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Hormones and the health of women: past, present, and future Keynote address*

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ABSTRACT

The past and possible future roles for hormone use to prevent or encourage pregnancy and to manage or prevent menopause are considered. Beginning in the 1880s, gonadal extracts were used for 50 years to improve health and vigor; evidence for the benefit of these extracts was lacking. Oral contraceptives revolutionized women's lives in the 1960s but had side effects unsuspected until after marketing. Hormone replacement therapy, used for 50 years without large clinical trials of disease outcomes, now proves to have rather similar side effects. Physicians and politicians played interesting roles in their initial distrust and later embrace of hormones. Future uses of sex hormones are likely to be viewed as overmedicalization initially, and time will tell whether these uses are healthy or merely controversial.

Key Words: Sex hormones – Oral contraceptives – Hormone replacement therapy.

The history of hormone replacement to promote health and vigor in old age antedates the use of gonadal hormones for contraception. Hormones used to prevent pregnancy have been more profoundly influenced by religion and politics than any other modern medication. The promotion of estrogen replacement to prolong youthfulness and prevent disease has been uniquely influenced by the growing population of aging postmenopausal women. This paper considers the parallels and differences between the past, present, and future use of hormones to prevent pregnancy and the consequences of aging.

VERY EARLY HORMONE REPLACEMENT THERAPY

This story begins before the end of the last century. As reviewed elsewhere,[1] by the late 1800s, famous physicians (including Brown-Séquard, often called the father of endocrinology) reported the beneficial effects observed in themselves and by their patients after receiving injections of extracts from the gonads of pigs, dogs, and other animals. By the 1920s, some Europeans had paid Voronoff up to $5000 for a chimpanzee testicular transplant.[2] The text of one 1930 advertisement in the US describes just how carefully the testes were selected from abattoir animals "in the prime of life," dissected from surrounding fatty tissues, examined under the microscope for quality, and then slowly baked and dried before being administered. It is doubtful that such products contained any quantity of active hormones or that hormonal health benefits could have been transferred.

The continued use of these 'hormone supplements' for 40 years is a testimony to wishful thinking and the placebo effect. Brown-Séquard himself considered and discarded the notion that his improved health could have been the result of "auto-suggestion."[3] The common characteristic of the evidence for the benefits of gonadal extracts was the absence of properly designed clinical trials with placebo-treated comparison groups. This lack has been a recurring theme in the history of sex hormone supplements for the promotion of youthfulness and health. As we shall see, nothing improves results like no control group.

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ORAL CONTRACEPTIVES, PAST AND PRESENT

The chemistry of most of the major gonadal hormones was discovered in the first half of the 1900s. The research was done by many European and Mexican investigators who were supported by the pharmaceutical industry at a time when there was no real plan for future use of the hormones they sought to produce.[4] Remarkable discoveries were made in fairly primitive laboratory conditions, including the isolation of progesterone from a hairy inedible Mexican yam. By 1955, most of the steroid hormones in use today had been synthesized.

The force behind the development of oral contraceptives was Margaret Sanger, who devoted her life to birth control. Although she was at times a supporter of eugenics and shared the common concerns of her era that uncontrolled population growth in developing nations would breed communists,[4] she was only interested in contraception for women, and believed that no woman is free who does not control her own body. Margaret Sanger was motivated by the death of her mother at age 50, a death she attributed to tuberculosis and too many pregnancies (11 living children), and by her experience as a nurse on the Lower East Side of New York, where she witnessed the poor health of women trying to cope with constant childbearing.[5]

Sanger was a powerful advocate without funds until she became friends with Katherine McCormick, a graduate of MIT and widow of the agriculture tycoon Cyrus McCormick.[6] In 1952, Sanger told McCormick about the possibilities of new hormone work being conducted on animals by Gregory Pincus, who was at that time co-director of the Worcester Laboratory for Experimental Biology in Massachusetts, an institute specializing in steroid hormone research. He had shown that hormones could prevent ovulation in animals. Together Sanger and McCormick supported and encouraged Gregory Pincus to extend his studies of ovulation with a view to creating a contraceptive for women.

Although ultimately Pincus was recognized for this work, frustrated, poorly funded scientists may be interested to know that his research career was not always smooth. At one point, Pincus received a letter from his boss that read, "To date your research, as a contribution to the commerce of the industry that was the sponsor, has been completely inadequate. You will get more money only if you produce something immediately."[6] Despite such discouraging feedback, studies by Pincus and others ultimately led to the first oral contraceptives.

