After humans pass their reproductive primes, estrogen and testosterone concentrations wane. The decline appears to have far-reaching health consequences—on the brain, bones, muscle, and the circulatory system. As scientists tease apart the ramifications of sex hormone loss, they hope to fine-tune therapeutic replacement of those hormones.

Acne, cracking voices, awkward body changes: When hormone concentrations swell during our early teen years, they can make life miserable. As amounts of these same chemicals subside decades later, bones weaken, hair thins, and mental acuity dulls. For decades, estrogen has been prescribed to alleviate acute symptoms of menopause, but now that scientists are expanding their knowledge of how both estrogen and its male counterpart testosterone affect the body, they are uncovering hints that hormone replacement might reverse other effects of aging as well.

Estrogen choreographs physiological events throughout the body, from a woman’s leg bones up to the neurons in her brain. “This hormone is not just a reproductive hormone but is critically important in the maintenance of bone, normal heart function, vascular function, immune function, and cognitive function,” says neuroendocrinologist Phyllis Wise of the University of California, Davis. “A lot of people who are not really reproductive endocrinologists have become very interested in what goes on.” And although research on testosterone trails behind, the male hormone seems to have similarly far-reaching effects. New knowledge from studies at the molecular level and in whole bodies is helping clarify how the hormones influence aging—and how hormone replacement can best minimize aging’s effects.

Ups and Downs
The amount of estrogen and testosterone people produce fluctuates over the lifetime, first rising at puberty (see graphic). Women pump out some testosterone and men some estrogen, but in general the active ingredient in men’s hormone cocktail is testosterone, whereas estrogen does most of the heavy hormonal lifting in women’s bodies. For instance, monthly estrogen cycles during a woman’s reproductive years help prompt the release of eggs. As this era passes, the pool of estrogen-producing follicles in the ovaries is depleted. Waves of estrogen deviate from their predictable shapes; they begin to spike and dip wildly. Then, as a woman enters menopause, hormone concentrations permanently plummet. In a man, testosterone concentrations escalate during puberty to a peak during the 20s then begin a slow, steady decline for the remainder of his life. Amounts of the hormone vary among individuals, however. Some men in their 70s have testosterone concentrations of an average 20-year-old, whereas others carry small quantities, reminiscent of testosterone-deficiency disorders in younger men.

With menopause come side effects beloved of female comedians of a certain age, including hot flashes and mood swings. Less likely to be the topic of good-natured coping strategies are more dangerous consequences: The risk of cardiovascular disease and osteoporosis increases dramatically as estrogen concentrations fall. Estrogen replacement therapy (ERT) is widely prescribed to counteract the symptoms of menopause, with additional benefits that were originally unforeseen. Postmenopausal women taking estrogen enjoy a reduced risk of cardiovascular disease and osteoporosis compared with women who aren’t ingesting the hormone—although estrogen treatment doesn’t appear to protect women who already have heart disease. High concentrations of estrogen substantially increase the chance that uterine cancer will strike, however, so women typically supplement estrogen with a synthetic version of the hormone progesterone. This molecule causes the lining of the uterus to shed, getting rid of damaged cells that could turn cancerous. ERT also might increase the risk of breast cancer and blood clots, especially in women already predisposed to these problems.

Sex Hormones on the Brain
A few years ago, new results provoked strong public interest. They hinted at another potential benefit of estrogen: preserving...
brain function. Women on ERT were less likely to be stricken with Alzheimer’s disease (AD) than were untreated women (see “Detangling Alzheimer's Disease”). Although suggestive, these results—as well as the effect of estrogen on heart disease—await proof from large-scale placebo-controlled clinical trials. Such studies for AD are under way. The first round of clinical trials will finish in 2003.

Lab studies suggest a molecular basis for the putative connection between estrogen and AD. Rodent brains and cultured neurons treated with the hormone accumulate less β-amyloid protein than their untreated counterparts; β-amyloid protein might precipitate AD and is the main ingredient in brain-gumming senile plaques, according to Samuel Gandy, a neurologist at Thomas Jefferson University in Philadelphia, and his colleagues. “We believe that [hormones] might play a role in the timing of Alzheimer’s,” he says. Individuals with a genetic predisposition to AD “might be teetering on the brink, and then when the hormone levels fall late in life and amyloid concentrations rise, that might tip them over.” His and other groups are mating mice deficient in one of the two types of estrogen receptor to animals carrying mutations that cause AD in humans. The offspring might help researchers understand how estrogen influences the speed at which plaques clump up in the brain.

