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Hot Flashes, Hormones
& Your Health

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To my husband, Christopher Ames, and our children, Jennifer, Jeffrey, and Joshua, for their boundless love, support, and forbearance. And to the memory of my mother, Theresa Palay Manson, who first inspired me to devote my life to women's health.

—JEM

To my husband, Paul Markowitz, and to the memory of my grandmother, Ann Ostrofsky, for their unwavering love and encouragement.

—SSB
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EVERY YEAR, MILLIONS of women worldwide enter menopause, a universal female experience. Although some women sail through the transition with few problems, three of every four experience symptoms due to the wide fluctuations of the female hormones estrogen and progesterone during this time, and one in four experiences major symptoms. The most common symptoms include bothersome hot flashes, drenching night sweats, disturbed sleep, mood swings, vaginal dryness, concerns about sexuality, and worries about memory slippage—all of which may affect a woman's most important relationships and her ability to function effectively at home and/or at work.

Although these symptoms can be quite troubling in the short term, the good news is that most symptoms will eventually subside over time as the hormonal tempest calms and one's body adjusts to its new steady state of lower estrogen levels. In the meantime, however, women are faced with one of the most complex healthcare decisions that many have ever had to make: to take or not to take hormone therapy. Many women (and their doctors) feel that they are in great need of guideposts in making informed and rational choices about this treatment.

There is little debate that hormone therapy offers highly effective relief from hot flashes and some (though not all) of the other menopause symptoms mentioned—it clearly does! Where the complexity arises is with regard to hormone therapy's safety and whether benefits will outweigh risks. Only a short time ago, hormone therapy was considered fairly safe for most women. But a seismic shift in attitudes toward hormone therapy has occurred in recent years because of apparent discrepancies among results of different types of studies. Dozens of observational studies, which examine large numbers of people over long periods of time and record their health-related characteristics and behavior in relation to their health outcomes, have suggested major health benefits of hormone therapy, including reductions in heart disease, hip fractures, and colon cancer, as well as major risks, such as breast cancer, stroke, and blood clots in the legs or lungs. More recent findings from randomized clinical trials, which use a figurative flip of the coin to assign either an active treatment or an inactive placebo to participants, have not only appeared to refute the idea that hormone therapy protects the heart but also suggest it may actually increase the risk of heart disease.

The largest of these clinical trials, which my colleagues and I carried out as part of a huge study called the Women's Health Initiative, assigned more than 27,000 women to a five- to seven-year course of hormone therapy or placebo to determine the impact of such treatment on a myriad of health outcomes. The heart disease findings became major news and convinced many women and their healthcare providers that the potential risks of hormone therapy outweighed the potential benefits. Women began to abandon hormone therapy in droves, feeling betrayed by the earlier assurances of its benefits.
While the pendulum has swung from the view that hormone therapy is good for all women to the view that it's harmful for all women, both positions are oversimplifications that have confused and alarmed women, not to mention their doctors. In my opinion, the answer is much more subtle and individual. A "one-size-fits-all" approach is inappropriate, yet very few physicians can provide women with truly satisfactory answers to their questions about hormone therapy—that is, answers tailored to a patient's particular situation and health profile. (Along with doctors, nurse practitioners and other health professionals are on the front line of giving advice and providing care to women as they navigate the menopausal transition. Although for brevity's sake I tend to use the words doctor or physician throughout this book, in most instances what I am saying also applies to other healthcare providers.)

After initially giving up hormone therapy, many women are now finding that their untreated menopausal symptoms are eroding their quality of life. In 2004, the American College of Obstetricians and Gynecologists stated that 25 percent of U.S. women who had stopped taking hormone therapy had restarted it—a mere two years after the Women's Health Initiative trial reported that such therapy increased the risk of cardiovascular disease. They apparently found the symptoms simply unbearable.

But how did it happen that decades of research suggested heart protection from hormone therapy only to have clinical trials, when finally undertaken, seem to show the opposite? What are the reasons for such discrepancies between earlier and later research? And why am I now saying that the new conclusion that hormone therapy is "bad" for all women is an inaccurate oversimplification?

Only in the past year have we come to a "unifying theory" that can explain the apparent discrepancies in the research and that can help women and their doctors make appropriate use of hormone therapy. I have had the privilege of being a lead investigator on two of the largest and most comprehensive research studies on the health of U.S. women undertaken to date—the Nurses' Health Study, which has observationally followed more than 121,000 female nurses for three decades and is still going strong, and the Women's Health Initiative, mentioned previously. My colleagues and I developed the unifying theory based on detailed analyses of data from these and other observational studies and randomized clinical trials. Some of the results have been recently published, and others will appear in the medical literature in the coming months. I have also had the opportunity to become involved with a new randomized clinical trial testing low-dose hormone therapy in recently menopausal women. This trial, the Kronos Early Estrogen Prevention Study (KEEPS), is assessing the effects of oral versus patch estrogen on the development of atherosclerosis as well as on quality of life and memory and thinking ability.

