer Risk*, BREASTCANCER.ORG (Apr. 5, 2011), http://www.breastcancer.org/risk/new_research/20110405.jsp.

36. *See, e.g.*, Parker-Pope, *supra* note 28; Tara Parker-Pope, *For Some in Menopause, Hormones May Be Only Option*, NYTIMES.COM (Aug. 15, 2011, 6:15 PM), http://well.blogs.nytimes.com/2011/08/15/for-some-in-menopause-hormones-may-be-only-option/.

are all grateful to every panelist for his or her contributions to the symposium. It well illustrated the remarkable synergy that can take place with interdisciplinary conversation and collaboration.

II. BACKGROUND

A. MENOPAUSE AND HORMONE THERAPY BEFORE WHI

Cynthia Stuenkel's article, beginning *post* page 45, provides an excellent overview of menopause and many of the trials and studies that took place prior to the WHI. The history of MHT in the United States alone makes clear that women have sought relief from symptoms generation after generation. In the early 1900s, when there were no pharmaceutical options, women actually ate or drank solutions containing extracts from animal ovaries to treat their symptoms. The first estrogen patch was developed in the late 1920s, and by the mid-1930s, pharmaceutical companies began producing hormonal treatments in injectible and pill form. The year 1941 ushered in Premarin, which was more potent than the earlier estrogen products. Sex researcher William Masters of Masters and Johnson fame experimented with estrogen in elderly patients in the 1940s, and in 1951 he began recommending it as a general health improver for both men and women.

Also in the early 1950s, autopsies on women were showing that women who had had their ovaries removed suffered more advanced atherosclerosis than women of the same age with intact ovaries, which led scientists at the Mayo Clinic to suggest that estrogen had a protective cardiovascular effect. But at the same time, the results of animal studies were showing elevated cancer risk associated with estrogen, so doctors responded by prescribing it only for short-term symptom relief in menopause.

Then, in the late 1960s, Dr. Robert Wilson's book, *Feminine Forever*, in which he argued that MHT would help women stay healthier for life, successfully promoted an increase in hormone therapy prescriptions.[37] In 1975, evidence emerged showing a link between estrogen therapy and endometrial (uterine) cancer in humans, which led to the addition of a progestin to existing MHT regimens to protect against this effect.[38] On the positive side, however, in 1979 a ten-year study was completed that found that estrogen taken within three years of the onset of menopause actually reversed bone loss[39] in study subjects. On the heels of that, in 1984, both

37. He also strenuously argued that they would look younger and more attractive, and avoid the dreaded stereotype of being old, "dried up" and past their prime. Cynthia A. Stuenkel, *Hormone Therapy for Postmenopausal Women: A Brief History of Time*, 23 HASTINGS WOMEN'S L. J. 45, 49-50 (2012).

38. *Id.* at 51.

39. Menopause is the most important risk factor for bone loss in midlife women. Women lose about 50% of their trabecular bone and 30% of their cortical bone during their lifetimes, half of which is lost during the first ten years after menopause. Joel S. Finkelstein et al.,

the NIH and the FDA declared that estrogen was the most effective drug treatment for osteoporosis.

From the mid-1980s through the 1990s, the sum of the evidence, including animal and human studies and *in vitro* research (discussed below), indicated that MHT not only relieved menopausal symptoms such as "hot flashes," insomnia, mood disturbances, and cognitive difficulties, but also conveyed protection from osteoporosis and bone fractures, cardiovascular disease and possibly neurological impairment such as dementia, including Alzheimer's disease. In 1992, the American College of Physicians recommended that all women entering menopause should be counseled about, and offered, hormone therapy.[40]

In the wake of all this good news, hormone therapy prescriptions soared. In the year 2000, forty-six million prescriptions were written for Premarin in the U.S., making it the second-most frequently prescribed drug and accounting for more than $1 billion in sales. More than twenty-two million prescriptions were written for PREMPRO. Sales of the two drugs peaked at $2 billion in 2001.[41]

B. OVERVIEW OF SCIENTIFIC EVIDENCE SHOWING BENEFITS OF MHT

While it is beyond the scope of this Article to set forth an exhaustive list of the scientific evidence about the benefits of MHT that had accumulated prior to the release of the WHI trial data, and has continued to accumulate since, it is important to cite at least a partial sample of this evidence. The prior decades of observational and epidemiological studies, some following women for more than twenty-five years, had indicated that MHT, in particular the estrogen component, provided not only relief from vasomotor symptoms ("hot flashes" and night sweats), sleep disruption, mood swings and vaginal discomfort, but also protection from osteoporosis and bone fractures, cardiovascular disease, and possibly neurological impairment such as dementia, including Alzheimer's disease. Obviously, the evidence was compelling enough by 1992 to lead to the near universal recommendation that women use MHT in menopause. It was the very breadth, depth, and robustness of this body of evidence that made the WHI trial results so unexpected. Research is ongoing, albeit with a relative dearth of federal funding, and scientists are working to understand and

Bone Mineral Density Changes During the Menopausal Transition in a Multiethnic Cohort of Women, 93 J. CLINICAL ENDOCRINOLOGY & METABOLISM 861, 861 (2008).

40. Am. Coll. of Physicians, *Guidelines for Counseling Postmenopausal Women About Preventative Hormone Therapy*, 117 ANNALS INTERNAL MED. 1039, 1039 (1992).

41. DAVID H. KRELING ET AL., THE KAISER FAMILY FOUNDATION, PRESCRIPTION DRUG TRENDS: A CHARTBOOK UPDATE (2001), *available at* http://kff.org/rxdrugs/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=13796.

reconcile all the scientific data in order to provide biologically plausible hypotheses that may explain the differing results.[42]

Because most of the beneficial effects of MHT seem to be linked to the estrogen component, and some of the harms shown in the WHI estrogen plus progestin trials ("E+P trials") are hypothesized to have been caused by the particular progestin in PREMPRO, it seems imperative that more research be done on different forms and methods of administration of MHT.

1. Cardiovascular/Heart Disease

The primary purpose of the WHI hormone trials was to try to replicate the findings of decades of observational trials that showed a cardioprotective effect of MHT. In addition to the observational trials, there is a large body of scientific evidence from cell and animal models that supports the existence of such an effect.

Women who undergo bilateral ovariectomy (removal of both ovaries), which causes premature menopause, show a progressively increased risk of heart attack; the younger a woman is at the time of surgery, and the longer the estrogen deficiency persists, the greater the risk of heart attack.[43] Those results converge with findings from a large epidemiological study that followed women who underwent natural menopause and did not add MHT: For each year delay in menopause, cardiovascular risk decreased 2%.[44] All of these findings are supported by robust evidence from animal studies, including studies on primates. For example, in one study, a group of reproductive-age female monkeys underwent bilateral ovariectomy. One group was treated with MHT beginning immediately post-surgery, whereas the other was not. The group treated with MHT developed little or no coronary artery plaque over time, whereas the control group developed plaque at an accelerated rate.[45]

42. The timing hypothesis is one. While research is ongoing, funding for MHT research became difficult to obtain after WHI.

43. L. Rosenberg et al., *Early Menopause and the Risk of Myocardial Infarction*, 139 AM. J. OBSTETRICS & GYNECOLOGY 47 (1981). The standard of care currently is to treat these women with MHT, at least until the median age of menopause, to prevent this increased risk. An early study, published in 1953, which looked at previously ovariectomized women once they reached the 50-59 year age group, in an era *before* the routine use of MHT following ovary removal, showed that they had almost the same rate of severe coronary atherosclerosis as men the same age (64% versus 76%) as opposed to women their age who had undergone natural menopause (25%). John H. Wuest, Jr. et al., *The Degree of Coronary Atherosclerosis in Bilaterally Oophorectomized Women*, 7 CIRCULATION 801 (1953).

44. *See, e.g.*, Yvonne T. van der Schouw et al., *Age at Menopause as a Risk Factor for Cardiovascular Mortality*, 347 LANCET 714 (1996).

45. *See, e.g.*, Thomas B. Clarkson, *Inhibition of Postmenopausal Atherosclerosis Progression: A Comparison of the Effects of Conjugated Equine Estrogens and Soy Phytoestrogens*, 86 J. CLINICAL ENDOCRINOLOGY & METABOLISM 41 (2001).

The many and varied observational trials provided substantial evidence of cardiovascular benefit.[46] Observational studies involve researchers following a certain population for a period of time, and gathering data on lifestyle choices such as diet, exercise, and medication use, along with ongoing data on various health outcomes. Probably the best known example is the Nurses' Health Study, which started in 1976 and has included over 238,000 participating nurses, focusing on cancer, cardiovascular disease, and diabetes, among other conditions. The Nurses' Health Study provides some interesting results on cardiovascular disease and MHT use, especially when one compares the results reported in 1985, in which MHT users overwhelmingly used unopposed estrogen alone, primarily Premarin, to the results reported in 2000, in which many MHT users used PREMPRO.[47] Users of the unopposed estrogen exhibited a 75% decrease in coronary heart disease risk compared to nonusers.[48] In contrast, later users with an intact uterus, who used estrogen plus a progestin, primarily PREMPRO, also experienced reduced cardiovascular disease risk, but only a 30% decrease, indicating that the daily addition of the manufactured progestin MPA attenuated, or "blunted," the positive effects of the estrogen.[49]

In the 1990s, data were released on the first two major randomized controlled clinical studies on MHT. The first, the Postmenopausal Estrogen/Progestin Intervention, or "PEPI" trial, found that MHT decreased levels of LDL cholesterol ("bad" cholesterol), elevated HDL cholesterol ("good" cholesterol) and lowered levels of fibrinogen, which is a blood clotting factor produced in the liver, high levels of which is a risk factor for cardiovascular disease.[50] So this study offered some biological plausibility for a protective effect of MHT.