Some scientists are focusing on memory impairment, an aspect of AD that is shared to some extent by aging brains in general. Initial studies failed to uncover a beneficial effect of estrogen on long-term memory in rodents. In work reported last spring in Behavioral Neuroscience, neuroscientists Christina Williams of Duke University in Durham, North Carolina, and Noah Sandstrom of Williams College in Williamstown, Massachusetts, tested whether estrogen improves rodents’ short-term memory—the kind most affected by AD. They removed the ovaries from a group of rats, then they administered estrogen to some of the animals and tested their memory by placing them one at a time in a pool of opaque liquid with a hidden escape platform (see photo). Rats treated with estrogen rediscovered the platform more quickly than untreated rats did. Work by other teams using different tests of short-term memory corroborates the finding.

Changes in brain structures might underlie these differences in recall. Catherine Woolley, a neuroscientist at Northwestern University in Evanston, Illinois, and colleagues have focused on the hippocampus, a learning and memory control center. Over the last decade, they have found that pyramidal neurons—which integrate signals from different parts of the brain—in rats treated with estrogen sprout a profusion of dendritic spines (see figure on next page). These spiky protrusions form synapses, points of contacts with other neurons that release chemical signals that tell the pyramidal neuron to fire. Like a bigger TV antenna, more dendritic spines might mean better reception of incoming signals. Compared to untreated animals, those exposed to hormones also churn out extra neuronal NMDA receptors, proteins on the cell surface that register chemical messages. Neural connections that rely on this type of receptor probably help store new memories. The increase in dendritic spines and NMDA receptors appears to have functional consequences: Pyramidal neurons removed from estrogen-treated rats respond more dramatically to their chemical triggers than do neurons from untreated animals.

Hippocampal neurons also receive input that tells them to quiet down. Excitatory and inhibitory signals act like zeroes and ones in computer code; neurons integrate the incoming information and fire accordingly. In the September 2001 Journal of Neuroscience, Woolley’s team extended its previous results to show that pyramidal cells in estrogen-treated neurons are more sensitive to dampening. With heightened sensitivity to a cacophony of neural signals, the brains of rats exposed to estrogen could be especially nimble at producing the transmissions that form memories. In addition to being in the right memory-related places, the new dendritic spines and synapses grow at the right time. They start to appear a few days after estrogen is administered—at the point when researchers measure an improvement in rat memory. Proof of a connection awaits further study, however. “We still don’t know how the changes induced by estrogen in the hippocampus are related to cognitive function,” says Woolley. And making the leap to human brain-power is even harder, she says.

Questions remain about whether animals of all ages would equally enjoy the brain-boosting benefits of estrogen. Studies have suggested that neurons in brains from old rats respond differently to hormone treatment than do those from their younger counterparts. The seasoned rodents do not ratchet up construction of dendritic spines and synapses in the hippocampus in response...
to estrogen injections, although the number of NMDA receptors does rise, according to work published in the 3 July 2001 issue of the Proceedings of the National Academy of Sciences (PNAS) by John Morrison, a neurobiologist at Mount Sinai School of Medicine in New York City, and colleagues. The result is a higher concentration of receptors, which “may be good under some circumstances,” says Bruce McEwen of Rockefeller University in New York City, “but that also raises the question as to whether estrogen makes the brain more vulnerable to certain kinds of damage from excitatory signals, such as what happens in stroke.”

Molecular Collaborations
Estrogen doesn’t work alone, and recent studies are identifying which molecules team up with the hormone to spur cellular changes in the brain and elsewhere. Estrogen, like other steroid hormones, acts by hooking onto a receptor protein that floats inside the cell. With the hormone in tow, the receptor enters the nucleus, where it binds to genes and turns them on and off. Two flavors of estrogen receptor (ER) exist: an α and a β form. Some studies suggest that the proteins can’t always compensate for one another’s absence even though they’re similar. Last year, Wise and colleagues reported in PNAS that ERβ is responsible for the protective effects of estrogen after stroke in an animal model. Mice that lack ERβ, meanwhile, suffer from increased blood pressure and constricted blood vessels, according to a report by Michael Mendelsohn and colleagues in the 18 January issue of Science (p. 505). Each type of tissue is likely to harness these receptors for particular purposes, and the receptors probably turn on different genes in different places. Further studies should identify the complement of genes that estrogen stimulates in the brain, blood vessels, and other systems, thereby revealing how the hormone imparts its diverse effects on different parts of the body.

Estrogen might also act through routes that don’t involve gene activation. Mendelsohn has found that the hormone can rapidly relax blood vessels by increasing the production of nitric oxide, a molecule that opens ion channels, which in turn makes smooth muscle cells more pliable. And estrogen boosts concentrations of nitric oxide without turning on genes, instead prodding a protein signaling pathway into action. Gene-independent estrogen pathways might operate in the brain, too. Several groups have found that estrogen receptors in neurons can activate cellular signaling networks, such as those that stimulate cell growth.

