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## **The Estrogen Dilemma**

**By CYNTHIA GORNEY**

**Here we are**, two fast-talking women on [estrogen](#), staring at a wall of live mitochondria from the brain of a rat. Mitochondria are cellular energy generators of unfathomably tiny size, but these are vivid and big because they were hit with dye in a petri dish and enlarged for projection purposes. They're winking and zooming, like shooting stars. "Oh, my God," Roberta Diaz Brinton said. "Look at that one. I love these. I love shooting mitochondria."

Brinton is a brain scientist. Estrogen, particularly in its relationship to the health of the brain, is her obsession. At present it is mine too, but for more selfish reasons. We're inside a darkened lab room in a research facility at the [University of Southern California](#), where Brinton works. We are both in our 50s. I use estrogen, by means of a small oval patch that adheres to my skin, because of something that began happening to me nine years ago — to my brain, as a matter of fact. Brinton uses estrogen and spends her work hours experimenting with it because of her own brain and also that of a woman whose name, Brinton will say, was Dr. A. She's dead now, this Dr. A. But during the closing years of her life she had [Alzheimer's](#), and Brinton would visit her in the hospital. Dr. A. was a distinguished psychotherapist and had vivid stories she could still call to mind about her years in Vienna amid the great European [psychologists](#). "We'd spend hours, me listening to her stories, and I'd walk out of the room," Brinton told me. "Thirty seconds later, I'd walk back in. I'd say, 'Dr. A., do you remember me?' And she was so lovely. She'd say: 'I'm so sorry. Should I?' "

The problem with the estrogen question in the year 2010 is that you set out one day to ask it in what sounds like a straightforward way — Yes or no? Do I or do I not go on sticking these patches on my back? Is hormone replacement as dangerous in the long term as people say it is? — and before long, warring medical articles are piling up, researchers are raising their voices and gesticulating excitedly and eventually you're in Los Angeles staring at a fluorescent rodent brain in the dark. "You want a statistic?" Brinton asked softly. Something about the shooting mitochondria has made us reverent. "Sixty-eight percent of all victims of Alzheimer's are women. Is it just because they live longer? Let's say it is, for purposes of discussion. Let's say it's just because these ladies get old. Do we just say, 'Who cares?' and move them into a nursing home? Or alternatively, maybe they are telling us something."

With their brains, she means. Their sputtering, fading Alzheimer's brains, which a few decades earlier were maybe healthy brains that might have been protected from eventual damage if those women had taken estrogen, and taken it *before* they were long past their [menopause](#), while their

own neural matter still looked as vigorous as those rat cells on the wall. This proposition, that estrogen's effects on our minds and our bodies may depend heavily upon when we first start taking it, is a controversial and very big idea. It has a working nickname: "the timing hypothesis." Alzheimer's is only one part of it. Because the timing hypothesis adds another layer of complication to the current conventional wisdom on hormone replacement, it has implications for heart disease, bone disease and the way all of us women now under 60 or so — the whole junior half of the baby boomers, that is, and all our younger sisters — could end up re-examining, again, everything the last decade was supposed to have taught us about the wisdom of taking hormones.

I first met Brinton at a scientific symposium at [Stanford University](#) in January that was entirely devoted to the timing hypothesis. The meeting was called Window of Opportunity of Estrogen Therapy for Neuroprotection, and it drew research scientists and physicians from all over the country. When I asked to listen in, the organizers hesitated; these are colleagues around a conference table, they pointed out. They're probing, interrogating, poking holes in one another's work in progress.

But I was finally permitted to take a chair in a corner, and as the day went on, I became aware of my patch, in a distracted, hallucinatory sort of way, as if I had started fixating on a smallish scar. One after another, their notes and empty coffee cups piling up around them, heart experts and brain experts and mood experts got up to talk about estrogen — experiments, clashing data, suppositions, mysteries. There are new hormone trials under way that are aimed at the 40-year-old to 60-year-old cohort, with first results due in 2012 and 2013. There are [depression](#) studies involving estrogen. There are [dementia](#) studies involving estrogen. There are menopausal lab monkeys taking estrogen, ovariectomized lab mice taking estrogen and young volunteers undergoing pharmaceutically induced menopause so researchers at the [National Institutes of Health](#) can study exactly what happens when the women's estrogen and [progesterone](#) are then cranked back up. I typed notes into my laptop for hours, imagining the patch easing its molecules into the skin of my back, and the whole time I was typing, working hard to follow the large estrogen-replacement thoughts of the scientists around the table, I had one small but persistent estrogen-replacement thought of my own: If I make the wrong decision about this, I am so screwed.