The Heart and Estrogen/Progestin Replacement Study ("HERS") set out to see whether MHT would lower cardiovascular disease risk in women who already had documented heart disease. The study found that it did not, and in fact MHT appeared to increase risk for cardiovascular disease

46. The observational studies have been criticized due to potential confounds, including "healthy user" and surveillance bias, rendering them possibly inapplicable to the general population. For example, in the Nurses' Health Study, one hypothesis is that healthier, and more health conscious, women were the ones opting for MHT in the first place, so that other health decisions could have accounted for the decrease in risk of heart disease and dementia in women who were MHT users.

47. *See* Lawrence S. Phillips et al., *Postmenopausal Hormone Therapy: Critical Reappraisal and a Unified Hypothosis*, 83 FERTILITY & STERILITY 558, 560 (2005).

48. *Id.*; *see also* Meir J. Stampfer, *A Prospective Study of Postmenopausal Estrogen Therapy and Coronary Heart Disease*, 313 N. ENG. J. MED. 1044 (1985).

49. Phillips et al., *supra* note 44. *See also* Francine Grodstein, *A Prospective, Observational Study of Postmenopausal Hormone Therapy and Primary Prevention of Cardiovascular Disease*, 133 ANNALS INTERNAL MED. 933 (2000).

50. Writing Grp. for the Pepi Trial, *Effects of Estrogen or Estrogen/Progestin Regimens on Heart Disease Risk Factors in Postmenopausal Women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial*, 273 JAMA 199 (1995).

events.[51] The results of this trial, while unexpected at the time, may be explained by the timing hypothesis.[52] Once coronary heart disease and atherosclerosis have progressed to the point of active disease, including cardiovascular events such as heart attack and stroke (as existed in the trial subjects, by design), the addition of MHT, especially through oral administration, might be expected to cause an elevated risk, due to the increased risk of blood clotting, combined with the existing atherosclerosis.[53]

Additionally, there is an emerging body of evidence that estrogen, particularly 17β-Estradiol,[54] acts directly on the blood vessels, protecting vascular health in women, and acting to prevent cardiovascular disease through several possible mechanisms as well as maintain good blood circulation to the brain, as discussed below.[55] These effects are thought by some to be more robust and more powerful than the lipid profile benefits such as those shown in the PEPI trial.[56]

2. The Brain: Brain Health, Cognitive Function, Mood, and Dementia Risk

a. Brain Health

Additionally, both *in vitro* and *in vivo* animal studies have shown protective and beneficial effects of estrogen, specifically 17β-Estradiol, otherwise referred to as E^2, on brain cells and brain function.[57] Both animal models and clinical studies show that estrogens exert actions on brain regions in addition to those involved in reproductive functions, including midbrain and brain stem neurons that produce critical neurotransmitters, the cerebral cortex, and the hippocampus, among others.[58] These areas are integral to learning and memory, emotional and affective state, motor coordination, and pain sensitivity.[59] It appears that estrogens act both by interacting with estrogen receptors on brain cells themselves, and through other mechanisms, including regulation of gene expression, increased cerebral blood flow, mediation of neurotransmitters, and anti-inflammatory and antioxidant action.

51. *See* Stuenkel, *supra* note 37 at 54. *See generally* Stephen Hulley et al., *Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women*, 280 JAMA 605, 610–12 (1998).

52. Harman et al., *supra* note 20.

53. *Id.*

54. This is the most prominent and biologically active estrogen in women of reproductive age.

55. *See, e.g.*, Andrea Cignarella et al., *Direct Effects of Estrogen on the Vessel Wall*, 21 MEDICINAL RES. REV. 171 (2001).

56. *Id.*

57. *See, e.g.*, Bruce McEwen, *Estrogen Actions Throughout the Brain*, 57 RECENT PROGRESS HORMONE RES. 357 (2002).

58. *Id.* at 358.

59. *Id.*

Animal studies have shown almost universally that the presence of reproductive-age levels of circulating estrogens is protective against brain neuron damage from stroke.[60] This is consistent with evidence in humans showing that higher levels of circulating estrogen protects against brain tissue damage when stroke occurs.[61] Women, at least before menopause, show less lasting damage from stroke than men.[62] After menopause, however, if no MHT is present, that phenomenon reverses and women suffer worse stroke outcomes.[63]

b. Cognitive Function

Although it is one of the most difficult areas to study, and is fraught with controversy, evidence strongly suggests that estrogen promotes higher cognitive function. Studies have shown that the highest working memory and verbal memory in younger women occurs when estrogen is at its highest in the monthly cycle. A 2002 U.S Department of Health and Human Services Evidence Review on MHT and Cognition, reviewing the twenty-nine studies that met their criteria for validity and reliability, found that women who had suffered symptoms from menopause who were treated with MHT showed improved memory, vigilance, reasoning and motor speed, while no benefits were seen in asymptomatic women.[64]

The large body of evidence about estrogen's effects on many brain regions, including the hippocampus, provides support for the hypothesis that estrogen has a powerful protective effect on memory. While memory is notoriously difficult to test, evidence has accumulated that strongly suggests estrogen is memory protective when present at the physiologic levels of a normal reproductive-age woman, and memory enhancing when restored to a woman in an estrogen-deprived state. For example, the overall import of studies looking at the association between estrogen and memory is that estrogen helps support and maintain short- and long-term

60. *See, e.g.*, Patricia D. Hurn & I. Mhairi Macrae, *Estrogen as Neuroprotectant in Stroke*, 20 J. CEREBRAL BLOOD FLOW METABOLISM 631 (2000).

61. *Id.* Although the WHI data revealed a slightly increased risk of stroke in the treatment groups, possibly due in part to the increased risk of blood clots (particularly with the use of the oral estrogen in Premarin and PREMPRO), the fact remains that pre-menopausal women are at a reduced risk of stroke compared to men. This risk advantage disappears shortly after menopause with no MHT, which suggests that higher circulating levels of E2 are also protective against having a stroke at all.

62. *See generally* Patricia D. Hurn & Lawrence M. Brass, *Estrogen and Stroke: A Balanced Analysis*, 34 STROKE 338 (2003); Hurn & Macrae, *supra* note 60.

63. Hurn & Brass, *supra* note 62.

64. ERIN LEBLANC ET AL., AGENCY FOR HEALTHCARE RESEARCH & QUALITY, HORMONE REPLACEMENT THERAPY AND COGNITION (2002). Randomized controlled trials and cohort studies were reviewed for the effects of HRT on cognitive decline; cohort and case-control studies were reviewed for dementia risk. No randomized controlled trials regarding dementia risk were identified.

verbal memory.[65] Women who are current users of MHT have been convincingly shown to score better than matched nonusers on several sexually dimorphic cognitive function measures.[66]

One of our panelists, USC neuroscientist Dr. Roberta Diaz Brinton, was quoted in Gorney's *New York Times Magazine* article thusly, when asked why she elected to begin MHT for symptoms: "Because with estrogen I don't have attention-deficit disorder."[67]

c. Mood

Multitudes of women describe debilitating mood swings and depressed mood in perimenopause and menopause. While this is discounted by some, and even passed off as a secondary effect of one of the more easy-to-document symptoms, such as insomnia, or related to life changes such as children growing up and leaving the "nest," there are reams of research to support a clear link between estrogen fluctuations or deprivation and depressed mood.[68] Multiple studies have shown that MHT is a powerful therapy for depression or mood disturbance in menopause.[69]

d. Dementia Risk, Including Alzheimer's Disease

In 1997, 2.32 million Americans were living with Alzheimer's disease.[70] A 1998 study projected that this number could quadruple to 8.64 million Americans with Alzheimer's by 2047.[71] The public health implications are enormous, and the costs associated with the care of dementia patients is staggering.[72]

A meta-analysis of twelve observational studies revealed that MHT was associated with a decreased risk of dementia. Among other

65. *See, e.g.*, Barbara B. Sherwin, Review, *Estrogen and Memory in Women: How Can We Reconcile the Findings?*, 47 HORMONES & BEHAVIOR 371 (2005); Doreen Kimura, *Estrogen Replacement Therapy May Protect Against Intellectual Decline in Postmenopausal Women*, 29 HORMONES & BEHAVIOR 312 (1995).

