



FROM BACH TO BEDOUINS, MANY STONES WERE TURNED IN SEARCH OF CLUES TO HOW PUBERTY BEGINS:
 An eighteenth-century choir // A gene that “kisses” // Harry Potter // Saudi cousins // Songbirds //
 And, of course, pimply faced adolescents.

To Grow Hairy

■ BY STEPHEN S. HALL

For 27 years, until his death in 1750, Johann Sebastian Bach led three male choirs in Leipzig. Most of the singers were teenagers, almost all of them musical prodigies. By the standards of the time, German school officials kept excellent records on each student, including his date of birth, academic performance and family history. More than two centuries later, an enterprising historian had the idea of poring over those records in an attempt to document, retrospectively, an adolescent trait that is very pertinent to the male choir business.

One of the classic physiological changes of puberty—indeed, one of the most gratefully obvious—is when a boy’s voice “cracks,” or deepens. In the late 1960s, S. F. Daw, a researcher at Worcester College in Oxford, England, attempted to correlate the change in voice, and thus the timing of puberty in eighteenth-century boys, with the part each of Bach’s choristers sang. (Music historians believe that boys whose voices had not yet broken sang soprano, the highest vocal part for male adolescents; boys in the midst of changing sang alto; and boys in whom the change was complete sang tenor and bass.) The results, which Daw published in 1970 in the journal *Human Biology*, suggested that the average age of a boy whose voice was changing was about 16½ to 17 years—some three years later than the comparative age for a modern European boy.

Many of the changes in physical features during puberty, such as height and shape and sexual maturation, are obvious, but less visible aspects of development also occur throughout the adolescent body. A voice breaks, for example, because of a growth spurt in the larynx, which stretches out the size of the vocal cords and, like loosening the strings on a guitar, lowers the voice.

The cycle of change generally unfolds during a three-year period, although the starting gun for these enormous transformations goes off at different times for different children. For some puberty starts early; for others, insufferably late. What’s more, the timing has significant—and, scientists think, life-long—ramifications for the psychological makeup and well-being of adults, affecting everything from self-esteem to such unhealthy behaviors as substance abuse. But that shouldn’t be surprising, really, when one considers that some of the most profound changes occur in the adolescent brain.

Scientists have been studying puberty (the word derives from the Latin *pubescere*, “to grow hairy”) in humans for decades, but until recently, there was still a central mystery: Boys and girls are suspended in childhood until the brain registers some unknown combination of environmental cues and genetic prompts, unleashing a cerebral signal—for puberty really begins in the head. All the tumultuous shudders of physical change in the armpits, bones and groin begin

when a small nub of neural tissue known as the hypothalamus emits a barely perceptible chemical whisper. But what flips the switch to initiate puberty? What tells the brain that it is time to change a sexually immature child into a reproductively competent adult?

In the 1970s, two scientists, one at the Salk Institute in San Diego (Roger Guillemin), the other at Tulane University in New Orleans (Andrew Schally), competed to discover the hormone that controls sexual development in humans. When the dust settled, both had a hand on the prize: a molecule known as gonadotropin-releasing hormone, usually abbreviated GnRH.

The discovery reshaped the working biochemical definition of puberty. “Everyone thought the pituitary was the master gland,” remembers William F. Crowley Jr., who began practicing endocrinology just after Schally and Guillemin did their pioneering work. “It turns out that the pituitary, like all of us, works for someone else. The real boss is the hypothalamus.”

The new, biochemical description of puberty goes like this: The hypothalamus releases tiny squirts of GnRH, sending a chemical message that travels just two or three millimeters—the length of a hyphen—to the pituitary gland, which, in turn, begins releasing small, pulsed secretions of two hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Those hormones act on the sexual organs of both boys (testicles) and girls (ovaries), causing them gradually to grow in size and to release more, increasingly potent, sex-specific hormones—estradiol in girls and testosterone in boys.