**I started taking** estrogen because I was under the impression that I was going crazy, which turns out to be not as unusual a reaction to midlife hormonal upheaval as I thought. This was in 2001. The year is significant, because the prevailing belief about hormone replacement in 2001 was still, as it had been for a quarter century, the distillation of extensive medical and pharmaceutical-company instruction: that once women start losing estrogen, taking replacement hormones protects against heart disease, cures hot flashes, keeps the bones strong, has happy

effects on the skin and sex life and carries a breast-[cancer](#) risk that's worth considering but not worrying about too much, absent some personal history of [breast cancer](#) or a history of breast cancer in the immediate family.

At first, as I was trying to locate a psychiatrist who would take me on, I wasn't aware I had reason to pay attention to advice about hormones at all. That year I turned 47, a normal age for beginning the drawn-out hormonal-confusion period called perimenopause, but I had none of the familiar signs. Menopausal holdouts run in the family; one of my grandmothers was nearly 60 by the time hers finally kicked in. My only problem was a new tendency to wake up some mornings with a great dark weight shoving my shoulders toward the floor and causing me to weep inside my car and basically haul myself around as if it were the world's biggest effort to stand up straight and carry on a conversation. Except for its having shown up so arbitrarily and then coming and going in waves, there was nothing interesting about my version of what my husband and I came to think of as the Pit; anybody who has been through a depression knows what a stretch of semidisabling despair feels like, and for my part I had a very nice life, a terrific family and a personal interior chorus of quarreling voices demanding to know why I didn't pull up my socks and carry on, which in fact was the first question I planned to ask a psychiatrist. But I went to my gynecologist first, so she could check my [blood pressure](#) or whatever seemed the prepsychiatrist thing to do. How often would you say you feel this way, she asked; and I said I didn't know, maybe every few weeks; and she told me to start keeping records. Note each day, she said. Check for patterns.

She was right. There was a pattern. I was falling into the Pit on schedule, around 11 days before each menstrual period, or M.P., which is one of many abbreviations I was to learn in my efforts to keep track of the ferocious hormones debate that started up in North America in 2002, one year after I stuck on the first estrogen patch that my gynecologist prescribed. The study at the center of the ruckus was called the Women's Health Initiative, or W.H.I. It was a federally financed examination of adult women's health, extraordinary in scale and ambition, that started up in the early 1990s; one of its drug trials enrolled more than 16,000 women for a multiyear comparison of hormone pills versus placebos. On July 9, 2002, W.H.I. investigators announced that they had ended the trial three years early, because they were persuaded that it was dangerous to the hormone-taking participants to let them continue.

The women on hormones were having more heart trouble than their placebo-taking counterparts, the investigators said, not less. Their risk for [stroke](#) went up. Their risk for blood clots went up. Their risk for breast cancer increased by 24 percent. The W.H.I. bulletins dominated medical news all summer and long into the fall, and so alarming were their broad-scale warnings that millions of women, myself included, gave up hormone replacement and resolved to forge ahead without it.

The patches my gynecologist prescribed worked, by the way. I didn't understand how, beyond the evident quieting of some vicious recurring hormonal hiccup, and neither did the gynecologist. But she had other women who came in sounding like me and then felt better on estrogen, and I would guess many of them, too, decided after the W.H.I. news that they could surely find other ways to manage their "mood swings," to use the wondrously bland phrasing of the medical texts. (I'm sorry, but only someone who has never experienced one could describe a day of "I would stab everyone I know with a fork if only I could stop weeping long enough to get out of this car" as a "mood swing.") We muddled along patchless, my mood swings and my patient family and I, until there came a time in 2006 when in the midst of some work stress, intense but not unfamiliar, I found myself in a particularly bad Pit episode and this time unable to pull out.

It was profoundly scary. In retrospect, I managed a surprising level of public discretion about what was going on; competence at the cover act is a skill commonly acquired by midlife women, I think, especially those with children and work lives. If the years have taught us nothing else, they have taught us how to do a half dozen things at once, at least a couple of them decently well. Like other women I have met recently with stories like this one, I relied for a few months on locked office doors, emergency midday face-washings and frequent visits to an increasingly concerned talk therapist. But one afternoon I got off my bicycle in the middle of a ride with my husband, because I had been crying so hard that I couldn't see the lane lines, and I sat down on the sidewalk and told him how much I had come to hate knowing that family obligations meant I wasn't allowed to end my life. The urgent-care people at my health clinic arranged a psychiatric consult fast, and after listening and nodding and grabbing scratch paper to draw me an explanatory graph with overlapping lines that peaked and plunged, the psychiatrist wrote me two [prescriptions](#). One was for an antidepressant.

The other — I recognized the name as soon as she wrote it down — was for Climara, my old estrogen patch.