66. *Id.*

67. Gorney, *supra* note 6. "'There are all these fundamental cognitive functions that many perimenopausal women complain about, and one of those fundamentals is attention,' Roberta Brinton, the U.S.C. scientist, told me. 'When you can't hold your attention to a thought. Where you're in constant start mode, and you never reach the finish mode. That is devastating.'" *Id.*

68. *See, e.g.*, George Fink et al., *Estrogen Control of Central Neurotransmission: Effect on Mood, Mental State, and Memory*, 16 CELLULAR & MOLECULAR NEUROBIOLOGY 325 (1996); Johanna S.M. Archer, *Relationship Between Estrogen, Serotonin, and Depression*, 6 MENOPAUSE 71 (1999); Zenab Amin et al., *Effect of Estrogen-Serotonin Interactions on Mood and Cognition*, 4 BEHAVIORAL & COGNITIVE NEUROSCIENCE REVS. 45 (2005).

69. *Id.*

70. Marilynn Larkin, *Alzheimer's Disease Prevalence May Quadruple*, 352 LANCET 965 (1998).

71. *Id.*

72. "For people with Alzheimer's disease and other dementias, aggregate payments for health care, long-term care and hospice are projected to increase from $183 billion in 2011 to $1.1 trillion in 2050 (in 2011 dollars). Medicare and Medicaid cover about 70% of the costs of care." Alzheimer's Assoc., *supra* note 16.

discoveries, scientists have shown *in vivo* that the presence of 17β-Estradiol protects neurons from damage that occurs in the presence of amyloid beta, the substance found in the tangled brains of Alzheimer's patients.[73] Further, potentially relevant to Alzheimer's disease, estrogen has been shown to promote the excretion of amyloid beta from the cerebrospinal fluid.[74]

Multiple studies have shown that the use of MHT during a woman's lifetime reduces the risk of developing Alzheimer's disease from 33% to 60%.[75] Many studies have shown additionally that MHT not only reduces this overall risk, but also significantly delayed the onset of the disease, *even in those at an increased hereditary risk of developing the disease*, due to the presence of the ApoE4 form of the apolipoprotein gene.[76]

3. Bone Health

Women will lose, on average, about 50% of their trabecular bone[77] and about 30% of their cortical bone[78] over their lifetimes. By far the biggest factor in bone loss is menopause, and half of the lifetime bone loss occurs during the first ten years after menopause, assuming no MHT.[79] Once bone mineral density reaches a critically low level, osteoporosis, a bone disease that leads to increased risk of fracture, is diagnosed.[80]

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73. *See, e.g.*, Jon Nilsen et al., *Estrogen Protects Neuronal Cells from Amyloid Beta-Induced Apoptosis via Regulation of Mitochondrial Proteins and Function*, 7 BMC NEUROSCIENCE 74 (2006). "During aging, especially during the development and progression of neurodegenerative diseases, including Alzheimer's disease (AD), damaged mitochondria are unable to maintain the energy demands of the cell. Interrupted energy metabolism is observed in many instances of neurodegeneration, including cerebral ischemia and Alzheimer's disease, two neurological conditions that account for the majority of all neurodegenerative conditions. . . . In this study we demonstrated that [17β-Estradiol] prevented the neurotoxic induced decline in mitochondrial respiratory function. This is consistent with the previous reports that [17β-Estradiol] is protective against cell death induced by energy depletion and blocks the decrease in mitochondrial membrane potential. . . [.] Thus [17β-Estradiol] may be able to prevent interruption of neuronal energy metabolism associated with neurodegeneration[.]" *Id.* at 80-3.

74. *See* Benecia C. Hong-Goka & Fen-Lei F. Chang, *Estrogen Receptors Alpha and Beta in Choroid Plexus Epithelial Cells in Alzheimer's Disease*, 360 NEUROSCIENCE LETTERS 113 (2004).

75. *See, e.g.*, Rachel A. Whitmer et al., *Timing of Hormone Therapy and Dementia: The Critical Window Theory Revisited*, 63 ANNALS NEUROLOGY 163 (2011).

76. Ming-Xin Tang et al., *Effect of Oestrogen During Menopause on Risk and Age at Onset of Alzheimer's Disease*, 348 LANCET 348 (1996).

77. This is the porous bone in the spine and articulating joints. *See generally, Biomechanics of Trabecular Bone*, BERKELEY ORTHOPAEDIC BIOMECHANICS, http://biomech2.me.berkeley.edu/trabecular.html (last visited Nov. 9, 2011).

78. This is the solid bone tissue found in the middle of the long bones of the body. *See generally Biomechanics of Cortical Bone*, BERKELEY ORTHOPAEDIC BIOMECHANICS, http://biomech2.me.berkeley.edu/cortical.html (last visited Nov. 9, 2011).

79. Finkelstein et al., *supra* note 39 at 831.

80. The World Health Organization lists the diagnostic criterion for osteoporosis in postmenopausal women and in men aged fifty or older as a femoral neck bone mineral density score that is 2.5 standard deviations below the young female adult mean. *See*

More than ten million Americans have osteoporosis, which leads to about two million bone fractures every year.[81] While it may not immediately come to mind as a major public health problem, it is a huge drain on health care resources. The National Osteoporosis Foundation estimates that in 2005, osteoporosis was responsible for $19 billion in costs of health care and lost productivity in the United States, and by 2025 it is predicted to cause three million fractures and lead to $25.3 billion in costs each year.[82] While fractures do not commonly lead to death as a primary outcome, a recent study showed that both older men and older women who suffer an osteoporotic fracture are at an increased risk of death for five to ten years after the injury, compared to the general population.[83] Risk of death is increased for an additional five years with a second fracture.[84]

Close to half of all menopausal women will experience at least one fracture.[85] Decades of observational data and meta-analyses of the effect of MHT on bone mineral density have shown that MHT, both estrogen-only and combined E+P, act to preserve bone and reduce the risk of fracture in postmenopausal women.[86] These findings were replicated in both arms of the WHI hormone trials.[87]

MHT was, up until the WHI, the first-line treatment for bone loss or osteoporosis in women during perimenopause or menopause. Post-WHI, however, the U.S. Preventative Services Task Force and FDA recommend against the use of MHT to prevent chronic diseases, including osteoporosis, and instead recommend the use of other prescription drugs, such as bisphosphonates and calcitonins.[88] The bisphosphonates, such as Fosamax and Boniva, slow down the breakdown and removal of bone, but not as efficiently as MHT, and may cause serious side effects. The FDA has recently issued new warnings about use of bisphosphonates being linked to necrosis (death) of the jaw bone and an unusual type of fracture of the

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WORLD HEALTH ORGANIZATION, WHO SCIENTIFIC GROUP ON THE ASSESSMENT OF OSTEOPOROSIS AT PRIMARY HEALTH CARE LEVEL 8 (2007).

81. Finkelstein et al., *supra* note 39 at 831. *See also, Why Bone Health is Important*, NAT'L OSTEOPOROSIS FOUND., http://www.nof.org/node/150 (last visited Nov. 9, 2011); B. Lawrence Riggs & L. Joseph Melton, *The Prevention and Treatment of Osteoporosis*, 327 NEW ENG. J. MED. 620 (1992).

82. *Why Bone Health is Important, supra* note 81.

83. *See generally* Dana Bliuc et al., *Mortality Risk Associated With Low-Trauma Osteoporotic Fracture and Subsequent Fracture in Men and Women*, 301 JAMA 513 (2009).

84. *Id.*

85. *See Why Bone Health is Important, supra* note 81; Riggs & Melton, *supra* note 81.

86. Jane A. Cauley et al., *Effects of Estrogen Plus Progestin on Risk of Fracture and Bone Mineral Density: The Women's Health Initiative Randomized Trial*, 290 JAMA 1729 (2003).

87. *Id.* at 1737.

88. *See generally* U.S. Preventative Servs. Task Force, *Hormone Therapy for the Prevention of Chronic Conditions in Postmenopausal Women: Recommendation Statement*, 142 ANNALS INTERNAL MED. 855 (2005).

femur bone in the leg.[89] Calcitonin, a thyroid hormone that regulates calcium concentrations in the body, has been shown to improve bone density in the spine, but not elsewhere in the body, at least as of yet, so other treatments are considered far superior for osteoporosis and bone loss.

4. Colon Cancer

Colorectal cancer is the third-most-common cancer in U.S. women, after breast and lung cancer. Prior to the WHI hormone trials, both a systematic review of twenty-one observational trials and a meta-analysis of eighteen studies reported overall findings of a protective effect of MHT on colon cancer.[90] The HERS trial revealed a reduced risk for colon cancer as well, after seven years of follow-up.[91] The reduced risk has been shown to be strongest in current users.

C. THE WOMEN'S HEALTH INITIATIVE: PURPOSE, METHODOLOGY, RESULTS, AND ANALYSIS

In the hierarchy of scientific evidence, large, randomized, controlled, double-blind clinical trials have traditionally been elevated as the "gold standard" of evidence to be considered when making health-care decisions, and especially when formulating public health guidelines.

Menopause, of course, affects all women who live long enough. It thus directly impacts half of the population, and, indirectly, the other half. Coronary heart disease is the biggest killer of women in the United States. Sixty-eight percent of diagnosed Alzheimer's victims are women. In just the last thirty years, the number of Americans diagnosed with memory diseases has doubled, and the frequency of dementia doubles every five years beginning at age sixty.