The key concept of the unifying theory is that hormone therapy tends to be beneficial when started early after menopause (as was done in the observational studies that seemed to show favorable results) and harmful when started late after menopause when women already have less-than-healthy blood vessels (as was the case with most women in the randomized clinical trials, which showed the negative results). In other words, a woman who starts taking hormone therapy
when she already has advanced atherosclerosis is particularly susceptible to having a heart attack or stroke while on treatment, while a woman just entering menopause who has healthy blood vessels may even receive heart protection. A similar pattern may apply to the effect of hormone therapy on memory and cognition: hormone use may help preserve thinking ability when initiated in newly menopausal women but hasten the progression of preexisting memory problems when started later in life.

There are several biological reasons for these differences in outcomes, which I'll explain in detail in these pages. But let me clarify—although the evidence is mounting, it is not yet conclusive, and no woman should begin taking hormones for the express purpose of preventing cardiovascular disease or cognitive decline. However, the findings to date can be reassuring to women who have recently entered menopause and are considering hormone therapy for treatment of moderate-to-severe menopausal symptoms. (At the very least, such women generally have an extremely low underlying risk of heart attack, stroke, and other complications.) This book is the first to present the unified theory in a way that I hope will be accessible to any woman who is struggling with the decision of whether or not to take hormones.

And I know that there are many of you out there. Besides having had the extraordinary opportunity to investigate the relation between hormone therapy and women's health in not just one but two landmark research studies, I've also been fortunate enough to have had nearly 20 years' experience as an internist and endocrinologist in a clinical practice largely devoted to women's health. In that role, I've been called upon by innumerable patients for advice on how to best navigate the menopausal transition. Some of my patients requested a prescription for hormone therapy for relief of their symptoms with nary a thought about the potential health consequences, while others wouldn't hear of taking hormones under any circumstances, even though their hot flashes and night sweats were making them miserable. Yet by far the most common situation I've encountered is that of the perplexed patient who sought a clear explanation of the benefits and risks of menopause hormones so that, with my input, she could ultimately make the choice with which she was most at ease. When I began practicing medicine, providing satisfactory answers to these women was hard to do, because I was acutely aware of how little information about the health outcomes of women on hormone therapy was actually out there. But now that such data have begun to accumulate, it's possible to give evidence-based answers to those questions. So that's why I wrote this book.

I'm often asked if there was a particular event that inspired my interest in women's health and my commitment to helping women get the health information they need. When I started medical school, I was curious about endocrinology and the effects of hormones on health, but I didn't know that medical research would become my mission. But early in my medical training, my mother died of ovarian cancer at a relatively young age, an event that raised my awareness—in a profoundly painful and personal way—of the relative inattention paid by the medical establishment to women's health issues in comparison to men's. Once I realized how little research had actually been done on health issues unique to women, including the effects of hormones on health, I decided to pursue my interest in endocrinology and plan a dual career in both research and patient care. But let's return to
Several health concerns should figure prominently when you weigh the potential benefits against the risks of hormone therapy, and heart disease is only one of many that should be factored into your choice. This book provides a step-by-step personalized framework for making the most informed hormone-therapy decision for your own symptoms and health profile. The following issues are addressed:

Which women are now considered good candidates for hormone therapy and who should avoid hormone therapy at all costs?

How can you calculate your personal risk for common conditions likely to be affected by hormone therapy—namely heart disease, stroke, blood clots in the legs and lungs, breast cancer, and hip fracture? How should these calculations guide your decision making about hormone therapy?

For women who are good candidates, what is the best formulation and dose of estrogen to take, the preferred progestogen, and the optimal duration of treatment?

For women who can't—or prefer not to—take hormone therapy, what are the best options for symptom relief and general health?

What is the appropriate role for soy, black cohosh, and other alternative remedies in relieving menopausal symptoms?

How can you work effectively with your healthcare provider to manage the transition to menopause?

In short, this book is my attempt to clear the confusion regarding the latest scientific data on hormone therapy—to make sense of the seeming chaos, so to speak—and present the facts you need to help you decide if hormone therapy is right for you. We are still in the thick of the learning process, but the evidence is now sufficiently firm that you can make an informed choice about using hormones for relieving symptoms of menopause with the reasonable expectation of keeping healthy and active for many years to come.