By this time we were four years past the 2002 W.H.I. hormone news. So I knew a few more things. I knew there had been a surge of industrious scrambling among former hormone-taking women, some of whom had tried multiple alternatives or going cold turkey and then changed their minds and re-upped on estrogen, deciding that life without it was so unpleasant that they no longer cared what the statistical prognoses said. I knew the prevailing medical sentiment had shifted slightly since the bombshell of 2002; certain articles and books still urged women to shun hormone replacement at all costs, but the more typical revised counsel was, essentially, proceed with great caution. If some menopausal malady is genuinely making you miserable, the new conventional wisdom advised, and no alternative remedy is working for you, then go ahead and take hormones — but keep the dose low and stop them as soon as possible.

I would like to be able to tell you that I weighed these matters thoughtfully, comparing my risks and benefits and bearing in mind the daunting influence of a drug industry that stands to profit handsomely from the medicalizing of normal female aging. But that would be nonsense, of course. I was too crazy. I went straight to the pharmacy and took everything they gave me. You don't read the fine print on package labels when you're being ushered through a psychiatric crisis, but after a while, I did. By last winter I was nearing the cumulative five-year mark as an estrogen user, and although "low dose, stop soon" is often an advisory without specifics attached, five years seemed to turn up here and there as an informal outer-limit guideline. And because it had worked again, because the estrogen so clearly helped repair something that was breaking (there's no way for me to separate the effects of estrogen from the effects of the antidepressant, except that on the few occasions when I've been haphazard about replacing the estrogen patches on time, I've experienced prompt and unmistakable intimations of oncoming Pit), I now had some rational faculties with which to go looking for explanations that might help me decide what to do. This was when I first began learning that in the controversy over hormone replacement, the fine print matters a very great deal.

First of all, the kind of estrogen in my patches — there are different forms of estrogenic molecules — is called estradiol. It's not the estrogen used in the W.H.I. study. Pharmaceutical estradiol like mine comes from plants whose molecules have been tweaked in labs until they are atom for atom identical to human estradiol, the most prominent of the estrogens premenopausal women produce naturally on their own. The W.H.I. estrogen, by contrast, was a concentrated soup of a pill that is manufactured from the urine of pregnant mares. The drug company Wyeth (now owned by Pfizer) sells it in two patented products, the pills Premarin and Prempro, and it's commonly referred to as "conjugated equine estrogens."

There was more in the fine print. Two years ago, after warning me that women who haven't had a [hysterectomy](#) run a higher risk of [uterine cancer](#) when they take only estrogen as hormone replacement, a new doctor added in progesterone, which has been shown to protect the uterus. The progesterone he prescribed for me, like the estradiol, is a molecular replica of the progesterone women make naturally. It's different from the progesterone-like synthetic hormone that was used for the W.H.I. study that ended in 2002. That medication was a formulation whose multisyllabic chemical name shortens to MPA and which has a problematic back story of its own: MPA takes care of the uterine-cancer risk, but there's reason to suspect it may be a factor in promoting breast cancer. And it's ingested as a pill, which means that like equine estrogens (and unlike, for example, my patch), MPA metabolizes through the liver, possibly creating additional complications en route, before going about its business.

The biggest difference between me and the W.H.I. women, though, has to do with age and timing. I started on the patches while my own estrogen, pernicious though its spikes and

plummet may have been, was still floating around at more or less full strength. The average age of the W.H.I. women was just over 63, though the study accepted women as young as 50. More significant, though, most of them were many years past their final menstrual period, which is the technical definition of menopause, when they began their trial hormones. The bulk of the group was at least 10 years past; factoring in the oldest women, the average number of years between the volunteers' menopause and their start on the trial medications was 13.4. Because women generally make decisions about hormones while they are in the throes of perimenopause — that term is now used to extend through the year following the final M.P. — you may find this as perplexing as I did. Why would the largest drug trial in the history of women's health select, for most of its participants, women already long past the critical phase? I heard one undiplomatic critic sum up the W.H.I. as “the wrong drugs, tested on the wrong population,” and those two factors, the drugs and the population, are actually directly linked. Equine estrogens and MPA were the only forms of hormones used in the W.H.I. trials. Among other reasons, that's because drug trials are expensive; this one was huge, and Wyeth was going to provide without cost an average of eight years' worth of its equine estrogens and MPA to 40 clinical centers.