It isn't as if estradiol and testosterone have been in hiding throughout a child's life. To the contrary, since early infancy, they've been sleeping in late like many adolescents, in a kind of molecular hibernation. LH and FSH are present in fairly substantial amounts during fetal development and in infants during their first

half-year. “Three-month-old boys have as much testosterone as you and I,” Crowley says. “And then, at around six months, it shuts down.” Boys enter “a mysterious period of dormancy during childhood,” Crowley and his colleagues have written, until being aroused at the beginning of puberty.

In the early 1980s, many physicians hoped that the discovery of GnRH would lead to better diagnosis of several rare disorders of sexual maturation, which can take the form of very early development (central precocious puberty) or, conversely, no puberty at all. Crowley, then a young doctor at the Massachusetts General Hospital (he now heads the reproductive endocrinology unit there), believed the hormone could be used therapeutically, and he had an astonishing case with which to make the point. It was that of a two-year-old girl who had already entered puberty, with rapid growth, vaginal bleeding, and breast and pubic-hair development.

A researcher at the University of Pittsburgh, Ernst Knobil, had shown that puberty could be triggered in primates by the administration of GnRH in pulses and then shut down again by the continuous administration of the same amount of hormone. In other words, the onset of puberty depended not only on the presence of the hormone but also on the way in which the body delivered it. So Crowley's team treated the girl with constant low doses of a synthetic agonist, or stimulant, of GnRH. That continuous stimulation actually fatigued the pituitary, which then stopped sending hormone messages to the sexual organs. After two months of treatment, the girl's development normalized, and she went back to being a toddler.



Next, Crowley tackled the opposite situation—inducing puberty in men who otherwise couldn't achieve it. He and colleague Andrew R. Hoffman began treating patients with GnRH. But to be effective, they discovered, the drug had to be given in pulses, just as the hypothalamus releases it, so they customized a portable infusion pump to release a dose of hormone every two hours. These pulses induced all the clinical and biochemical changes of normal puberty within three months, and the patients achieved normal sexual development.

By then the researchers had a keen interest in identifying the genes that controlled the timed release of this crucial hormone, but they would have to wait more than a decade for the genetic tools—and the good fortune—that would allow them to make real progress in that search. The tools came as a by-product of the Human Genome Project (the federally funded effort to decipher the 3 billion biochemical letters of human DNA), and the good fortune happened when a researcher in Crowley's lab, Yousef Bo-Abbas, returned to his native Kuwait during the late 1990s.



The onset of puberty depended not only on the hormone but also on the way in which the body delivered it.

Crowley had sent Bo-Abbas there on an unusual assignment. “I told him to find me a good Bedouin family,” Crowley recalls, knowing that the group’s frequent practice of intermarriage increases the odds of finding significant gene mutations. “He went on TV with one of those portable IV pumps we had rigged up, and asked if anyone knew families suffering from infertility. Remarkably, Bo-Abbas found some.”

In one large Saudi Arabian extended family in particular, in which there were three marriages between first cousins, six of 17 children had failed to achieve puberty (the technical term is idiopathic hypogonadotropic hypogonadism, meaning that the chemical that triggers puberty is essentially undetectable). To a geneticist searching for a gene related to puberty, this increased the number of needles while dramatically diminishing the size of the haystack.

The initiation of puberty, at least in this instance, required the activity of a gene occupying a small segment on human chromosome 19. The gene contains the instructions for a protein, GPR54, which is a receptor—a kind of biochemical satellite dish—sitting on the surface of certain cells in the hypothalamus. In 2003, using the DNA of the original six Saudi patients, Crowley, endocrinologist Stephanie Seminara and others within their group, along with researchers in England and Kuwait, figured out that a tiny defect in a single bead in the string of amino acids that make GPR54 was enough to warp its antenna, obliterating its ability to receive signals.

By coincidence, a biotech company in England working with Crowley’s group had isolated and systematically examined dozens of unknown genes belonging to this same family of receptors and had named each uncharacterized gene after a

The neural makeover that puberty unleashes in the brain involves not the creation of new brain mass, but rather the sculpting and grooming of what is already there.

famous orphan. Thus, it turned out that the company had independently identified the gene responsible for making GPR54 and dubbed it Harry Potter. Crowley's response? "I told them they gave it the wrong name," he says. "They should have named it the Peter Pan gene because these kids never grow up."