Given the major public health implications if MHT has a protective effect on these two classes of disease, it made scientific sense, and good public health sense, for the NIH to push to fund high quality randomized clinical trials, similar to the PEPI and HERS studies. The data from observational studies, *in vitro* bench science, *in vivo* animal studies, and earlier randomized control trials in humans seemed to provide convergent validity for the hypothesis that MHT was protective, and if those results could be replicated in a large scale clinical trial, it might be good public health policy to recommend MHT for almost all women. On the basis of this accumulated evidence, the NIH jointly sponsored, with the National Heart, Lung and Blood Institute, the WHI.

89. Duff Wilson, *Stronger Cautions Backed on Bone Drugs for Women*, N.Y. TIMES, Sept. 9, 2011, at B1.

90. See Francine Grodstein et al., Postmenopausal Hormone Therapy and the Risk of Colorectal Cancer: A Review and Meta-analysis, 106 Am. J. Med. 574 (1999).

91. See Stephen Hulley et al., Noncardiovascular Disease Outcomes During 6.8 Years of Hormone Therapy: Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II), 288 JAMA 58 (2001).

All told, WHI involved 161,808 women between the ages of fifty and seventy-nine, and it was supported by NIH and Congress in large part to try to make up for the historic inequities in women's health research. It included both observational and randomized, controlled clinical trial components. In addition to the pair of randomized trials that involved MHT,[92] one randomized trial studied the effects of a low fat diet, hypothesized to prevent breast cancer and colorectal cancer (and, secondarily, coronary heart disease), and another trial focused on calcium and vitamin D supplementation, hypothesized to prevent hip fractures (and, secondarily, other fractures and colorectal cancer).[93]

In the E+P PREMPRO study group, 8,500 women received PREMPRO, and 8,100 received the placebo. In the estrogen-alone Premarin study group, 5,300 women got Premarin and 5,400 received the placebo. Recruitment began in September 1993 and women were continuously enrolled through October 1998.

The study was originally planned to follow the women for at least eight years, but in 2002 the PREMPRO trial was halted early due to findings that coronary heart disease actually *increased* by 24% in the estrogen plus progestin group.[94] Breast cancer risk also increased, by 24%,[95] but this increase was not statistically significant and amounted to only an additional nine cases per ten thousand women per year.[96]

Final results and analysis showed that the apparent increase in coronary heart disease was not statistically significant, meaning it could have occurred by chance, so now, in 2011, it is no longer scientifically defensible to state that MHT increases coronary heart disease. Risk of stroke and deep vein thrombosis did increase.

In the estrogen-alone trial, the treatment group had a 44% lower risk of colorectal cancer and a 24% lower risk of bone fracture. The risk of death from any cause was almost equal between the treatment and placebo groups. The estrogen-alone trial was halted in 2004, not due to increased breast cancer risk,[97] but just a generalized perceived lack of a likelihood of

92. To review, the hormone therapy trials within the WHI were randomized, double-blind, placebo-controlled studies in women from ages 50 to 79. There were two groups: women with a uterus, who were given PREMPRO or a placebo, and those without, who were given Premarin alone or a placebo.

93. Women's Health Initiative Study Grp., *Design of the Women's Health Initiative Clinical Trial and Observational Study*, 19 CONTROLLED CLINICAL TRIALS 61 (1998).

94. Writing Grp. for the Women's Health Initiative Investigators, *supra* note 10.

95. *But see* discussion, *infra* p. 37, about absolute vs. relative risk.

96. While an increase of 24% may seem large to a casual observer, one needs to look at the absolute risk of breast cancer in the control group to properly assess the meaning of the percentage increase. In scientific studies, if an observed difference does not rise to the level of "statistical significance," it essentially means that the observed findings could have occurred by chance.

97. In fact the data ultimately showed a decreased breast cancer risk in the treatment group, although, as in the E+P trial, the difference was not statistically significant.

an ultimate net benefit because researchers determined that the data indicated that the apparent risks of the hormone therapy outweighed the apparent benefits.

The data from the PREMPRO E+P study group indicated the following:[98]

- Deaths: risk of death from any cause was almost equal between the treatment and placebo groups.

- Fractures: reduced by 24% in the treatment group.

- Colon Cancer: 44% lower risk of colorectal cancer in the treatment group (decrease of six cases per ten thousand women per year)

- Breast Cancer: 26% greater risk of breast cancer in the treatment group (not statistically significant—increase of eight cases per ten thousand women per year).

- Deep Vein Thrombosis or Pulmonary Embolism: twofold increase in risk in the treatment group (increase of eighteen cases per ten thousand women per year).

- Stroke: 31% increased risk for stroke in treatment group (increase of seven strokes per ten thousand women per year—from 24 to 31 women in ten thousand).

- Coronary Heart Disease: 24% overall increased risk of CHD in the treatment group (increase of six heart attacks per ten thousand women per year); but an 81% increased risk of CHD *within the first year* in the treatment group.

The data from the Premarin (estrogen alone) WHI study group (women without a uterus) indicated the following:[99]

- Stroke: increased risk in the treatment group to thirty-eight out of ten thousand women per year, compared with twenty-five out of ten thousand in the placebo group.

- Breast Cancer: 20% lower risk of breast cancer in the treatment group (not statistically significant—decrease of six cases per ten

98. *See* Writing Grp. For the Women's Health Initiative Investigators, *supra* note 10.

99. Women's Health Initiative Steering Comm., *Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy: The Women's Health Initiative Randomized Controlled Trial*, 291 JAMA 1701 (2004).

thousand women per year, from thirty-eight to thirty-four women in ten thousand).

- Coronary Heart Disease: was not increased, and Coronary Artery Calcification (CAC, a predictor for future heart attacks), which was measured only in women ages fifty to fifty-nine using CT scans, was lower. In women who were taking their study pills regularly (at least 80% of the time), the risk of mild-to-moderate CAC was 40-50% lower and the risk of severe CAC was 60% lower in the treatment group compared to placebo.

An ancillary WHI study, called WHIMS, the Women's Health Initiative Memory Study, which followed a small subgroup of the women sixty-five and over, did cognitive assessments to detect development of dementia or mild cognitive impairment. Each woman suspected of having dementia then underwent testing to confirm the clinical diagnosis and classify the type of dementia. There were no significant differences between groups on either measure in the Premarin (estrogen alone) group.[100] In the PREMPRO E+P group, while there was no increase seen in mild cognitive impairment in the treatment group compared to the placebo group, there was an increase in the likelihood of developing dementia (forty of 2,229 women, or 1.8%, in the combined treatment group and twenty-one of 2,303 women, or 0.9%, in the placebo group).[101]

The WHIMS data contradict the bulk of case-control and cohort studies, which have consistently revealed that MHT has a protective effect on cognition when begun in early menopause, around ages fifty to sixty.[102] Even though these findings, which are observational, have been criticized due to potential confounds such as better overall health, higher levels of education, and/or higher socioeconomic status in the group opting for MHT, the timing hypothesis might explain why cognitive protection was found.[103] Because the women in the WHIMS trial were aged sixty-five to

100. Sally A. Shumaker et al., Women's Health Initiative Memory Study Investigators, *Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women: Women's Health Initiative Memory Study*, 291 JAMA 2947 (2004).

101. 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 JAMA 2651 (2003).

102. *See, e.g.*, Erin S. LeBlanc et al., *Hormone Replacement Therapy and Cognition: Systematic Review and Meta-Analysis*, 285 JAMA 1489 (2001); Peter P. Zandi et al., Cache Cnty. Memory Study Investigators, *Hormone Replacement Therapy and Incidence of Alzheimer Disease in Older Women: The Cache County Study*, 288 JAMA 2123 (2002); S. C. Waring et al., *Postmenopausal Estrogen Replacement Therapy and Risk of AD: A Population-based Study*, 52 NEUROLOGY 965 (1999).

103. *See* Walter A. Rocca et al., *Oophorectomy, Menopause, Estrogen, and Cognitive Aging: The Timing Hypothesis*, 7 NEURODEGENERATIVE DISEASES 163 (2010).

seventy-nine and were initiating MHT for the first time at these advanced ages, it is possible that what occurred in those cases was an age-related degeneration of the cardiovascular system and brain (probably due in part to estrogen deprivation postmenopause). WHIMS may have shown that adding estrogen this many years after onset of menopause cannot reverse these age-related declines, and may even be harmful. The methodological flaw of WHIMS, namely using women so far outside the normal window when MHT would be commonly prescribed, makes its data inapplicable to younger women, however. There is an ongoing need for better-designed trials to test the timing hypothesis with regard to cognitive protection.[104]

The results of the trials were the subject of a huge media blitz, and this resulted in a drastic decline in MHT prescriptions and use by women in the United States.[105] The controversy began shortly after the E+P trial was ended prematurely, and that controversy continues to this day. The majority of the forty WHI investigators from sites all over the country were not informed of the decision to stop the trial until they were summoned to a meeting only eleven days before the public announcement.[106] The article that was eventually published in the *Journal of the American Medical Association*[107] about the data was already drafted by the time the investigators arrived for the meeting, so they were excluded from a first review of the data.[108]

Some investigators spoke out and complained about having devoted some ten years to the WHI trials and then being allowed no input on the major publication.[109] Many of them believed that the data were interpreted in a rushed manner and much too broadly.[110]

One of the principal investigators, Dr. Jacques Rossouw, has admitted that a conscious decision was made to limit input on the paper disseminating the data to a small, selectively chosen group, and that the publication authors were aiming to make strong statements.[111] A quote from a *Wall Street Journal* article is telling: "Our main job at the time was

104. JoAnn E. Manson et al., Personal Perspective, *Postmenopausal Hormone Therapy: New Questions and the Case for New Clinical Trials*, 13 MENOPAUSE: J. N. AM. MENOPAUSE SOC'Y 139 (2006). *See also infra* pp. 32–33 for discussion of the KEEPS trial.