And millions of women were using those very hormones already, partly because aggressive Wyeth marketing had for three decades insisted that hormone replacement was the ticket to a vigorous and sexually satisfactory postmenopausal life. To a certain extent, evidence backed up that claim; wide-scale though less rigorous earlier studies appeared to demonstrate hormone replacement's benefits so clearly that many physicians were suggesting it almost automatically to midlife women, whether or not they had perimenopausal complaints. Hormones raised the breast-cancer risk in those earlier studies, but nearly every other health factor showed improvement when women who took hormones were compared with those who didn't. Hot flashes disappeared, [osteoporosis](#) was milder, women reported feeling better and women who took hormones showed a markedly lower rate of heart disease than women who did not. Because heart disease ultimately kills many more women than all cancers combined, some doctors had also taken to urging older women, even those past menopause, to start hormones for cardiac-health purposes. The W.H.I. trials were supposed to provide conclusive evidence, finally, as to whether all this wide-scale prescribing was truly a sound idea. But cardiovascular disease tends to make its bids for attention — its “events,” as clinicians say, like [heart attack](#) and death — when we're quite a bit past 51, the average age at which American women hit menopause. The only way the W.H.I. was going to tally up a scientifically useful number of cardiac events was to enroll plenty of women already old enough to reach that danger stage before the study's time ran out. So that's what they did, and once the final data was reparsed many times, it was clear that the trial had shown physicians something highly important about

the perils of starting older postmenopausal women (that's qualifier No. 1) on pills (No. 2) containing equine estrogens (No. 3) plus MPA (No. 4).

Those four qualifiers make the chief message of the W.H.I. — that taking hormones, in the long run, is more likely to hurt you than help — far more specific than the one most women heard. For those of us not yet on the far side of menopause, or who don't match the other qualifiers (as I write this, for example, I'm zero for four), a daunting proportion of what we thought we learned about hormone replacement over the last eight years remains unsettled, more confusing than ever and conceivably — we don't know yet — wrong. “I mean, if you're a 70-year-old,” says S. Mitchell Harman, a Phoenix-based endocrinologist and coordinator of one of the national trials currently examining hormones' effects on younger women, “and your question is, Should I start taking estrogen? the W.H.I. answered that for you beautifully. *No*. Unfortunately, it wasn't designed to answer that question for a 50-year-old. So now we're trying to fill in the blanks.”

One afternoon last month, I reported to the Northern California site for an N.I.H.-financed cognitive trial that is part of the Kronos Early Estrogen Prevention Study that Harman is leading. Keeps, as it's called, has enrolled women at nine such sites around the country; this one was inside a medical building at the [University of California, San Francisco](#), and the cognition test I asked to try proved to be a low-tech experience: a table with chairs, pens and pencils and a gentle-voiced psychologist asking me to do things with my brain. Number sequences repeated backward, lists of random objects to recall, designs to remember and copy — I promised not to describe specifics, because making details public could compromise the trial results. But imagine a stranger holding up a stopwatch and giving you 30 seconds to name every dessert item you can think of. The brain charges off into a comical panic grope, and it's like a cross between a back-seat car game and the SATs.

The only grading marker, though, is self compared to self. If I were a Keeps participant, I would be on a four-year regimen of some mystery medication — either estrogen, in one of two forms (estradiol patches or equine-estrogen pills, to see whether differences emerge between the two), or placebo patches or placebo pills. Then in another year, I would retake the cognition test, which lasted about an hour and a half, so researchers could track any change. Brain function is a major element of the Keeps agenda; the other is heart health, so the test administrators would conduct annual ultrasounds of my carotid artery, to check for the thickening that signals heart disease. That's how they are trying to circumvent the doesn't-manifest-until-you're-older problem, by measuring for known warning markers rather than waiting for the actual big events. They would check my blood and [cholesterol](#) for signs of other cardiovascular trouble.

With about 730 participants, Keeps is relatively small; hormone research has been tough to finance in the post-W.H.I. years, and every scientist and physician I've spoken to said there will

never again be another hormone trial as costly and ambitious as the W.H.I. A second study, based in Los Angeles, called the Early Versus Late Intervention Trial With Estradiol, is following more than 600 women — comparing a group that has been post-menopausal for an average of 15 years and that is on estradiol or on a placebo with a second, younger group that is an average of three years post-menopausal. “*This* is the age when we should really study estrogen,” says Sanjay Asthana, a [University of Wisconsin](#) medical professor who is a designer of the cognition component of Keeps. “People like me are really waiting to see what this data looks like. Either way. We need to know.”

Asthana is a geriatrician, with a specialty in Alzheimer’s and other forms of age-related [memory loss](#). That makes him a member of what I came to think of, in my travels among estrogen researchers this winter, as the brain contingent. Their working material includes neuroimaging; magnified slices of rodent brains; and live cells that carry on in petri dishes, shooting mitochondria around or struggling under the burden of disease. All these things allow the brain contingent to see, sometimes literally, estrogen in action. It’s an amazing process. When cells are healthy, estrogenic molecules slide right in, searching for special receptors that are shaped precisely for the estrogens: the receptors are tiny locks, waiting for the right molecular keys to turn them on. Then, once they are activated by the key-turning process, the work estrogen receptors do is richly complex, if only partly understood. They prod genes into action; they raise good cholesterol; they affect the neurotransmitter chemicals associated with mood and stress, like serotonin and [dopamine](#).