The first clinical trials of sex hormones in humans were designed to evaluate hormone use as a contraceptive. Clinical trials were necessary to show that the prevention of ovulation in animals could be applied to the prevention of pregnancy in humans. John Rock, a charismatic Catholic physician, was an advocate for sex hormones as contraceptives. He promoted clinical trials to test their efficacy, even though (or perhaps because) he was working in Massachusetts at a time when teaching even a barrier method of contraception was illegal in that state. Rock helped design the first large clinical trial in Puerto Rico that showed hormones could prevent pregnancy. Other early trials using his protocol were performed in Haiti, Mexico, Japan, Israel, Hong Kong, and Britain, as well as the United States. Although Rock has been criticized for the study of poor, desperate women and inadequate informed consent, his protocol, which was very early in the history of clinical trials, was ahead of its time in including explanations of risks and benefits. More recently, he has been unfairly criticized[7] for promoting an oral contraceptive that required that women bleed every month. However, the choice was deliberate; he thought that regular menses would be more acceptable to the Catholic Church and to women (to be sure they were not pregnant). In addition, as long as women continued to menstruate, regulation of fertility could be considered a normal process. As it turned out, John Rock was unable to convince the then-new Pope that it was possible to be a good Catholic and use oral contraceptives.

Nonetheless, acceptance of oral contraceptives was remarkably rapid. After approval of sex hormones for the regulation of menses by the FDA in 1957, it was a short 3 years before the FDA also approved their use to prevent pregnancy. Even before FDA approval as a contraceptive, there was a curious epidemic of women complaining of irregular menses who required sex hormone treatment.

Women's enthusiastic acceptance of the "Pill" was immortalized in a 1970s hit song by Loretta Lynn, whose lyrics were quite explicit:

> For several years I stayed at home, while you had all the fun.
> And every year that came by, another baby come.
> There's going to be some changes made right here on nursery hill.
> You set this chicken one last time 'cause now I've got the Pill.'[8]

Incredible changes did follow the availability of oral contraceptives. Family size decreased, and maternal and infant mortality rates fell.[9] Women's adult life ex-

pectancy was not only lengthened but also dramatically changed; married and unmarried women were able to plan their lives and choose the timing to complete their education, begin a career, or have a baby.

In December 1999, the Centers for Disease Control listed family planning as one of the top ten public health advances of the last century.[10] As noted in a recent review of major advances in reproductive endocrinology and health in the 20th century, after 40 years the pill is still the only widely used, effective, relatively safe contraceptive.[11]

In the wake of contraceptives, family planning changed, becoming less expensive and more accessible. Ultimately, clinics outside the hospital setting such as Planned Parenthood not only made oral contraceptives available but also provided access to early, relatively inexpensive legal abortion.

Nonetheless, family planning remains a political and religious issue. One cartoon published in 1991[12] shows a woman whose body parts are labeled by ownership. All parts are hers except the reproductive organs, which belong to politics, law, and religion (Fig. 1). This perspective persists, and not only among religious fundamentalists and in cultures where women have no personal freedom or options. Remarkably, Japan did not allow the sale of oral contraceptives until 1999. An editorial marking the occasion in the *New York Times* lamented that terrible things happen to the fabric of society when women have access to oral contraceptives,[13] specifically, that the introduction of oral contraceptives to Japan would enable women to obtain equal pay for equal work, which would then allow them to leave their husbands when they were unhappy. (For the record, John Rock was not a proponent of equal opportunity either: he strongly opposed the admission of women to Harvard Medical School).

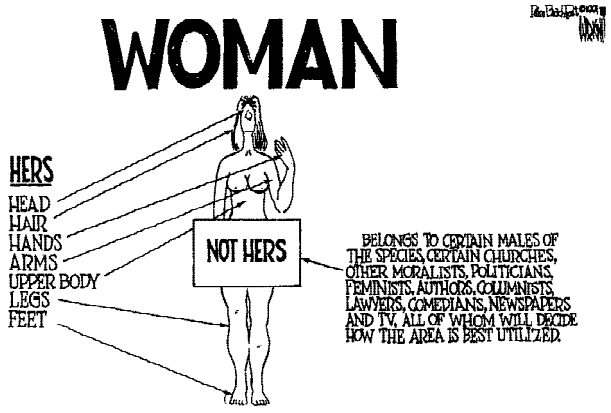

FIG. 1. 'Woman' by Don Wright. © Copyright 1991. *Palm Beach Post*. All rights reserved. Used by permission.

