J. W. STEWART

Menopause and the Brain

New studies suggest that the brain may be an important player in the timing of menopause

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A regular menstrual cycle is like a well-oiled machine. Each component must move in time with and match the rhythms of the others. Similarly, hormones in the body that control the menstrual cycle must be released with accurate timing, in the right amounts and in the proper locations. If the rhythms or fine-tuning falls out of step just slightly, menstruation becomes irregular or even stops.

Menopause marks a permanent end to a woman's natural menstrual cycle; on average, women in the U.S. cease menstruating around the age of 50. With increasing numbers of women living into their 70s, 80s and beyond, it is essential that researchers gather reliable and detailed information about what happens before, during and after menopause.

Certain facts have become clear concerning what happens to women after menopause. For instance, levels of the female hormone estrogen fall off; this decline has been linked to an increased risk among postmenopausal women for osteoporosis, heart disease and possibly even Alzheimer's disease.

But what about before and during menopause? Scientists have long recognized that fertility gradually declines among women starting in their mid-30s, as the number of follicles (the structures in the ovary that contain developing eggs) dwindles. Simultaneously, women's hormone levels start to fluctuate wildly: while estrogen drops off, levels of other hormones involved in a woman's reproductive cycle, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), begin to soar.

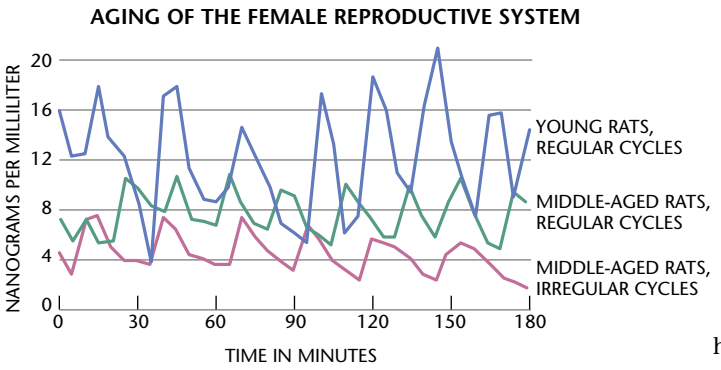
Menopause was once thought to occur when the ovaries ran out of eggs. But hormonal signals from the brain may prompt the end of a woman's menstrual cycles.

For many years, scientists accepted the view that menopause results simply from the gradual exhaustion of the supply of follicles in a woman's ovaries and that the associated hormonal changes are simply side effects of aging ovaries. More recently, however, researchers have begun to question this simple notion and to propose an alternative hypothesis: menopause may result in part from the aging of the brain.

The Aging Ovary

The original concept that aging ovaries are the primary cause of menopause derives from the fact that female mammals are born with a large, but finite, nonrenewable reserve of dormant follicles. (This situation stands in contrast to male mammals, which continually regenerate their supplies of sperm.) The number of follicles in a woman's ovaries is set during fetal development; once the supply is exhausted, menstrual cycles stop and a woman can no longer become pregnant unless she receives a donor egg. Females are born with, on average, about half a million dormant ovarian follicles, but the vast majority of these perish before they have a chance to mature. During a woman's life, these follicles are constantly reawakening and entering the growing pool of follicles, but only a minute fraction—less than one tenth of 1 percent on average—complete the path to ovulation, in which an egg is released from the ovaries ready for possible fertilization.

A woman's body regulates the development of the egg inside the follicle by an elaborate biochemical process. Briefly, at the start of the menstrual cycle, the hypothalamus (located at the base of the brain) produces carefully orchestrated pulses of the compound gonadotropin-releas-



LAURIE GRACE; SOURCE: K. SCARBROUGH AND P. M. WISE

The pattern of secretion of luteinizing hormone, a reproductive hormone released from the pituitary, becomes erratic with age. The author measured levels of LH in laboratory rats for three hours and found that in young rats (blue) *the pulses of LH were quite large; however, as the rats aged* (green) *and their reproductive cycles became irregular* (red)*, the pulses of LH became smaller. A similar pattern can be seen in women approaching menopause.*

ing hormone (GnRH). These pulses of GnRH in turn stimulate the pituitary (which protrudes from the base of the brain) to secrete LH and FSH, in another precisely timed pattern. The exact pattern of LH and FSH secretion determines the rate and number of follicles that will undergo the final stages of maturation.