And the brain, scientists have learned in recent decades, is loaded with these receptors. Knowing this makes it easier to understand how perimenopause could start inside aging ovaries and set off such a wild cascade of effects. If you’re a typical woman moving through your 40s or 50s, your lifetime egg supply is running out; as that happens, the intricate, multihormone reproductive-signaling loop grows confounded, its triggers altered by the biology of change. The brain and ovaries, the primary stops along this loop, start misreading each other’s demands for action. This can make estrogen production crank up frantically, crash and then crank up again. Something also goes awry with most women’s thermoregulatory systems, producing hot flashes in around three-quarters of us — nobody yet knows why, exactly, nor why certain women go on flashing for many years while some escape the whole must-remove-outer-garments-*now* phenomenon entirely. There’s an admirably clear explanation of the complete process in a recent book called “Hot Flashes, Hormones and Your Health,” by JoAnn Manson, a Harvard medical professor who worked with both W.H.I. and Keeps. My favorite illustration in Manson’s book shows an actual woman’s hormone fluctuations as measured before, during and after perimenopause; the “before” graph is a row of calm, evenly spaced ups and downs, various hormones rising and falling in counterpoint and on cue. The lines in the “after” graph are



virtually flat. The “during” graph looks as if somebody dynamited a mountain range. Not all women, Manson notes, experience disruptions as robust as this unidentified patient’s. But consider the mess of internal rearrangement we’re looking at: the body’s overall estrogen production is waning as the ovaries start atrophying into full retirement; and here simultaneously, at least for some of us, is this great Upheaval of During. The combination of the two can be — how could it *not*, I thought, the first time I studied the three graphs — a hellacious strain on the brain. Tracing the exact mechanics is still a work in progress, but they surely include some disruption of signaling to the neurotransmitters that make us remember things, experience emotions and generally choreograph the whole thinking operation of the human self.

“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.”

This was Brinton, as it happens, describing herself. It’s why she first went on estrogen (estradiol, accompanied by natural progesterone) when her own perimenopause kicked in a few years ago. We were sitting in a campus garage in her Prius one day, and I asked her what made her so sure her own midlife difficulties — she had the hot flashes, which were obvious, but also the sleep disruption and the infuriating distractibility — were the product of hormonal events, not some womanly existential crisis. We get a lot of that, societally. It’s meant to be empathetic. Your role in life is changing, Mrs. Brain Seized by Aliens! Your children are growing up, you’re buying expensive wrinkle cream, ice cream makes you gain weight now, of course you’re distraught! “Because with estrogen —” Brinton looked at me sharply, and then smiled — “I don’t have attention-deficit disorder.”

We walked back up to her laboratories, which are spread along a many-roomed warren full of cell incubators, centrifuges and computers. Brinton has thick black hair and a demeanor of lively, good-humored authority; it’s easy to envision her as the passionate science professor in crowded lecture halls. But in her labs the work is all rats and mice, many of them surgically or genetically altered to serve as surrogates for adult humans in various stages of maturation or disease. Removing the ovaries from female rats, for example, sends them into low-estrogen mode. Mice can be ordered bred with Alzheimer’s. The plaque that clogs the brains of Alzheimer’s sufferers, a noxious memory-disrupting substance called beta amyloid, is available as a chemical distillate, which means Brinton’s team can experiment with that too — beta amyloid dropped into the brain cells of healthy low-estrogen rodents; or estrogen dropped into cells already damaged by beta amyloid.

That’s why Brinton says that the timing hypothesis — the proposition that estrogen could bring

great benefit to a woman who starts it in her 50s while having the reverse effect on a woman 10 years older — makes sense even though it is still experimental. She and other scientists know there are ways estrogen improves and protects the brain when it is added to healthy tissue. It makes new cells grow. It increases what's called "plasticity," the brain's ability to change and respond to stimulation. It builds up the density and number of dendritic spines, the barbs that stick out along the long tails of brain cells, like thorns on a blackberry stem, and hook up with other neurons to transmit information back and forth. (The thinning of those spines is a classic sign of Alzheimer's.)