Increased knowledge of the molecular details of estrogen’s machinery will help refine estrogen therapy. The work could also direct researchers toward estrogen substitutes that specifically protect against heart disease, osteoporosis, or mental decline. Some of those compounds—known as selective estrogen receptor modulators, or SERMs—are already in use: The drugs tamoxifen, used to treat breast cancer, and raloxifene, prescribed for osteoporosis, thwart estrogen receptors in breast tissue but activate the proteins in bone and blood vessels. Both drugs were developed as estrogen blockers, but their effects turned out to be more complicated. Clinical trials are already under way to examine whether raloxifene also delivers a brain-saving benefit, and new SERMs will likely be tested as well.

Men Play Catch-Up
Although the health effects of declining estrogen concentrations could fill books, similar information about testosterone would barely occupy a pamphlet. But some studies hint that testosterone might also prevent symptoms of aging, and scientists are eager to explore the possibilities. Patients of all ages with hypogonadism—a disease in which the testes produce very little testosterone—suffer several maladies that commonly afflict generally healthy older men: feeble muscles, flabby bellies, and brittle bones. Testosterone therapy can reverse the consequences of hypogonadism, which can strike males during fetal development, puberty, or adulthood. But whether these symptoms in older men represent a “male menopause” is difficult to prove, in part because the normal fall in testosterone is gradual and variable, compared with the sudden drop in estrogen that characterizes menopause in women.

No one knows whether testosterone therapy can deliver the same benefit to healthy older men as it does to patients with hypogonadism. Some work suggests that reviving testosterone concentrations can tone aged male bodies, although muscle strength and the incidence of cardiovascular disease aren’t dramatically affected. Additional studies that are currently being finished offer hints that testosterone also improves cognitive function and mood. Those investigations, however, follow small populations for short periods of time. Researchers are hoping that a larger scale clinical trial might clarify the long-term effects of testosterone. A proposal that aims to take on that challenge received positive reviews last year, according to Marc Blackman, an endocrinologist at the National Center for Complementary and Alternative Medicine in Bethesda, Maryland, but “whether it will get funded and will happen is unclear,” he says. To drum up additional support, andrologists will gather in May at a meeting convened by the International Longevity Center, an aging research and education organiza-
tion associated with Mount Sinai Hospital in New York City, and the Kronos Longevity Research Institute in Phoenix, Arizona, to draft a position paper. They intend to convince lawmakers that research on the male sex hormone is crucial. Given the age and gender of the average member of Congress, the audience just might grasp the issue’s importance.

Testosterone therapy is tainted by images from uncontrolled, nonclinical steroid trials carried out illicitly in locker rooms: visions of dangerously aggressive, acne-covered bodybuilders with huge muscles and shrunk testicles. In large doses, testosterone can spur combative behavior, and “you wouldn’t want to end up with a bunch of bullies,” says Gloria Hoffman, a neuroendocrinologist at the University of Maryland, Baltimore. But hormone therapy to treat aging wouldn’t aim to create graying superheroes. It would only nudge testosterone back up to normal concentrations, similar to treatment of hypogonadal patients—who do not get overly bellicose, says Mitchell Harman, director of the Kronos Longevity Research Institute.

Some researchers already see a more positive attitude toward the potential of testosterone therapy. “I attribute a lot of this raised consciousness to Viagra,” says Gandy of Thomas Jefferson University. The visibility of the pill, he says, has helped men open up about health problems associated with aging—and in particular, impotence, one potential application for testosterone therapy.

As clinicians decide whether to replace or not to replace, researchers who study basic biological mechanisms of hormone action are fleshing out the molecular details of testosterone’s mode of action and probing why its concentration subsides with age. But andrologists face a considerable problem, because nature has inadvertently thrown up a block to studies of testosterone in animal models. In rodents, unlike humans, the hormone doesn’t play a crucial role in creating key physical differences between males and females, robbing researchers of their favorite animal models. “The bottom line,” says endocrinologist Harman, “is: If we get testosterone levels back up to normal, what are the clinical outcomes?” That’s a question that only a well-designed, large-scale clinical trial will answer.

**Behind the Fall**

Although many researchers track hormonal signals through the cell or measure its effects on the body, no one knows why hormone concentrations dwindle with age. Humans now far outlive their reproductive usefulness (women spend nearly half their life postmenopausal), so there’s no obvious reason for the body to continue to invest in sex hormone maintenance. Or perhaps menopause shifts a woman’s energy away from reproduction—which becomes riskier in middle age—to caring for younger generations, a controversial idea known as the grandmother hypothesis (see Holmes Perspective†). But—evolutionary pressures aside—figuring out how and why hormones ebb during aging and the molecular consequences of these declines will help refine treatments for age-related disorders. Such advances might not make junior high school less awkward, but they could help keep older people healthy enough to guide their pimply grandchildren through that troubling time.

R. John Davenport is an associate editor of SAGE KE. He struggles to bench-press his own body weight, but he gains strength from the knowledge that he does it without hormone injections.

**Further Reading**


† sageke.sciencemag.org/cgi/content/full/sageke;2002/7/pe3