105. For example, from 2001 to 2003, there was a 38% decline in prescriptions, from ninety-one million to fifty-seven million, and a decline in use from fifteen million to ten million women. *See, e.g.*, Jung Ki Kim et al., *Changes in Postmenopausal Hormone Therapy Use Since 1988*, 17 WOMEN'S HEALTH ISSUES 338 (2007); Diana S. M. Buist et al., *Hormone Therapy Prescribing Patterns in the United States*, 104 OBSTETRICS & GYNECOLOGY 1042 (2004).

106. Parker-Pope, *supra* note 19.

107. Writing Grp. for the Women's Health Initiative Investigators, *supra* note 10.

108. Parker-Pope, *supra* note 19.

109. *Id.*

110. *Id.* Symposium panelist Dr. Robert D. Langer was quoted thusly: "I think that had the initial report been written by a broader group, as almost all of our later papers have been, it would have been framed differently."

111. *Id.*

to turn around the prevailing notion that hormones would be useful for long-term prevention of heart disease. That was our objective. That was a worthy objective which we achieved."[112] If this quote is accurate, it is distressingly close to an admission that at least some of the investigators were operating with an agenda rather than in keeping with scientific principles and ethics. A stated goal of "turning around" any notion based solely upon the WHI data seems much closer to politics than science.

The NIH and the FDA came out with new guidelines shortly after the trials were halted, stating that MHT should not be taken to prevent heart disease or dementia, and that, although MHT is an approved therapy for treating moderate to severe hot flashes and night sweats, moderate to severe vaginal dryness, and prevention of osteoporosis associated with menopause, the recommendations were (and still are) that MHT be used at the lowest doses for the shortest duration needed to achieve treatment goals.[113] Further, the recommendations state that even though MHT is effective for the prevention of postmenopausal osteoporosis, it should only be considered for women at significant risk of osteoporosis who cannot take one of the non-estrogen medications, such as an oral bisphosphonate like FOSAMAX.[114]

So the question is, did WHI provide all the answers? There are some in the clinical community, and even some in the research community, who say that we now know that MHT is not protective against cardiovascular disease or dementia (and in fact *increases* those risks). They believe that the results of the WHI randomized, controlled, double-blind trials, involving large numbers of women, should be elevated above, and credited to the exclusion of all the other evidence, because in the hierarchy of "evidence-based medicine," such trials are the gold standard, without regard to methodological limitations. They think the data are rock solid and that the questions *have* been answered. On the other hand, many reputable, prominent and respected scientists, including some of the original WHI investigators, believe that MHT *may*, or *does* have a protective effect against cardiovascular disease and dementia, when started at or around the time of menopause. Others are still not sure. Why were the results so different than expected, and at odds with the observational studies that evidenced multiple benefits of MHT? What about the

112. Parker-Pope, *supra* note 19.

113. *See, e.g.*, NAT'L HEART, LUNG, & BLOOD INST., NAT'L INST. OF HEALTH, PUB NO. 05-5200, FACTS ABOUT MENOPAUSAL HORMONE THERAPY, *available at* http://www.nhlbi.nih.gov/health/women/pht_facts.pdf; News Release, U.S. Food and Drug Administration, FDA Updates Hormone Therapy Information for Post Menopausal Women (Feb. 10, 2004), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108243.htm; *Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm135318.htm (last visited Nov. 7, 2011).

114. NAT'L HEART, LUNG, AND BLOOD INST., *supra* note 113.

biological plausibility of a protective effect that was seemingly demonstrated in the *in vitro* and animal studies?

While there is some evidence that MHT use has been reinitiated by some women in the years since the WHI results were released, in particular among middle-class women with good access to quality health care, the percentage of women opting for MHT is still much lower than before.[115]

Since 2002, the WHI hormone trial methodology has been analyzed and critiqued by scientists, and the data obtained has been reanalyzed in light of newer findings and hypotheses, the timing hypothesis in particular. In short, the developing body of research contributing to the timing hypothesis indicates that both *when* a woman begins hormone therapy and with *which* hormones in *which* form may be critical factors that influence whether the hormone treatment increases or decreases the woman's risk for coronary heart disease and Alzheimer's disease, among other health concerns.

For example, on the coronary heart disease front, the timing hypothesis supports the belief that initiating MHT at or near menopause does, in fact, have a protective effect, as was observed for so many decades. The data obtained in WHI can be explained if one assumes that initiating treatment after a certain window of opportunity has passed allows the steep increase of atherosclerotic plaques and the menopause-related cholesterol changes to take hold. This may also allow the deactivation of cellular estrogen receptors, so that the addition of estrogen at a later point has no protective effect and may even have an adverse effect, especially in the first year of treatment, possibly due to the increased blood clotting risk. Both *in vitro* laboratory studies and animal studies support this hypothesis and similar ones regarding hormone effects on the brain and nerve cells.

The timing hypothesis is further bolstered by a closer analysis of the methodological shortcomings of the WHI trial designs.[116] To begin, it is necessary to discuss the goals of a particular trial. What some scientists like to say is that an observational study, like the Nurses' Study, discussed *supra* page 17, is most useful as a hypothesis generator rather than as proof

115. Elizabeth Barrett-Connor et al., *The Rise and Fall of Menopausal Hormone Therapy*, 26 ANN. REV. PUB. HEALTH 115 (2005).

116. There is nothing surprising about scientists learning about methodological flaws in study design only *after* data accumulates. In fact, for most scientists in most fields of endeavor, it is simply a fact of life. Critique of methodology is an integral part of the scientific peer review process and should be expected by any scientist when data and publications are presented for outside review and public consumption. Sometimes recognition of methodological limitations actually contributes as much to the advancement of the knowledge base as the data themselves. There seems to be, however, unusual defensiveness among some WHI investigators when they are confronted with criticism of their methodology, and critics have been sometimes dismissed as "WHI bashers." One investigator, who was invited to participate in the symposium as a panelist, responded by saying, in an email, "I am not eager to continue discussing the WHI findings, and the 'limitations' of WHI."

of a cause and effect relationship. When scientists seek to test hypotheses generated by observational studies, conventional wisdom dictates that the design of the clinical study should parallel as closely as possible *both* the study population and the treatment circumstances in the observational studies.

One obvious example of both study population and treatment circumstances is that women like those in the Nurses' Study opt for MHT at or near the time of menopause, because this is when they are having symptoms. These women were beginning treatment either just before or probably shortly after menopause. That might have been a good place to start when designing the MHT trials for WHI. However, the WHI protocol did not follow this basic rule of clinical study design, at least not in every aspect.

First, in order to obtain statistically significant results about coronary heart disease events in the main MHT trials, the study enrolled women who were, on average, sixty-three years of age and twelve years postmenopause, the vast majority of whom had never used MHT. There were relatively few women between forty-five and fifty-five, which has led scientists to note that the study was underpowered to asses any cardioprotective effects of MHT given at the time of menopause. The same limitation applies to the study of development of dementia in the WHIMS ancillary trial, which enrolled women over sixty-five (average age seventy-one). These decisions are somewhat defensible, since women at or near the time of menopause have been protected by their own circulating estrogen for decades, so are at very low risk for cardiovascular events like heart attack. If the control groups in the studies have a vanishingly low risk of such events, it would in all likelihood not be possible to detect any lessening of the risk with MHT, and so there is no great shame in the logic behind using older trial subjects.

Retrospectively, however, it is apparent that many of the trial subjects may have had advanced cardiovascular disease that was "subclinical" (not apparent to investigators). Even though the women in WHI had not had major cardiac events, it has been hypothesized that up to half of them had risky plaques in their arteries *before* starting MHT. In the PREMPRO® trial, about 5,000 women were between fifty and fifty-nine years of age, 7,500 were between sixty and sixty-nine, and 3,600 were over seventy. They were, on average, slightly overweight. While 6% were current HT users, and 20% were past users, the vast majority, 74%, had never used HT before entering the study. If this was the case, the increase in thrombosis (blood clotting) risk from the MHT could easily explain any increase in cardiovascular events in the treatment group, if blood vessels were narrowed by the presence of fatty deposits or plaques.[117]

117. *See generally* Harman et al., *supra* note 20.