Oral contraceptives represent a great advance, but they do have untoward effects. The first recognized serious adverse event was the significantly increased risk of venous thromboembolic disease. The estrogen component of oral contraceptives was readily recognized as the cause of this side effect, and this observation led to reduction in the amount of estrogen in oral contraceptives, with subsequent decreases to the present.[14] Somewhat later, but still early in the history of oral contraceptives, came the recognition that a cluster of abnormalities now known as the metabolic syndrome was associated with the progestin component, which led to a reduced dose of progestin as well.[14]

An increased risk of stroke was suspected soon after the introduction of the high-dose oral contraceptives; early recognition was possible because young women rarely have strokes. A recent systematic review confirms a nearly two-fold increase in the relative risk of stroke in women using oral contraceptives, but the absolute risk is very low, approximately four excess strokes per 10,000 treated women.[15]

A small but significantly increased risk of breast cancer in women who had used oral contraceptives was most convincingly shown in a recent reanalysis of observational data from many sources.[16] Today's oral contraceptives have much lower hormone levels than those administered to most of the women included in this analysis. Lower-dose oral contraceptives may not carry the same breast cancer risk.

Not only have the regimens changed, but the women who use them have also changed. In the first decades of oral contraceptives, most users were married women who began the pill after they had had the desired number of children. In a large reanalysis study of older women, less than one percent had used oral contraceptives for more than 5 years.[16] Risk may be very different for today's women, whose use often precedes their first pregnancy by at least 10 years.[17]

WHAT DO ORAL CONTRACEPTIVES HAVE TO DO WITH MENOPAUSE?

There are several interfaces between oral contraceptives and the postmenopausal woman. At the turn of the last century, the average woman in the United States had a life expectancy of less than 50 years. Today a US woman who lives to age 50 has an average life expectancy of nearly 83 years. This greater longevity after age 50 is in part a consequence of women's ability to control the number and timing of their pregnancies. Over the next 50 years, the actual number of older women will increase exponentially, with very large increments in China and India.[18] This is not a guess; these

women are here and already middle-aged. The increasing number of older women will pose severe challenges for health care and disease prevention in all countries, but particularly in the developing countries, where the average income is often less than $1.00 a day.

In developed countries, today's postmenopausal women are likely to be healthier than their mothers were if their mothers achieved the same age. When women were pregnant nearly every year until menopause, they had little time to worry about their own health. Survivors who lived to enjoy a healthy old age were the exception, not the rule. Now that more women have better health for more years, they have higher expectations. Women in the developed world are more knowledgeable about osteoporosis, heart disease, and cancer, and they expect their doctors, nurses, or other advisors to help them make the right decisions to maintain quality of life into their later years. In much of the western world, women becoming postmenopausal today have used oral contraceptives, are familiar with the concept of using hormones for prevention, and are thus more likely to accept hormone therapy. However, physicians' prescriptions and women's acceptance of postmenopausal hormone therapy are colored by the breast cancer and vascular disease risks related to oral contraceptives and awareness of the time it took to recognize these risks and modify doses.

HORMONE REPLACEMENT THERAPY

More than 60 years ago, Ayerst (now Wyeth-Ayerst) provided the estrogen drug called Premarin for the treatment of menopausal symptoms. Initially, its use remained limited even among symptomatic women, who were often told that they were experiencing a midlife neurosis or were depressed by aging or the "empty nest." The move toward postmenopausal hormone use for asymptomatic women came even later. In 1959, Oliver and Boyd[19] reported an excess of coronary artery disease in women who had been oophorectomized, and they wrote, "A case could even be made out for administering small doses of oestrogens for a number of years to all menopausal women." In 1963, Wilson and colleagues used the term "estrogen deficiency" and predicted long-term consequences.[20] Going straight to the public, in 1966 Wilson published *Feminine Forever*, a best-selling book popularizing the thesis that postmenopausal estrogen "replacement" could prevent the cosmetic and pathological vicissitudes of aging.[21] The promise of fewer wrinkles turns out to be an ongoing, clearly exploited marketing tool, as observed in some advertisements showing hormone spokespersons who tend to be younger and more beautiful than most postmenopausal women I know. Industry is aware that women will take almost anything if it can promise them youth; this is the reason why the prevention of osteoporosis has been successfully marketed as the prevention of kyphosis, a cosmetic benefit. 'Estrogen replacement equals healthy aging" is a popular idea, but less popular than "young and feminine forever."