But when estrogen hits cells that are already sick — because they're dying off as part of the natural aging process or because they've been damaged by beta amyloid — something else seems to happen. Dropped in as a new agent, like the wrong kind of chemical solvent sloshed onto rusting metal, estrogen doesn't strengthen or repair. It appears useless. Sometimes it sets off discernible harm. You may recall additional W.H.I. news a few years ago about hormones increasing the risk for aging-related dementia; those stories emerged from a subgroup of W.H.I. participants who were all at least 65 when they started the hormones. There are arguments about that data, like nearly everything else connected to the W.H.I., but the age factor alone reinforces what Brinton and other timing-hypothesis researchers observe in the labs when they give estrogen to ailing cells. "It's like the estrogen is egging on the negative now, rather than the positive," she said. "We know that if you give neurons estrogen, and then expose them to beta amyloid, many more will survive. But when we expose them to amyloid and *then* give them estrogen — now you don't have survival of the neurons. In some instances, you can actually exacerbate their death."

The heart contingent exploring the timing hypothesis is reasoning the same way. Monkeys get both cardiovascular disease and their own version of menopause; there is a primate team at [Wake Forest University](#) in North Carolina that has found estrogen to be a strong protectant for females against future heart disease — but only when it's given at monkey perimenopause. Give estrogen the equivalent of six human years later, says Tom Clarkson, the pathology professor who has been leading this work for decades, and there is no protective effect at all. Clarkson, who is 78, told me that if he were 30 years younger and a woman, with hot flashes or sleep trouble or sudden crashes of mood, he would have no hesitation about taking hormones. "I absolutely believe in the timing hypothesis," he said. Then, being a scientist, he corrected himself. "I would have to say my level of certainty is 95 percent or greater," he said. "I live a life of believing in the experimental evidence."

So noted, I replied. And what if the symptoms were annoying but bearable or there were no symptoms at all? I've asked the same questions to every researcher I talked to this spring, and nearly all of them reply the same way: if they were deciding for themselves personally, they

would tip the risk-benefit scale strongly in favor of hormones as a remedy for immediate ailments of perimenopause. But estrogen solely as a protectant for the heart and brain, to be taken for many years, absent any immediate serious complaints? There was a pause, and I heard Clarkson sigh. “We just don’t know about that yet,” he said.

**The personal calculus** of risk is an exhausting exercise in the modern era, what with litigation-jumpy physicians, the researchers’ candid “We just don’t know” and the bottomless learn-it-yourself maw of the Internet. Of all the conversations I had this winter, as I weighed and reweighed the stopping of the patch, the one that most resonates took place on a snowy morning in Washington, in the office of a nursery-school director named Julia Berry. Berry lives not far from the headquarters of the National Institutes of Health in Bethesda, Md., which is why last September she pulled from her mailbox a card the N.I.H. has been mailing to local women within a certain age range. “If you struggle with irritability, anxiety, sadness or loss of enjoyment at the time of the menopausal transition,” the card reads, “please call us and help yourself while helping others.”

The N.I.H., it turns out, has been quietly conducting mood and hormone studies for more than two decades under the direction of a psychiatrist named Peter Schmidt and his predecessor, David Rubinow, who is now chairman of the [psychiatry](#) department at the [University of North Carolina](#). The research was first set into motion by Rubinow’s postgraduate interest in [premenstrual syndrome](#); the idea of giving younger women drugs to lower and flatten temporarily their estrogen and progesterone levels, essentially inducing menopause, was initially conceived to determine the role of hormones in PMS — to see whether these young women got relief when their hormones stopped the cresting and dropping of the normal menstrual cycle. (It often worked as a short-term treatment and yes, the young women often got hot flashes.) In recent years, the induced-menopause experiments have continued, among many other studies, as part of an effort to try to understand the chemistry of women like Julia Berry and me — women for whom perimenopause turns into what Berry described to me as “psychological misery, not myself and absent from the world.”

Berry is 55, ponytailed and roundish and pretty. She was divorced a long time ago, raised three good kids mostly on her own and has a firm handshake and a job she loves. Her troubles started in her late 40s, in the standard way, with hot flashes and jerking awake at 3 a.m. and then escalated into something much fiercer. Like me, at the worst of it, she occasionally found herself in traffic, wishing silently for an oncoming truck that might exit her swiftly from this life without qualifying as a [suicide](#). A physician prescribed [antidepressants](#). They helped, with both the anguish and the flashes, but not enough. “I am one of the most steady, even-keeled, hard to ruffle, really unflappable . . . truly,” Berry told me. “I *am*. I, generally speaking, can be completely relied upon to do the sensible right thing almost all the time. Which is one of the

reasons this period in my life has been so weird.”