The age of the trial subjects might also be important because the high quality scientific data underpinning the timing hypothesis strongly suggests that being in an estrogen-deprived state over a certain critical amount of time might affect estrogen's ability to confer protection. Animal studies have shown this to be the case. For example, monkeys who were given MHT at the time of menopause had lower cardiovascular risk, but when menopausal monkeys were deprived of estrogen for the equivalent of about six human years, the estrogen had negative effects similar to the WHI results.[118]

While WHI has been criticized for using PREMPRO and Premarin, the free hormone medication received from Wyeth, this was actually methodologically sound, since these were by far the most prescribed MHT formulations used by women in the observational trials. However, the vast majority of the *animal* studies that showed cardioprotective effects of estrogen used 17β-Estradiol, the main circulating estrogen in humans. Here is where collaboration between scientists could have been helpful in the study design, because the animal and *in vitro* researchers would have encouraged having a group that used 17β-Estradiol, probably in patch form, with a placebo patch group. Especially considering the unique circumstances of WHI, with its generous funding stream, this would have been a good opportunity to test other formulations.

PREMPRO and Premarin contain hormones that are not biochemically identical to hormones naturally produced by the human body. Additionally, the use of hormones in pill form may contribute to heightened risk, because when hormones are ingested orally they must go through the liver before entering the blood stream. This factor alone may account for much of the apparent increase in risks seen in the WHI trials, especially the increased risk of blood clots. Estrogen is available in FDA-approved patches, creams, and spray mist, which allows for transdermal (through the skin) absorption directly into the bloodstream, bypassing the liver, which does not have the same increase in thrombosis and clotting risk that oral drugs do. There is now a form of progesterone available in pill form that is identical to the human-produced progesterone. The fact that WHI did not include comparison groups using these "bioidentical" hormones and groups using transdermal estrogen products is a methodological limitation.

In the observational studies, women were followed for, on average, ten to fifteen years, but in the WHI clinical trials they were not followed this long, in part due to the premature stoppage. There is some evidence that a cardioprotective effect might have been seen if the study had continued.[119] The study was stopped because of a predetermined agreed-upon end point

118. *See* Thomas B. Clarkson & Margaret H. Mehaffey, *Coronary Heart Disease of Females: Lessons Learned from Nonhuman Primates*, 71 AM. J. PRIMATOLOGY 785 (2009).
119. Harman et al., *supra* note 20.

if breast cancer risk appeared to be elevated in participants using the treatment–this threshold has been criticized as being too conservative, which is in part borne out by the fact that the slight increase in breast cancer risk in the PREMPRO group turned out not to be statistically significant.

There is an ongoing study, the Kronos Early Estrogen Prevention Study ("KEEPS") that was designed by a group of women's health researchers to test the timing hypothesis and to determine, with a "gold standard" randomized trial, whether MHT does provide cardiovascular protection when initiated during the right window of opportunity in early menopause.[120] KEEPS is a four-year, randomized, placebo-controlled, double-blind study of 729 women at nine sites around the country. Study subjects are between the ages of forty-two and fifty-eight, are at least six months but no more than thirty-six months postmenopause, and are in good general health with normal mammograms. They are divided into three groups and will receive either transdermal 17β-Estradiol via a skin patch, oral estrogen (conjugated equine estrogen, probably Premarin, which was used in WHI), or a placebo.

All women who are receiving active estrogen will also receive progesterone in a bioidentical form for twelve days per month (not the MPA progestin used in WHI). The study will measure atherosclerosis progression by using x-ray tomography to asses carotid artery thickening and coronary artery calcification, and other risk factors will also be assessed over time, including lipid levels (like cholesterol), inflammatory factors such as C-reactive protein, blood coagulation indicators, and hormone levels.

We were honored to have the principal investigator of the KEEPS trial, Dr. S. Mitchell Harman, as a panelist at the symposium, and we, along with many others, eagerly await the trial results.

III. MAJOR THEMES AND ISSUES EXPLORED IN THE SYMPOSIUM AND ANCILLARY EVENTS.

There are two main areas of concern that we wanted to address at the symposium:

(1) there is a dearth of clear, understandable information available to women about what the WHI study data mean, and what questions the study did and did not answer. This is primarily due to the relative lack of media coverage about the limitations and flaws in the study methodology, and

120. Miller, *supra* note 20; THE KRONOS EARLY INTERVENTION PREVENTION STUDY, http://www.keepstudy.org/ (last visited Nov. 10, 2011). The Early Versus Late Intervention with Estradiol (ELITE) is similarly designed, and should generate extremely valuable data. *See ELITE: Early Versus Late Intervention Trial With Estradiol*, U.S. NAT'L INST. OF HEALTH, http://clinicaltrials.gov/ct2/show/NCT00114517 (last visited Nov. 10, 2011).

about the more recent research regarding the timing hypothesis. As a consequence, there is a large number of women, especially in the late "baby-boomer" generation, who may be missing their window of opportunity to make informed individualized decisions about whether to start MHT to protect their future health.

(2) on the public health side, if the timing hypothesis is true, there could be a huge increase in heart disease and dementia, and a decrease in women's quality of life as they age, if many fewer women than in earlier years opt to begin MHT during the critical time frame during or soon after the menopause transition. This has obvious implications for exploding health care costs as this post-WHI generation of women age.

It was our goal for the conference to appeal to a broad and diverse group of people: members of the research and clinical medical and mental health communities; lawyers; legal scholars; public policy experts and policymakers; and members of the lay public. We offered both continuing medical education and continuing legal education, and drew exactly the diverse group of attendees we hoped for.

There were six panels of speakers, three in the morning and three in the afternoon, along with Dr. Legato's compelling lunchtime keynote address. The panel titles were as follows:

- Panel 1: "Hormone Therapy: What We Know (and Don't Know) After the Women's Health Initiative Hormone Trials"
- Panel 2: "Translational Research and the 'Timing Hypothesis'"
- Panel 3: "Government Agency and Health Policy Decision Making: Recommendations in an Environment of Empirical Uncertainty"
- Panel 4: "Public Support, Public Advocacy, and the Role of the Media"
- Panel 5: "Informed Consent / Litigation Over Hormone Therapy"
- Panel 6: "Legal Relevance of 'Real Differences': Constitutional Issues; Work and Family; Health Care and Aging"

Below is just a partial description of issues and questions that were raised and discussed at the symposium. This is my interpretation of the issues, so the observations and questions below reflect, to a large extent, my own analysis and opinions. That said, we strove in planning the conference to invite speakers with diverse points of view and to organize

panels that provided for a balanced presentation and discussion of each topic. By most accounts, we succeeded.

A. SETTING FUNDING PRIORITIES IN PUBLIC HEALTH RESEARCH AND POLICYMAKING

There is indication of a deprioritization and a lack of interest (or a lack of willingness) on the part of NIH entities in aggressively funding follow-up research to fill in the large gaps left after the WHI hormone trials. Women's health research has traditionally been given short shrift, and WHI itself was conceived in part to try to make up for that. Five hundred million dollars, give or take, was spent, and there seems to be little chance of substantial additional public money being spent on follow-up studies, at least as things stand today.

Most scientists understand that no one study can ever answer all the scientific questions inherent in a particular area. What can be said about WHI is that it answered the question of whether women who are more than seven to ten years past menopause without having been on MHT should begin MHT to prevent cardiovascular disease. The short answer to that question is "no," but even on that question, as discussed above, some scientists have hypothesized that a protective effect for many of the WHI women would have become apparent if the trials had been allowed to continue, as the estrogen prevented a worsening of existing atherosclerosis in the treatment women as compared to the controls.

The timing hypothesis adds a layer of urgency to the need for immediate continued research. This is especially true given the potential health care cost implications of an increase in cardiovascular disease, dementia, and osteoporosis among women in the baby boomer generation and beyond, who may forgo MHT due to the WHI trial results even if they are suffering from debilitating menopause symptoms.

One might expect that a study like the KEEPS trial, discussed *supra* pages 32–33, would be eagerly and generously funded by NIH, but in fact it is being privately funded. This lack of federal dollar support has limited the scope of the trial, mainly by limiting the number of sites and the number of women enrolled.[121] As discussed *supra* note 14, the possibly flawed interpretation and belief that the WHI trial results provide proof that the potential harms of MHT outweigh its potential benefits might be contributing to NIH's reluctance to fund hormone research. Obtaining institutional review board approval at a major research university or institution for a clinical trial of MHT might also be difficult; it might be considered unethical to expose trial subjects to a potentially harmful treatment. Therefore, the early, broad interpretation of the WHI results,

121. The ELITE trial is being co-sponsored by the National Institute on Aging. *See ELITE: Early Versus Late Intervention Trial With Estradiol*, *supra* note 120.

along with the resulting governmental recommendations and guidelines, may have created barriers to continued research.

In the arena of scientific funding, it might be particularly interesting to look at the dollars spent on breast cancer research, for example, in comparison to research on heart disease and dementia in women. A woman's risk of dying of heart disease is ten times greater than the risk of dying of breast cancer, accounting for about 40% of total mortality, as compared to 5% for breast cancer.[122] Yet, studies and polls have shown that women perceive the risk of breast cancer as much higher than it actually is, and discount the risk of heart disease.[123] Are funds being allocated to disease research in proportion to the numbers of women potentially affected? If not, should they be?