Both public education and actual research on the menopause and postmenopausal hormones are relatively recent. Cyran reported a 1969 study of hormone awareness in which 400 women from each of five countries were asked whether they knew of any medication for menopause.[22] With the exception of Germany, only about half of women or fewer in each country knew that there was a medication for menopause. A second question asked women whether they had ever asked their doctor about the menopause; here the numbers were universally 51% or less.

Only 20 years ago, Sonia Hamburger, an early advocate of menopause education, said the word "menopause" to a friend in a crowded elevator; all conversation in the elevator came to an abrupt halt, followed by an appalled silence. This word was simply not used in polite company. Now, for better or for worse, you hear "the M word" everywhere.

At the end of the last century came the single most important contribution to understanding the risks and benefits of postmenopausal hormones and which conditions were actually caused by estrogen deficiency: their belated study in randomized placebo-controlled clinical trials. The surprising results of recent trials have convinced all but the most confident in their clinical judgment that such trials are necessary to know whether hormones do what we think they do.[23]

All of the main criteria for a good clinical trial (primary hypothesis, predefined outcome, sample size based on power calculations, randomization, placebo-control, double-blind, and analysis by intention to treat) were in place by the late 1960s. However, large trials of postmenopausal hormones with disease outcomes were late in coming.

The first clinical trial, based on the idea that women have less heart disease than men because of their higher estrogen levels, was The Coronary Drug Project.[24] In the 1950s, a group of male scientists decided to do a clinical trial to test the hypothesis that estrogen was cardioprotective. Ironically, they decided to do the estrogen trial in *men* with heart disease. They had no idea then (or now) what a good estrogen level would be for men. To be sure the dose was large enough to be cardioprotective, men were treated with 2.5 or 5 mg/day of Premarin, doses large enough to cause gynecomastia,

impotence, or both in many men. Both estrogen regimens were stopped prematurely because there was an early excess of venous thromboembolic disease and coronary heart disease in men assigned to this therapy.

The first clinical trial to study the long-term effects of hormone replacement therapy in postmenopausal women was conducted by the Nachtigals and reported in 1979.[25] They randomly assigned 84 pairs of institutionalized women to placebo or conjugated estrogens and cyclic progesterone for 10 years. This trial was well ahead of its time but nevertheless too small to answer questions about heart disease or breast cancer.

Only recently, 50 years after the introduction of Premarin, do we have large clinical trials (HERS;[26] ERA;[27] WHI[28]) designed to evaluate the effect of postmenopausal hormone therapy on heart disease in women. The Heart Estrogen/progestin Replacement Study (HERS) [26] was the first large randomized, double-blind trial of hormones and cardiovascular outcomes. Nearly 3000 women with known coronary heart disease were randomly assigned to Prempro (0.625 mg/day of conjugated equine estrogen with 2.5 mg/day medroxyprogesterone acetate) or placebo. After 4 years, the frequency of the primary outcome, fatal and nonfatal heart disease combined, did not differ between the two groups.

The absence of overall benefit was a surprise. There was, in fact, a 50% excess of coronary events during the first year in the hormone-group. This early harm was an even bigger surprise. During the last 3 years of the trial, there was a (not statistically significant) trend toward improvement. The published results showing a significant trend toward benefit over time ($p = 0.009$) were incorrect, because this analysis incorporated the first year of excess disease as the baseline for the trend. Calculated from year 2 (after the early harm), the test for trend was not statistically significant ($p = 0.48$). At this time, there is no good evidence for a delayed cardiovascular benefit of postmenopausal hormone therapy.

Although the early coronary event rate was significantly higher in the hormone-treated group compared with the rate in the placebo group in this first large trial, it is rarely a good idea to accept the results of a single clinical trial, particularly when the results are contrary to expectation. HERS is not the only trial finding early harm, however. An analysis of 22 short published trials and six unpublished trials (data from the Finnish regulatory agency) showed a pooled relative risk of 1.8 for cardiovascular disease (excluding venous thromboembolism); unlike HERS, these women did not have heart disease and were assigned to estrogen alone or in combination.[29]

In the year 2000, the Women's Health Initiative (WHI) sent a letter to all of its 27,348 postmenopausal participants advising them that women assigned to hormones had experienced a small but significant excess number of fatal and nonfatal heart attacks and strokes during the first year of the trial. The accompanying press release[28] indicated that the excess risk had occurred in both the estrogen only and the estrogen plus progestin treatment groups, and was seen in women with and without known heart disease. In 2001, WHI women were told in another letter that the cardiovascular harm period continued but that the overall risk and benefit remained unclear. The WHI is fortunately continuing. It is essential that we get an unequivocal answer to the question, "Does estrogen therapy protect against coronary heart disease?"