Disclaimer: The Women's Health Initiative (WHI) study and Nurses' Health Study (NHS) are supported by the National Institutes of Health (NIH) and conducted in collaboration with study investigators. This book does not necessarily reflect the opinions or views of the NIH or of study coinvestigators. Guidelines in this book are not intended to replace advice and medical care provided by your personal physician or other healthcare provider.
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Our understanding of the benefits and risks of hormone therapy has been made possible not only by talented scientists but also by the dedicated women who participate in research studies. Advances in medical knowledge depend on these volunteers' commitment and altruism. In particular, I thank the participants in the Nurses' Health Study and the Women's Health Initiative, and add to this my appreciation for the hundreds of thousands of participants in other research studies throughout the United States and worldwide. I have also learned a great deal from the patients in my care during nearly 20 years of clinical practice and have strived to earn the trust that they have placed in me.

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I also thank my coauthor, Dr. Shari Bassuk, whose extraordinary talent and commitment helped make this book possible. An experienced science writer, Shari was able to transform an enormous mass of complex medical research into highly lucid and accessible information. Sharing a commitment to the book's mission to help clear the confusion about hormone therapy and provide guidance to women in their decision making, Shari selflessly embraced each and every demand of this project. Her diligence, rare ability to combine attention to detail with "big picture" thinking, keen intelligence, and unusually lucid writing style are evident throughout this book. It has been an honor and privilege to have worked with Shari on this important project.

Finally, I thank my husband, Christopher Ames, and our children, Jennifer, Jeffrey, and Joshua, who have sustained me by their love, support, encouragement, and patience.
EXPLAINING PERIMENOPAUSE AND MENOPAUSE

Menopause is the beginning of a new, and often liberating and empowering, phase of life for women. Although it marks the end of cyclic functioning of the ovaries and thus of menstrual periods, it is a natural transition to a phase of life that can last 30 to 40 years, or even longer! After roughly four decades of nurturing and releasing an egg each month (pregnancy excepted), your ovaries call it quits on the reproductive front. Given that the average age of U.S. women at menopause is 51 years, most of us will spend more than one-third of our lives in the post-menopause. Symptoms of the underlying hormonal shifts that lead up to this event may manifest themselves for up to 10 years beforehand.

Perimenopause (the prefix peri- is Greek for "around" or "near") refers to the interval before menopause when fertility wanes and menstrual cycles become irregular, through the first year after the final menstrual period. Perimenopause varies greatly from one woman to the next. On average, it lasts three to four years, although it can be compressed into just a few months before the final menstrual period or extend as long as a decade. Some women feel buffeted by hot flashes or mood swings and wiped out by heavy periods or insomnia, while others have no bothersome symptoms. Menstrual periods may cease rather abruptly or continue erratically for years.

For someone planning a pregnancy, confronting her declining fertility can be a major issue. Even for those who do not wish to become pregnant, harbingers of menopause such as hot flashes and fluctuating periods that occur well before the actual event can be bewildering. To demystify what is happening to you, let's take a look at the midlife hormonal changes that underlie your symptoms.

WHAT'S HAPPENING TO MY BODY? UNDERSTANDING HORMONAL CHANGES

Hormones are chemicals that are produced and released into the bloodstream by a variety of specialized endocrine glands and by a region of the brain called the hypothalamus. (Listed in order from head to toe, these glands are the pineal and pituitary glands near the brain, the thyroid gland in the neck, the adrenal gland and the pancreas in the midsection, and, further down, the ovary [in women] and testes [in men]. Other select cells throughout the body, such as those in the fat tissue, also have the ability to make hormones.)

The word hormone, derived from the Greek word for "messenger," is a fitting name. Hormones travel to cells and tissues throughout the body, exerting a powerful influence on our health, feelings, and behaviors. During the menopausal transition, the starring hormone is the estrogen produced—or, as we will see, not reliably produced—by the ovaries. To understand
Estrogen's importance, we first need to back up and examine its role in reproduction—and health—earlier in life.

**Menstrual Cycles: A Carefully Orchestrated Hormonal Dance**

Women are born with a large reserve of eggs—one to two million of them—in their ovaries. Each egg is enclosed in a tiny, fluid-filled sac called a follicle. Although the ovary makes estrogen and other hormones throughout the life span, the egg containing follicles are dormant in childhood. But as we enter puberty, the follicles become active, which greatly boosts the ovaries' production of estrogen.