Scientists today are competing for a piece of an ever-shrinking research funding pie. While planning and preparing for the conference I noted an undercurrent of tension between scientists specializing in different research areas regarding MHT. This is especially apparent when comparing the attitudes of breast cancer researchers to cardiovascular, cognitive, and psychological researchers. The same seems to be true for clinicians specializing in, say, breast cancer treatment, versus cardiology or Alzheimer's care. While it is understandable that an oncologist who spends her days treating breast cancer patients might take the position that no one should use MHT, it is disappointing to imagine scientists and clinicians staking out rigid "positions," potentially at the expense of advancing the state of the art of the science of women's health. One hopes that the cause of promoting women's health on all fronts will remain the central focus, especially since women's health research is still playing "catch up" after decades of scientific focus on men, with women an afterthought.

As an example of the potential for advancement that would be cheered by everyone interested in women's health, there is growing interest in working to develop medication regimens that protect the brain and cardiovascular system without having negative effects on breast and uterine tissue. For example, it has been hypothesized that MHT could be combined with a selective estrogen receptor modulator ("SERM").[124]

122. *See, e.g.,* Sherry L. Murphy, Div. of Statistics, *Deaths: Final Data for 1998*, NAT'L VITAL STAT. REP., Jul. 2000, *available at* http://www.http://rkba.org/research/cdc/nchs/nvs48_11.pdf.

123. *See, e.g.,* Lori Mosca et al., Am. Heart Ass'n Women's Heart Disease & Stroke Campaign Task Force, *Awareness, Perception, and Knowledge of Heart Disease Risk and Prevention Among Women in the United States*, 9 ARCH. FAM. MED. 506 (2000).

124. B. Lawrence Riggs & Lynn C. Hartmann, *Selective Estrogen-Receptor Modulators – Mechanisms of Action and Application to Clinical Practice*, 348 NEW ENG. J. MED. 618 (2003). Some SERMs that are in current use in medicine, and the conditions they treat, include: tamoxifen (breast cancer), raloxifene (breast cancer, osteoporosis), and clomifene (infertility due to anovulation). There is a SERM formulation currently marketed as a supplement for the treatment of menopausal symptoms, called Femarelle. Supplements are

SERMs are molecules that bind to estrogen receptors. Unlike estrogen, though, SERMs do not uniformly act as agonists when they bind to estrogen receptors, and they can in fact act as agonists in receptors in some parts of the body and antagonists in others.[125] So, in theory, women could be treated with MHT plus a SERM that selectively turns down estrogen receptors in the breasts and/or uterus without turning down receptors in the arteries and brain.

While the SERM research is particularly exciting, because it could lead to the best of all worlds in terms of treatment options for MHT, without adequate funding, these types of treatments will be a long time in coming.

B. LEGAL STANDARDS SURROUNDING INFORMED CONSENT UNDER CONDITIONS OF EMPIRICAL UNCERTAINTY

Should doctors be fully advising women of the timing hypothesis and the consequences of missing the window of opportunity? Are there risks in doing so, given the current FDA guidelines? What legal standards do, and should, apply in these and similar medical contexts? These are just a few of the questions on the minds of practitioners, legal scholars, and public health policymakers in regard to MHT.

There is a large volume of legal scholarship addressing what counts as *legally adequate* information disclosure, in addition to case law that has developed in the United States over decades. Medical practitioners, including those who attended our symposium, are of course concerned about the prospect of malpractice suits arising out of claimed inadequate or misleading information provided to a patient.

Our panel discussed the basics of the law of informed consent, and there was a presentation about what is referred to as "shared medical decisionmaking," basically a "process by which patients and providers consider outcome probabilities and patient preferences and reach a health care decision based on mutual agreement."[126] There are many models currently in use, and research is being conducted on the effectiveness of different approaches. The use of "Patient Decision Aids" is particularly intriguing. Decision aids are modules (written materials or electronically presented information in the form of DVDs or online interfaces) that are designed to be used by patients and their families, in addition to direct

not regulated or controlled by the FDA. There is published research regarding the efficacy of Femarelle. *See, e.g.*, I. Yoles et al., *Efficacy and Safety of Standard Versus Low-Dose Femarelle (DT56a) for the Treatment of Menopausal Symptoms*, 31 CLINICAL & EXPERIMENTAL OBSTETRICS & GYNECOLOGY 123 (2004).

125. In biochemistry, generally, an agonist stimulates an action and an antagonist acts against or blocks an action.

126. Dominick L. Frosch et al., *Shared Decision Making in Clinical Medicine: Past Research and Future Directions*, 17 AM. J. PREVENTATIVE MED. 285 (1999).

counseling by a medical practitioner.[127] The aids are designed to present a balanced view of treatment options, including the risks and benefits, and advantages and disadvantages, of each, to facilitate an individualized decision based upon the patient's goals and value choices. Some modules have been developed and are already in use, including one for choosing menopause treatment.[128]

One issue that seems to be critical in the informed consent arena, and one that is certainly at issue in explaining the risks and benefits of MHT to patients, is the difficulty that the lay public has in understanding the difference between absolute and relative risk. This is illustrated well in the MHT area by looking at the increased risk of breast cancer that was reported in the WHI E+P trial. The popular media accounts of the WHI results reported a 26% increase in breast cancer risk and a 41% increase in stroke risk in the PREMPRO® treatment group compared to the placebo group. This sounds like a large increased risk, but in fact one must look at the baseline risk before interpreting the meaning of any percentage increase. The absolute risk of breast cancer and stroke must be considered. Another way of stating the exact same data from the E+P trial is that the increase in breast cancer cases seen in the treatment groups was equivalent to an increase in *eight cases per ten thousand women per year*–from an expected baseline rate of about thirty cases per ten thousand women per year to thirty-eight. The stroke data showed an increased risk from the expected rate of twenty-one strokes per ten thousand women per year, to twenty-nine.[129] How data is presented can have a huge effect on a person's perception of that data, and this understanding is critical in any analysis of informed consent.

C. CRITICAL RACE/SOCIOECONOMIC PERSPECTIVES

The media blitz surrounding the WHI findings may have had an outsized effect on women of color and women of lower socioeconomic status, who traditionally have poor access to quality medical care. Such women have almost certainly not, as a rule, been informed about the limitations of the WHI data and may not be making informed individualized decisions about MHT even when they are suffering severe symptoms.

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127. *See generally,* Jaime Staples King & Benjamin Moulton, *Rethinking Informed Consent: The Case for Shared Medical Decision-Making*, 32 AM. J. L. & MED. 429 (2006).

128. *See Patient Decision Aids*, FOUND. FOR INFORMED MED. DECISION MAKING, http://informedmedicaldecisions.org/patient_decision_aids.html (last visited Nov. 9, 2011).

129. *See* Ctr. for Drug Evaluation & Res., U.S. Dep't of Health & Human Servs., *Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms: Recommended Prescribing Information for Health Care Providers and Patient Labeling*, U.S. FOOD & DRUG ADMIN. (Nov. 2005), http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM135336.pdf.

This group may end up foregoing MHT in higher numbers than women with good access to information and care, and they may as a result miss their windows of opportunity for protection of their future health. Racial minority women, in particular, may be suspicious of the health care system in general, due to historical racism and inequity in access to care. They may have been particularly frightened by the media reports following WHI, and may be difficult to reach for education on actual risks and benefits of MHT.

With the United States on the cusp of implementing broad health care reform, we are facing the happy prospect of greater access to care for a larger percentage of our population, including especially traditionally underserved populations. With more women potentially having access to care, it is critical that balanced and factually complete information on the risks and benefits of MHT be disseminated by physicians and health care practitioners, rather than simply a parroting of the guidelines currently in place. In many cases this will require educating the health care practitioners themselves. The reality is that many health care practitioners who are practicing in women's health are not fully educated on and aware of the methodological flaws in the WHI hormone trials, and how those flaws affect the trial data's appropriateness as a basis for MHT decisionmaking by women at or near the menopause transition.

D. FDA AND OTHER AGENCIES' USE OF "EVIDENCE-BASED MEDICINE" TO FORMULATE PUBLIC HEALTH GUIDELINES

In keeping with the conventional wisdom that randomized, controlled clinical studies are the "gold standard" in scientific research, the WHI study seems to have been given much more emphasis in developing guidelines for the use of MHT in menopausal women than the decades of observational and epidemiological studies, the animal and *in vitro* studies, and anecdotal data from clinicians. Should this always be the case, even when, as with the WHI study, it is shown after the fact that the study had major flaws and limitations and answered only very limited questions for a specific group of women, namely older women years past the menopausal transition period? With the rise in interest in evidence-based medicine to improve health care outcomes as well as promoting the efficient use of limited resources, a sophisticated and nuanced understanding of what makes "good" science good is critical.