The risk of breast cancer is the other serious concern about postmenopausal estrogen therapy. Clinicians have been reassuring their patients for years that the literature showed no consistent association between estrogen therapy and breast cancer. This was true but misleading, because most women in these observational studies had taken estrogen for less than 2 years. The inconsistent data were likely due to the inclusion of the majority of ever users who do not take estrogen for at least 5 years.

When data from 51 published studies were reanalyzed by duration of hormone therapy, the pooled data showed that women who had taken estrogen for more than 5 years had a significantly increased risk of breast cancer.[30] The increased risk per year of use was similar to the increased risk per year of delayed menopause. In this reanalysis, the increased risk was statistically significant, but the absolute risk was small, with only 1–3 excess breast cancer cases per 1000 estrogen-treated women after 5 years of use, and a maximum estimate of 20 excess cases per 1000 women treated for 15 years. Thus, while it is misleading to tell patients there is no increased risk of breast cancer associated with hormone replacement therapy, the risk does appear to be small.

Such reassurance may apply only to women taking unopposed estrogen, however. Only 12% of the women in the collaborative reanalysis had used estrogen plus progestin.[31] Some more recent large studies confirm an excess breast cancer risk with more than 4 or 5 years of hormone therapy, and also suggest that estrogen plus progestin carries a higher breast cancer risk than estrogen alone.[31] As a consequence, the excess risk calculated from the 51 studies may be too low. Only time will tell.

One reassuring thing we can tell patients who are trying to weigh the risks and benefits of hormone

therapy is that at least nine studies have shown a better prognosis in women who developed breast cancer while taking estrogen, compared with women who developed breast cancer without hormone replacement therapy.[32] It is not clear whether this better outcome is because women taking estrogen have more frequent breast examinations and mammograms, leading to earlier diagnosis, or because estrogen promotes a type of cancer with a better prognosis.

Everything just said about breast cancer is based on observational studies. There are no clinical trial data showing that estrogen causes breast cancer, but there is one piece of randomized trial data supporting a causal hormone-breast cancer association and a higher risk for estrogen plus a progestin than for estrogen alone. Data from the Postmenopausal Estrogen Progestin Investigation (PEPI) trial showed that about 15% of women taking estrogen alone and about one-third of women taking estrogen plus a progestin developed significantly more mammographic breast density, a change not observed in women taking placebo.[33] In most women who developed denser breast tissue, this change occurred during the first year of hormone therapy and was reversible when estrogen was stopped. Increased breast density is important because it has been a very strong marker for an increased risk of breast cancer in observational studies.[34] Thus, PEPI clinical trial data provide the strongest evidence to date that estrogen does increase the risk of breast cancer, and that estrogen plus progestin may carry a significantly larger risk than estrogen alone. The data also raise the possibility that we can identify women at higher risk for estrogen-induced breast cancer by comparing their pre- and one-year post-treatment mammograms.

Beginning in the 1970s, several case-control studies confirmed an excess of endometrial cancer in women taking unopposed estrogen versus rates in women taking estrogen plus a progestin.[35] Endometrial hyperplasia is unquestionably a consequence of unopposed estrogen, with the risk apparent within one year and increasing with duration of use. In the PEPI trial, each year 10% of women taking unopposed estrogen developed at least simple hyperplasia on endometrial biopsy. The women assigned to estrogen plus continuous or cyclic progestin had no atypical hyperplasia, a cancer precursor.[36] This is the closest one can comfortably come to demonstrating increased risk in a clinical trial.

With regard to osteoporosis, an abundance of clinical trial data shows that postmenopausal estrogen given at any age, with or without a progestin, maintains bone mineral density. But there are no clinical trial data showing that estrogen prevents hip fractures, and rather unsatisfactory data exist regarding the prevention of vertebral fractures. In HERS, a study of women with heart disease, not osteoporosis, there was no difference in the clinical fracture rate or height loss (a marker for vertebral fracture) between the treated and the untreated group.[26] The few other clinical trials were too small or too short, with too few fractures, or are difficult to interpret because of methodological problems. No large placebo-controlled trial of hormone therapy with fracture outcomes has been reported in women selected for low bone density or prior fractures, the entry criteria used in the clinical trials of other pharmacologic interventions showing fracture prevention.