Some scientists have hypothesized that to maintain a constant stream of ripening follicles, the ovaries must contain an enormous excess of dormant follicles waiting to mature. It turns out that some of the hormones required to promote the growth of a follicle—such as estradiol (a form of estrogen), activin, inhibin or other growth factors—are actually released by other, maturing follicles. So as the number of follicles drops over a woman's lifetime, levels of these crucial compounds fall off as well. As a result, not only are there fewer follicles around to start developing as a woman ages, but even fewer of the ones that do start will be able to mature fully.

After a woman reaches age 35, the rate at which her follicles die increases dramatically; scientists don't fully understand why. But many investigators believe the rate of the loss begins to accelerate when the number of follicles in a woman's ovaries drops below a critical threshold; below this point, the hormonal fine-tuning necessary for the other follicles to mature is so disrupted that more and more follicles die during the growth and maturation process. In short, the loss of follicles becomes a self-perpetuating cycle—as follicles die, the ones left behind die even more rapidly. Eventually, by age 50 or so, all of a woman's ovarian follicles are gone, and her menstrual cycles cease for good.

The Aging Brain

The line of reasoning I outlined above focuses on events taking place in the ovaries. For the past 20 years, I have been looking to the brain to understand what happens as the reproductive system ages and ultimately ceases to function. Because, as I described earlier, the brain plays such a critical role in a woman's menstrual cycle, it makes sense that the aging brain would play a role in menopause as well.

Several investigators, including Dennis W. Matt of Virginia Commonwealth University, Joseph Meites, a professor emeritus at Michigan State University, and myself, have described the hypothalamus as the possible pacemaker of menopause. We contend that the increased loss of ovarian follicles observed after age 35 could be caused not by aging ovaries but by alterations in the secretion of hormones from the brain. In particular, I suspect that changes in the patterns of the signals governing the release of GnRH from the hypothalamus play an important part in the process. Although we do not know precisely what controls the release of GnRH, it appears that many factors are involved, including compounds such as norepinephrine, dopamine and serotonin, all of which perform numerous tasks throughout the brain. Intriguingly, other signs of menopause, such as hot flashes and sleep disturbances, may result from normal, age-related deterioration of the hypothalamus.

To test the hypothesis that the timing of menopause is dictated by the brain, scientists need to determine whether and how GnRH levels shift in postmenopausal women. Because most reproductive hormones normally fluctuate not just over the course of a woman's monthly cycle but also over the course of a single day, it would be ideal to measure the amount of GnRH in the blood samples of a group of women every few minutes over a period of a day and to repeat the sampling every several weeks for three to five years, beginning as soon as the women show any signs of approaching menopause. (This time is known as the perimenopausal period and typically begins in a woman's late 30s or early 40s.)

Unfortunately, though, there are no tests currently available that are sensitive enough to detect GnRH in the blood, so investigators, including Dennis Matt and Nancy E. Reame of the University of Michigan, have instead measured LH, which can be detected in the blood and which serves as an indirect marker for GnRH. (Recall that when the hypothalamus secretes GnRH, the pituitary responds by releasing LH as well as FSH.)

These researchers tested perimenopausal women every five to 10 minutes for several hours on different days of their menstrual cycles. Some of the women were still experiencing regular cycles; others were more irregular. In this way, the scientists were able to monitor LH pulses as well as levels of other critical reproductive hormones, such as estradiol, progesterone and inhibin, for women in different stages of the menopausal transition. In another approach, Nanette Santoro of the University of Medicine and Dentistry of New Jersey took urine samples to assess how estradiol levels change in perimenopausal women. (Urine tests have one big advantage—because they are noninvasive, data can be collected for longer intervals.)

Hormonal Fluctuations

The outcome of these studies has been revealing. Typically in young women, the pituitary pumps out LH in very predictable, rhythmic pulses. But, as Matt has shown, among women between the ages of 40 to 45 who still exhibit menstrual cycles of normal length, the release of LH becomes erratic, consisting of longer but less frequent pulses, indicating that the hypothalamus is sending out irregular pulses of GnRH. Women approaching menopause also have an unusually high level of FSH during the early part of their menstrual cycles; this condition can result not just when levels of inhibin are low (the standard explanation) but also when the hypothalamus sends out very low levels of GnRH or when the pulses of GnRH are some-

how altered from their typical frequency.