E. ROLE OF THE "TRANSLATIONAL RESEARCH" MOVEMENT IN IMPROVING STUDY/TRIAL DESIGN AND INTEGRATION OF SCIENTIFIC FINDINGS INTO CLINICAL PRACTICE

There is a growing interest in encouraging the translation of findings from basic research into clinical medical practice more quickly and efficiently than has been accomplished in the past. This is being pursued, in part, by removing barriers to multidisciplinary collaboration, and in the

medical context this has sometimes been referred to as a "bench to bedside" approach, attempting to move from laboratory research through clinical trials to point-of-care patient applications. To that end, in October 2006, the NIH launched the Clinical and Translational Science Awards ("CTSA") Consortium, which now includes forty-six academic health centers nationwide.

Many bench researchers have expressed disappointment that their findings on the protective effects of hormones on epithelial, brain and nerve cells, and the findings of animal and *in vitro* studies, have not been integrated into health policy guidelines, or at least into the design and implementation of new clinical studies on MHT, especially given the potential implications of the timing hypothesis. There should be a sense of urgency to generate better data, given that women may have a limited window of opportunity to obtain health protection with MHT.

F. HEALTH POLICY DECISION-MAKING IN AN ENVIRONMENT OF CLINICAL UNCERTAINTY

Government entities such as NIH and FDA must constantly weigh competing concerns on the way to setting health policy and offering guideline recommendations. When, as is the case with MHT, the scientific evidence is still incomplete and apparently contradictory, the difficulty of performing these tasks increases exponentially. It is almost assuredly impossible to keep political and interest-group pressures on the sidelines. How do we determine when evidence strong enough to justify public health recommendations?

To illustrate this idea, here is an interesting contrast between the government's guidelines regarding MHT, promulgated in response to the WHI study, as compared to its guidelines regarding breast cancer screening, taking into account the available evidence on mammography.

In November 2009, the U.S. Preventative Task Force ("USPSTF") updated its recommendations for breast cancer screening, recommending against routine screening mammography for women ages forty to forty-nine who have no individualized increased risk for breast cancer, in large part because of the potential negative effects of the high rate of false positive results in this age group, often leading to overdiagnosis and unnecessary treatment. Further, the USPSTF recommended a change from annual to biennial (every two years) screening mammography in women ages fifty to seventy four, to reduce the potential harms of screening by nearly half.

The recommendation for women ages forty to forty nine was significantly soft-pedaled, set forth as a "level C recommendation," meaning that although the USPTF recommends against routine screening in this age group and that there is good evidence that any net benefit is small, the task force recognized that there may be individualized considerations to

support screening in individual patients, and it encouraged individualized, informed decision-making on mammography screening.

Despite a measured tone of the change in recommendations, there was a huge outcry across the country, including personal and professional attacks on members of the Task Force, and accusing the Task Force of political motivation to deny insurance coverage for mammography in the midst of the national debate on health care. Members of the Task Force were forced to defend their recommendations in a climate of near hysteria, and they reiterated in testimony before the House Energy and Commerce Health Subcommittee their support for individualized informed decision-making, weighing the scientific evidence. Task Force chair Dr. Ned Calonge testified: "Screening starting at age 40 should not be automatic. Nor should it be denied. What we are saying is that the decision to have a mammogram for women in their 40s should be based on a discussion between a woman and her doctor. Many doctors and many women, perhaps even most women, will decide to have mammography screening starting at age 40."

This approach stands in contrast to the current USPSTF guidelines on MHT, which recommend *against* the use of MHT for the prevention of chronic conditions in postmenopausal women. Although the USPSTF does mention on its website that "[t]he balance of benefits and harms for a woman will be influenced by her personal preferences, her risks for specific chronic diseases, and the presence of menopausal symptoms," and the results from some of the observational studies are discussed along with the results of WHI, the recommendation is still a strong "D" rating (recommending against the treatment), and no mention is made of the timing hypothesis or of the limitations of the WHI methodology.

Ongoing consideration and discussion of this topic might delve into other government decision-making in the face of clinical uncertainty, such as the Gardasil human papilloma virus and H1N1 vaccines, and the burgeoning area of personalized medicine based on genetics.

G. WHAT'S A "GOOD" FEMINIST TO DO?

The issue of hormone therapy in menopause provides a fascinating backdrop for a discussion of feminism in today's world. As the title of this section asks, what's a good feminist to think, or do, about MHT? Should we rail against the "medicalization" of a "natural" process? Should we be offended and imagine that this "medicalization" is really just "them" telling us we need to use hormones in menopause lest we dry up and become unattractive to men?

Or perhaps we should instead be furious that there has been, over the decades, such a dearth of funding for women's health research, including regarding hormones and heart disease, dementia, and osteoporosis. Anyone reading this Article will probably understand that this is where I come out on the issue. Isn't this part of the equality we have been fighting

for all along–the right to access to quality information to help us make decisions about our health? Of course, before there can be free access to information, quality research must be done to fill in the missing pieces of the puzzle.

Along with access to information, we must be free to make decisions in a climate of understanding and support – understanding of the fact that we are all different and experience life and health transitions differently, and support for each of our personal choices. Several months ago, I was speaking to a young legal academic at a conference about our symposium, and she commented that she thinks using hormones in menopause is becoming a bit like using any kind of pain relief in labor and delivery. It is frowned upon by many, and perhaps women are considered, by some other women, to be incapable of "sucking it up" if they need hormones for symptom relief. This phenomenon is apparent if one peruses the "comments" section after every online article about MHT.

Then there are all the pressures to do everything "naturally." My estradiol patch is providing my body the bioidentical "natural" form of estrogen that I have had coursing through my veins for decades. Why is that less "natural" than taking several other prescription medications to treat my perimenopausal symptoms? A garden-variety symptomatic menopausal woman could end up taking all of the following, under today's guidelines: (1) a statin to maintain a good cholesterol balance; (2) a sleeping medication, for insomnia; (3) an antidepressant, for "mood disturbance"; and (4) a bisphosphonate or prescription injection, for bone loss, for starters. And all these medications present risks of side effects, some of them quite serious. In comparison, my little patch seems quite "natural."

We invited Dr. Joan Wolf, a professor of women's and gender studies, and the author of the book *Is Breast Best?* to serve as a panelist. Her book is about the fact that much of the scientific evidence that is cited as proof of the benefits of breast feeding to both child and mother is in fact suspect and vulnerable to multiple confounds. I have to say, as a woman who breast-fed three children, I have all along taken for granted the touted benefits (and of course patted myself on the back as each new popular media article came out), and even engaged in judging women who either could not or chose not to breast feed. Yet this is a classic area where women end up being divided, for example by socioeconomic status, in terms of their ability to take a long maternity leave and/or breastfeed and still hold down a job.

Women, as I see it, are incredibly good at beating each other up for making the "wrong" choices. After Cynthia Gorney's *Estrogen Dilemma* article was published in the *New York Times Magazine*, Tara Parker-Pope put a blog post about the article on the *New York Times* website, and women just went to town criticizing each others' choices.

So what I want to know is: *why* are women taking the warnings related to using hormone therapy in menopause lying down? After this limited data came out, FDA slapped a black box warning on hormones, and what they are telling women now is: *don't use hormones*. Instead, use all the prescription medications I listed above, possibly combined with psychotherapy, yoga, meditation and a gym membership. And many women are not questioning the advice at all, and are either loading up with prescriptions or suffering with debilitating symptoms, terrified of MHT.

Why are so many of us behaving like scared sheep? In part, I think it is simply because women do not really know that the WHI data are limited in what they can tell us; just as happened with the breastfeeding studies, when the popular press gets ahold of something, it is usually published in a simplistic way. Combine that with people's phobia of science, math, and statistics, and you cannot expect people to seek out information. And in truth, in the hormone arena, it is hard to find even if you do seek it out.

Then there is the breast cancer angle. One WHI hormone trial showed a small increase in breast cancer risk, and one showed a decreased risk– neither statistically significant. But the *increased* risk was one of the most publicized aspects of the trial. Women are terrified of breast cancer, far outsized in relation to their actual risk of breast cancer, especially compared to their risk for heart disease. The breast cancer advocacy movement has been so successful in raising awareness, for which of course it is to be applauded, but along with the rise in awareness has come a rise in fear.

IV. CONCLUSION

I have been acutely aware while writing this essay that the symposium raised more questions than we could adequately address, let alone answer, in two days. The scientific, legal, and policy questions are infinitely complex and fascinating, as well as controversial. This is the stuff of which legendary symposia are made.

Women threw their hormones away in droves after WHI, in large part due to the publicized increase in breast cancer risk. People who reflexively say that randomized, placebo-controlled studies are the "gold standard" no matter what the circumstances would say, perhaps, that they were right to throw them away, under the general "evidence-based" decision-making rules.

The answers to the questions surrounding the safety and efficacy of MHT and the role of hormones in aging are far from complete, but there is a great deal at stake, both for society as a whole and for each of us as individuals. We envisioned this symposium as an arena for information sharing and interdisciplinary collaboration. We succeeded beyond our wildest expectations. It is our hope that the attendees and those who watched the conference online or who will access the archival video will

advocate for funding so that scientists can continue to seek the answers we need to live our best lives. And in the meantime, we need to talk to each other, support each other, and educate the next generation of women so that they will be empowered to live their best lives, too.