As noted before, an excess risk of venous thromboembolism was recognized soon after the introduction of oral contraceptives. In contrast, this risk for women using hormone replacement therapy was not universally accepted for many years.[37] This difference illustrates that it is easier to recognize adverse effects in young women who are otherwise at low risk of complications than in older women who have a higher background risk. This problem of identifying risk against a background of relatively common disease probably explains why the early excess of heart attacks and strokes with hormone therapy in older women was not recognized by clinicians.

It is now abundantly clear that only large clinical trials can provide the unbiased risk-benefit data needed to make informed decisions about hormone replacement therapy.

HORMONES: NEW DEVELOPMENTS

Hormone-related discoveries of the last two decades have been astounding. New findings include two estrogen receptors, estrogen receptor knockout animal models (ERKO and DERKO), studies examining estrogen's intracellular effects in different tissues, and the development of improved selective estrogen receptor modulators and aromatase inhibitors.

The estrogen receptors, alpha and beta, are located in many organs; some tissues have more alpha and some have more beta receptors, with the potential for tissue-targeted therapy. Knockout mice without alpha or beta estrogen receptors teach us what estrogen does and does not do by receptor-mediated action. Mice without either estrogen receptor do not all die, leading to the possibility that at least one other estrogen receptor (currently named the gamma estrogen receptor) remains to be discovered.[38]

The estrogen receptor is very promiscuous, meaning that it will accept almost anything that looks a little like an estrogen, even though in a different configuration.

This means that selective estrogen receptor modulators (SERMs) can produce an estrogen-like (estrogen-agonist) effect in some tissues and can block the estrogen receptor in other tissues, leading to an estrogen antagonist effect. Raloxifene, the first of this iteration to reach the market, has been shown in a large randomized clinical trial to reduce the risk of vertebral fractures[39] and estrogen-receptor positive breast cancer.[40]

Raloxifene is a first-generation SERM. Other pharmaceutical companies are trying to develop a better SERM, one that, unlike raloxifene, will have a favorable effect on vasomotor and urogenital symptoms, and that, like raloxifene, will have about the same bone-sparing effect as low-dose estrogen. In theory, it should be possible to develop a SERM that also prevents heart disease and does not have the same risk of venous thromboembolic disease as estrogen.

Curiously, one of the potential breakthroughs near the end of the last century was the rethinking of the concept of the ductless gland. The classical definition of a hormone was an active substance produced by a gland, which when transported in the bloodstream exerted an effect in remote target tissues. Next came autocrine (acts at the surface of the producing cells) and paracrine (acts on neighboring cells) concepts. We now know that locally produced estrogens or androgens can exert their action on the cells where the synthesis took place.[41] This process, called intracrinology, requires small amounts of hormone to produce maximum effects, in contrast to classical hormone systems where there is a time delay transporting the hormone to the target tissues and only a small fraction is used while the rest is degraded. This may be one reason why studies of circulating endogenous hormone levels often do not predict the expected outcome.

Women vary in the way they metabolize hormones within different tissues, another potential reason why disease associations with circulating hormones are weak or absent. Thus, some women appear to irreversibly metabolize most of their estradiol to the 2-OH-estrone, an inactive product that may or may not act as an anti-estrogen, while others produce more of the 16-OH-estrone, an estrogen agonist. The 2 to 16 ratio appears to be low in postmenopausal women who have or develop breast cancer[42, 43] and may serve as an in vivo biomarker of estrogen activity. Knowledge of metabolite levels could thus be a powerful predictor of hormone-related health or pathology, one that would not be detected if only the precursor estrogen were measured. Knowledge about which metabolite predominates in an individual woman could lead to development of new medications or to decisions about which postmenopausal women should not use hormone therapy.

Finally, aromatase inhibitors could prevent selected tissues from making estrogen from another hormone, such as estrogen from testosterone. New more specific aromatase inhibitors can influence aromatization in just one tissue. These third-generation aromatase inhibitors are being studied in women whose breast cancer did not respond to traditional treatment. Preliminary trial results look promising.[44]

WHAT DOES THE FUTURE HOLD?