My colleagues and I at the University of Kentucky are studying laboratory rats to find out more about how the activity of chemicals in the brain changes with age. In particular, we hope to learn more about what regulates the release of GnRH from the hypothalamus. We chose to work with rats because this species has already taught scientists a great deal about many aspects of human reproduction, including puberty, ovulation, pregnancy and lactation. Although there are differences among species, there are also many important common features.

For instance, the pathways by which the hypothalamus controls the ovaries are quite similar in both rats and humans. We have found that in middle-aged female rats that are still regularly cycling, there are measurable changes in the release of LH from the pituitary, analogous to the changes seen in middle-aged women approaching menopause.

Furthermore, we have found correlating variations in the levels of specific compounds in the brain, such as norepinephrine, serotonin and beta-endorphin, suggesting that these chemicals, which control GnRH, may cause the changes in LH secretion that we observe in aging rats. We have also observed changes in the activity of the nerve cells in the brain that modulate the release of GnRH, suggesting that the ability of these neurons to function correctly might be deteriorating with age.

I mentioned earlier that the menstrual cycle relies on the interplay of hormones and other compounds that all must function in tempo with one another. Indeed, GnRH, LH and FSH are just a few of the players involved in a woman's reproductive system. And as a woman ages, the coordination between these hormones and the neurotransmitters in the brain, such as norepinephrine, dopamine and serotonin, gradually deteriorates. The effects—hormones being secreted in the wrong amounts or at the wrong times—are quite subtle at first; indeed, they may not even show up in average measurements of a menopausal woman's hormones, but only in daily or even hourly readings.

Eventually, though, the release of crucial reproductive hormones from the brain becomes completely unsynchronized; the changing levels of hormones such as FSH and LH then interfere with the proper development of ovarian follicles, leaving more and more of them to perish. Finally, a woman's regular menstrual cycle ceases completely.

Your Biological Clock

So what's going on in the brain as women grow older? Why does the timing of hormone secretion become so erratic? The adage about the ticking of your biological clock may not be too far from the truth. A region of the hypothalamus known as the suprachiasmatic nucleus serves as the body's internal clock, regulating a variety of functions, such as sleep, that each have their own 24-hour cycle. (Body temperature also typically follows a daily cycle—you cool down at night and warm up through the day.)

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The secretion of virtually all hormones fluctuates throughout the day as well. I suspect that parts of the body's internal clock deteriorate with age, causing the release of hormones to become gradually unsynchronized. This hypothesis is bolstered by the observation that other daily rhythms known to be controlled by the suprachiasmatic nucleus are also thrown off as people age: for instance, older women (and men) tend to get up earlier, go to bed earlier and sleep for shorter stretches.

The suprachiasmatic nucleus does not work in a vacuum, however. Many other parts of the body communicate with it and convey information about the environment, largely through the neurons that interconnect the entire central nervous system. For example, when we fly to Paris, our biological clock shifts because of environmental cues, such as when the sun rises and when we eat meals. In older people, the suprachiasmatic nucleus does not seem to work as well: for instance, our so-called free-running period, which is, in effect, what the body recognizes as one day, grows shorter (hence the altered sleeping patterns), and our ability to respond to environmental signals also deteriorates.

Scientists are still studying what prompts these changes. Perhaps they reflect aberrations in the suprachiasmatic nucleus itself, or perhaps the neurons that communicate with the suprachiasmatic nucleus become altered with age. How does all of this affect a woman's menstrual cycle? I believe that as the ability of the suprachiasmatic nucleus to tell time diminishes, vital neurochemical signals from the body's internal clock to the neurons in charge of GnRH release become desynchronized, gradually disrupting the pattern of hormone secretion from the brain.

Researchers in my lab and elsewhere are only beginning to unravel the biological processes—both in the brain and in the ovaries—that control menstruation and menopause. The more we learn about what happens before and during menopause, the more choices women will have when confronting their health concerns as they grow older. For example, patients and physicians alike wonder about the risks and benefits of hormone replacement therapy for menopausal and postmenopausal women. A deeper understanding of the biochemistry of menopause might enable scientists to produce other options beyond estrogen with the benefits of today's therapies but not the risks.

Better options for hormone replacement therapy are particularly important because we and other investigators have found that when estrogen levels are low, as they are after a woman goes through menopause, the brain and other organs are particularly vulnerable to injury. This occurrence may explain why postmenopausal women suffer from increased incidences of stroke, Alzheimer's disease, heart disease and problems in cognitive function. Ultimately, a richer awareness of how the brain ages will benefit both women and men. SA

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