During our peak reproductive years, the amount of estrogen in circulation rises and falls fairly predictably throughout the menstrual cycle as part of a finely tuned hormonal messaging system that operates between your brain, pituitary gland, and ovaries each month (see Figure 1.1).

The process is kicked off (on day one of the menstrual cycle) with a hormone called gonadotropin-releasing hormone (GnRH) secreted by the brain's hypothalamus. When the GnRH reaches the pituitary, it tells that gland to start producing follicle-stimulating hormone (FSH). This hormone then signals the ovaries to rouse some of the long-dormant egg-containing follicles, stimulating them to grow and to produce large quantities of estrogen. About a week later (on day seven of the

**Figure 1.1 Hormonal Control of the Menstrual Cycle**
cycle), one of the group of growing follicles becomes significantly larger than the others; the others eventually die off and are reabsorbed by the ovary.

When the estrogen—along with more recently discovered hormones called inhibins—secreted by the follicles reaches a certain level, the hypothalamus directs the pituitary to turn off the FSH and to release luteinizing hormone (LH). This hormone prompts the dominant follicle to rupture and release its egg (usually around day 14 of the cycle), an event known as ovulation. The egg bursts through the ovary wall and enters the nearby fallopian tube, where it may or may not meet up with sperm from a male partner and be fertilized. Meanwhile, the empty follicle left behind in the ovary is transformed into a gland-like structure known as the corpus luteum that secretes large amounts of estrogen and a hormone called progesterone (see Figure 1.2).

This torrent of activity in the ovaries leads to changes in the lining of the uterus—the endometrium. It thickens in response to the estrogen produced by the developing follicles and is further stabilized by the progesterone produced by the corpus luteum. These changes prepare the
endometrium for a possible pregnancy and increase the chance that a fertilized egg will successfully implant itself in the uterine lining.

If fertilization does not happen, the corpus luteum starts to degenerate, leading to a precipitous drop in progesterone and estrogen levels (around day 24 of the cycle). The fall in progesterone triggers the constriction of blood vessels and the contraction of muscle tissue in the uterus. Deprived of its oxygen and nutrient supply, the uterine lining rapidly disintegrates (around day 28 of the cycle) and is sloughed off as menstrual blood beginning on day 1 of the next cycle. And the low estrogen levels prompt the hypothalamus to secrete GnRH, thus starting the hormonal dance all over again.

**PERIMENOPAUSE: A MIDLIFE TRANSITION AND A TIME OF FLUCTUATING HORMONES**

As nature would have it, the body wasn't meant to have babies indefinitely. Your ovaries have peak reproductive function throughout your twenties and into your early thirties. Researchers aren't exactly sure what triggers the loss of fertility but surmise that it has to do in part with a dwindling supply of eggs and in part with a breakdown in the delicate hormonal communication system between the ovaries and the brain.

An average 40-year-old woman has only 5,000 to 10,000 eggs left in her ovaries, and the number falls off sharply after that. Moreover, the follicles that do remain often respond poorly to the FSH signal sent by the pituitary. For example, although

**Figure 1.2 Changes During the Menstrual Cycle**
Day 1 is the first day of menstrual bleeding.

*Source: Merck Manuals Online Medical Library: Home Edition. (with permission)*

If there is no ovulation, the developing follicles may produce enough estrogen to thicken the uterine lining, the amount may no longer be sufficient to trigger the LH surge that prompts the dominant follicle to release its egg. Therefore, ovulation will not reliably occur in every cycle.

If there is no ovulation, there is no corpus luteum to make progesterone. And if there is no progesterone, there is no way to stabilize the uterine lining for pregnancy. Moreover, because there is no progesterone drop to trigger endometrial shedding, there may be irregular menstrual bleeding. That is, the uterine lining may either disintegrate prematurely or continue to proliferate over time,
shedding only when it grows too thick for its blood supply. Alternatively, even if ovulation does take place, the levels of estrogen and progesterone produced may not be enough to keep the hormonal dance in sync, so your cycle may lengthen or shorten, and your menstrual flow may become heavier or lighter. Eventually, your periods will stop altogether.

Unlike menopause, which is associated with consistently lower—but not completely absent—levels of estrogen, perimenopause is actually a time of wild swings in estrogen levels. As the follicles become less responsive to FSH, the pituitary responds by cranking out ever larger amounts of this hormone in an attempt to prod the ovary to create a dominant follicle and achieve ovulation.

During some cycles, the high FSH levels will trigger a very powerful response from the ovary, which activates multiple follicles and sends estrogen levels spiking. In other cycles, the ovary will not produce follicles in response to the increasingly [End of Sample]