New oral contraceptives will be developed with even fewer side effects, but probably not within the United States where very little money is being put into contraception and where drug developers are understandably reluctant to invest research and development in drugs likely to evoke so much political controversy.

Another likely future development will be oral contraceptives that prevent menses, as recently outlined in the provocative book *Is Menstruation Obsolete?*[45] Those who think that healthy women's bodies are already entirely too medicalized will be dismayed to contemplate the unknown consequences of a lifetime of suppressed menses. It could take another fifty years to sort out the risk-benefit ratio of such medication.

Other investigators are studying how to make ovarian follicles last a lifetime, so women will no longer agonize about their biological clocks.[46] We may be ambivalent about enabling 70-year-old women with viable eggs to become pregnant, but it will happen.

It would be nice to predict a future of broadened attitudes toward different methods of birth control, but the US government continues to involve itself in family planning at home and in the rest of the world, recently withdrawing several types of aid to countries that disagree with "our" family planning policies. For the near future we will continue to send our restrictive message to countries where families cannot afford to feed 2 children, never mind 10.

The future of hormone replacement for healthy aging is uncertain, because the potential benefits and risks are still being sorted out. The growing number of postmenopausal women ensures that new medications will continue to be added to our armamentarium to promote healthy aging if not to prevent aging entirely. Mapping the human genome will likely influence hormone therapy in women. In less than 50 years we may each have our own little DNA card, the size of a credit card, that can be read by a machine to determine whether we are metabolizing our estradiol to the active or inactive

form. Estrogen and many other medications will be tailored to individual genotypes.

Not all of the advances will be good news, and it will be a difficult time for medical ethics. We already have the ability to pick the sex of our children, and we know what occurs when that is done, as happened most famously in China; there will be a preference for boys who will become adult men without women to marry. We may be offering designer children, which occurs to some extent now, when women select the height, attractiveness, and/or IQ of their spouse or sperm donor. Reproduction outside of the body does not seem implausible, and we will certainly have more postmenopausal mothers, assuming we will still have a menopause.

As all these new "advances" proceed in the developed nations, there will continue to be high maternal and infant mortality in the developing nations where women have limited access to health care and cannot afford today's medications. The difference between the haves and have nots is likely to increase. Thus, the next 50 years will be both interesting and challenging: interesting in the potential medical advances we can barely imagine and challenging to the global community to foster prevention and deliver health care where it is sorely needed.

SUMMARY AND CONCLUSIONS

We now have terrific opportunities and responsibilities. We know so much more about women's health, and women have so many more choices than they had only 25 years ago. Twenty years ago, women who wanted estrogen were told that they were just unhappy because their husbands were looking at or leaving for younger women and because their children had left home. Some of today's leaders started in this field because they wanted to help make the menopause transition less miserable for such women. In the last 10 or 20 years, however, we came to believe that estrogen deficiency was a disease, the cause of heart disease, and that doctors had a moral obligation to encourage women to take estrogen. (There are people in this field who still believe that, and who would be quite happy if we had put estrogen in the drinking water). However, we were making decisions without controlled trials. The history of medicine, like most history, repeats itself. In the history of replacement hormones, as I have shown, ground-up gonads were given to men and women and they felt better, as people often seem to do when there is no control group. Without a control group, we cannot know what works and what does not. Now, in the last 10 years, we have gotten results from large clinical trials, results that surprise and dismay our patients and ourselves.

Confusing results make it hard to practice medicine, but they have been very good for women's health. Women now get (or should get) more dialogue and more choices. We can expect some exciting answers in the next 5 years. Five years is a short time when you consider 60 years of estrogen treatment without trials.

In the meantime, it is challenging to practice medicine when you are uncertain. In defense of having presented few certainties to take to the patient, I want to close by paraphrasing a thought from George Pickering, written in 1964: If you are a clinician, you must believe that you know what will help your patient; otherwise, you cannot counsel, you cannot prescribe. If you are a scientist, however, you must be uncertain –a scientist who no longer asks questions is a bad scientist.[47] Few have the luxury of being both clinician and scientist, but we need each other. We also need to hear the experience, questions, and ideas of our patients. And we need to keep asking whether what we have recommended is actually working and is as useful and safe as we thought.

Nevertheless, we must have been doing something right. Only a generation ago, women belonged at home, reliable family planning and oral contraceptives were not available, the menopause and HRT were little studied, and most women did not have or expect a healthy maturity.

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