She called the N.I.H. number at once. She was quickly evaluated, enrolled in a double-blind study of the effects of estrogen on perimenopausal depression and sent home with a paper bag containing a mystery patch. When I asked Berry to describe the sensation of the next few weeks, she looked up at the ceiling for a second to think. “Kind of like having been in a smoky room, waving your arms and now seeing that the exhaust fan is taking a little at a time,” she said. “My mood lifted. First time in three years I wasn’t waking up at 3 in the morning. That’s when I knew I wasn’t on the placebo. It was very clear to me that there was something fundamentally wrong with my chemical systems, and that whatever was in this patch was setting things right, so that I could function like a regular human being — the human being I was familiar with.”

What medicine doesn’t know about the chemistry of mood, including clinical depression, dwarfs what medicine doesn’t know about hormones. It would be handy for science if Berry and I could have made our heads available for dissection at certain points in recent years; as it is, we’re able to answer as many elaborations on “I feel bad” or “I feel good” as researchers might wish to throw at us, but they still have no way of pinning down where we belong on the scale of menopausal distress, or what exactly we’re doing there. We could be extra-high-volume versions of the women who are having an ordinary rough time of it, like Roberta Brinton — the women who hot-flash and can’t sleep and cast about for vocabulary with which to describe feeling, as Brinton puts it, “just off.” Or we could belong to some subcategory of anomalies, women with a wired-in susceptibility to depression — gene pools, childhoods, whatever — that was fired up by abrupt hormonal change.

Some psychological surveys will tell you there’s no evidence for a surge of clinical depression at menopause. I believe that, given how many other phases of life can unhinge us, but I also believe — no, actually, I *know* — that there is a difficult thing that happens to some women in the perimenopausally affected brain. Hostile as I am to generalizations involving women rendered fragile by biology, here I am, and here, too, is Berry, both of us pulled out of something terrible by a pharmaceutical infusion of estrogen. Two physicians who specialize in hormones and mood, Louann Brizendine, a neuropsychiatrist at the University of California, San Francisco, and Claudio Soares, a Canadian research psychiatrist who works at McMaster University in Ontario, told me that women who seek them out tell variations of the same story Berry and I took to our doctors: I know that something is wrong with me because I also know, somewhere in the noncrazy part of myself, that there is such pleasure to be offered by the circumstances of my grown-up life.

“These women thought they were losing their minds,” Brizendine told me, describing the 40-to-60-year-old patients she began seeing when she opened the Women’s Mood and Hormone

Clinic at the university in 1994. “In 1994 we didn’t have words for it,” she said. “Now we do. It’s called perimenopausal depression.”

Brizendine and Soares, like Schmidt and Rubinow, have found that various combinations work with varying degrees of effectiveness for many of us — hormones with an antidepressant, hormones without an antidepressant, sometimes antidepressants on their own. The alternatives-to-hormones recommendations are mostly fine things in their own right, varying from certainly useful to harmless: exercise regularly, keep the weight down, easy on the caffeine, calm yourself with [deep breathing](#) or [yoga](#), try black cohosh. (You could start a bar brawl over the efficacy of black cohosh, but the general consensus seems to be: if it works for you, go for it.) But the troubles set off by ricocheting hormones are reliably fixed by making the hormones stop ricocheting. And the laborious weighing of hormones’ benefits versus hormones’ harms — maybe not at the crisis moment, for those of us at our most distraught, but later, one or two or five years down the road — is something still undertaken by millions of women along the full breadth of the perimenopausal spectrum.

**How in the world** to do it wisely enough so the calculation is as right for each of us as it can possibly be? JoAnn Manson’s book contains the most careful checklist I’ve seen yet; by the time you answer all the personal-history questions the book asks you to consider, you’ve read 82 pages. [Breast cancer](#) is a factor, to be sure, but so are [colorectal cancer](#), [ovarian cancer](#), stroke, hip [fracture](#) and [diabetes](#). If the timing hypothesis proves right and estrogen really does protect our brains and our hearts as long as we start it early enough, the calculation only grows that much more important and complex. There are moving pieces involved in working out every one of these risks in relation to everything else, and anyone who thinks there’s a bumper-sticker answer to the hormones question — don’t take them, you’re sure to be better off — is, like me that day in the psych unit, neither listening to scientific argument nor reading the fine print. Here’s one example from the many to which researchers have pointed me this winter.

Remember MPA? The synthetic progesterone-like substance used along with equine estrogens in the W.H.I.? There was a second W.H.I. hormones-versus-placebo trial, of nearly 11,000 women, that was also started in the early 1990s, just like the one that was halted in 2002. All the women enrolled in this second study had undergone hysterectomies, which meant they had zero risk for uterine cancer. So the women on medications in this trial were taking only equine estrogens — no MPA, which you’ll recall is given to protect the uterus. Their study was stopped in 2004, also before its planned end date, because the estrogen-taking women were showing a higher risk of stroke than the women on the placebo. But their breast-cancer rate was *lower*. The hormone-taking women with hysterectomies in that second study, who used estrogen without MPA, showed a 23 percent lower risk of invasive breast cancer than their counterparts who were taking no hormones at all.

Nobody's persuaded that this means MPA promotes breast cancer while estrogen does not. It's clear that estrogen acts aggressively on certain breast malignancies and that any woman who has had breast cancer or has a history of it in her immediate family should stay off estrogen. This is one of the principal reasons such intense work is under way right now, in labs like Roberta Brinton's, to develop estrogenic variants — molecular substances designed to latch only to certain receptors (in the brain, say, where the activated receptors can do their good works) while ignoring receptors in the breast and uterus. And there are plenty of confounding factors, as scientists say, with regard to the women in the no-MPA trial. They all had undergone hysterectomies, for one thing; maybe whatever caused them to require uterine removal in the first place affected their reactions to the estrogen.

Or it could have been a fluke. But the MPA wrinkle adds suspicion and urgency to the timing-hypothesis questions about what really goes on when women of our demographic use hormones, and Julia Berry and I spent a long time talking about this, the adding and subtracting, the guessing and weighing, the balancing of what we think we know about ourselves against what we cannot possibly foresee. We will both, for the present, continue wearing estrogen patches. Berry turned out to be right, of course; she wasn't on the placebo, which the N.I.H. doctors told her when she finished the study. And as she hurried to fill her own patch prescription, she found her gratitude mixed with more than a little frustration. "Why did my primary-care physician give me an antidepressant when I could have had something simple, like estrogen?" she asked. "Why don't they know?"

We talked about breast cancer, because that is the nightmare illness in nearly all our calculations, for most of us the visual closest to hand. Three of my best friends have endured the full breast-cancer horror show and by now have retired their wigs. All have survived. None had been on hormone replacement. This is information that batters me steadily but not helpfully, like my ex-smoker paternal aunt's fatal lung cancer and the fact that I'm a lifetime nonsmoker and regular exerciser with extremely good cholesterol levels. How do my lowered risks from one column balance against my question marks over in another column? What to do?

"I'd rather monitor something I know can go wrong than go on living in the state I was in," Berry said. "I could have my breasts removed. I like them. But they're not my life."

We've spent a fair bit of time by now, Julia Berry and I, shaking these uncertainties out and squinting at them. Do we wear these patches forever? We don't know. What happens when we do take them off, if we do? We don't know. Have we done nothing except delay a biological process, complete with hot flashes and another round of truck-crash fantasies, that at some point we'll have to bully our way through? We don't know, nor does any researcher I talked to this spring.

And there's this: Should luck and longevity cooperate, we are going to grow old. We're already

old, by the standards of our children and our ancestors, but the generation to which we belong expects to live a rich messy life full of extremely loud rock music for another 30 years after menopause. Every midlife woman I know keeps redrawing for herself the defensible lines of intervention in the “natural” sequence of human aging. Obsessive multiple plastic surgeries are silly and desperate. Muscles kept in good working order are not. Where on that spectrum is a hormones-saturated pharmaceutical patch? What if the timing hypothesis is even partly right? Suppose all we learn about replacement estrogen, in the end, is that if it’s started early enough it *might* protect the heart and the brain, and that its chemistry makes some of us feel more the way we did at 40 than the way our mothers did at 65? Not an elixir of youth. More like . . . reading glasses. Or [calcium](#) supplements, or painkillers that stop the knee from hurting but carry risk warnings of their own. It has occurred to me that the better analogy might be a 13-year-old trying to ward off [puberty](#) by binding her breasts, but most of the time I don’t think so, and if I do try stopping the patches, I know this to a certainty: I will keep a few extras in reserve, just in case.

*Cynthia Gorney is a contributing writer to the magazine. She teaches at the Graduate School of Journalism at the University of California, Berkeley.*

At the same time, biologists have identified estrogen receptors in brain cells that are important for memory. And estrogen may halt the brain's production of the toxic beta amyloid protein associated with Alzheimer's. Balanced against these benefits of estrogen replacement is an 800-pound gorilla: breast cancer. The Estrogen Dilemma By CYNTHIA GORNEY Here we are, two fast-talking women on estrogen, staring at a wall of live mitochondria from the brain of a rat. Mitochondria are cellular energy generators of unfathomably tiny size, but these are vivid and big because they were hit with dye in a petri dish and enlarged for projection purposes. The Estrogen Dilemma. New science is showing that estrogen's effects on women's minds and bodies may depend upon when they first start taking it. What should you do? Author: Cynthia Gorney. Source: The New York Times.