What molecular message did the brain fail to receive when the GPR54 receptor wobbled like a wind-tossed satellite dish? Last year Crowley, along with researchers at the University of Pittsburgh and the Oregon National Primate Research Center in Beaverton, provided the beginnings of an answer. Specifically, they reported that puberty begins when another brain protein, with the suggestive name kisspeptin, "kisses" the GPR54 receptor and flips the switch on puberty.

What triggers kisspeptin? No one knows—yet. But as in other areas of growth biology, the ultimate answer, at least in part, appears to come from the environment. Cheryl L. Sisk, a psychologist at Michigan State University, and reproductive science researcher Douglas L. Foster of the University of Michigan, in a recent review article in *Nature Neuroscience*, pointed out that for puberty to begin, "the individual must perceive whether it has grown sufficiently (through metabolic cues), what its relationship is to other individuals (through social cues), and whether conditions are optimal to begin the reproductive process (through environmental cues)." Those are a lot of cues coming from the outside world, and probably a lot of neural circuitry to integrate all those inputs into a single, coherent message.

The neural makeover that puberty unleashes in the brain involves not the creation of new brain mass, but rather the sculpting and grooming of what is already there. In 1992 a research team headed by Judith Rapaport at the National Institute of Mental Health (NIMH) in Bethesda, Md., began tracking this neural development in more than 1,000 children. She and her colleagues have since reported that there is a "second wave of neural development" during the teenage years, even as the brain simultaneously shrinks.

"The number of nerve cells is not changing," says Jay N. Giedd, a member of the NIMH team, "but they are growing

more connections. My best working hypothesis is that in children the nerve connections are bushier, but after puberty the advance is made by pruning. So even though the bush is skinnier, the quality is better. I guess the best analogy is to Michelangelo and a block of marble, where the quality improves as you take things away. That's what experience teaches—what to keep and what to throw away."

Ready or Not? //

The name of the gene that codes for kisspeptin, first identified by cancer researchers in Hershey, Pa., land of the eponymous chocolate Kisses, became doubly apt with the discovery of the gene's role in puberty. Once awakened in neurons deep within the hypothalamus, the *Kiss1* gene begins to churn out kisspeptin, which sets in motion the production of sex hormones, ushering in sexual maturity.

The *Kiss1* system, says Stephanie Seminara, a Massachusetts General Hospital endocrinologist who played a lead role in its discovery, "is pivotal, indispensable and potent." But it's not the beginning of the story: What tells *Kiss1* when the time is ripe?

Part of the answer is hormones, which report to the brain the status of all body systems. A main indicator of a child's metabolic resources, for example, is a hormone called leptin. Secreted by body fat, it reveals how much energy the body has stored. (The body needs enough energy resources to support fertility and, in girls, pregnancy. That's why malnourishment, anorexia or extreme exercise can delay puberty or stop menstruation.) Among its other duties, leptin activates the *Kiss1* gene in selected neurons. Thus, very low body fat causes low leptin levels and, consequently, low kisspeptin and sex hormone levels.

Recent research points to a potential therapy to counter such problems. Scientists have known that giving leptin to underfed animals can start the production of sex hormones. Now, though, researchers have discovered that giving the animals kisspeptin alone can also launch puberty. Studies by Robert Steiner, professor of obstetrics and gynecology and physiology and biophysics at the University of Washington, suggest that leptin works upstream of kisspeptin, binding to receptors on *Kiss1* neurons and directly activating the gene to produce kisspeptin. Giving kisspeptin appears to trump leptin by acting further along in the process, a finding that could lead to new treatments for reproductive disorders and hormonal contraceptives.

Seminara cautions, however, that there is still much work ahead before any such treatment becomes a reality. "People always look for an A to B to C pathway," she says. "That's too simplistic when we're talking about puberty." —CATHRYN M. DELUDE

One of the biggest questions in neuroscience today is whether puberty “seals off” brain growth the way sex hormones seal off the ends of bones. During the physical growth that typifies the adolescent growth spurt, height is achieved through a continual, incremental lengthening of skeletal bones at the growth plates, small disks of tissue at the ends of long bones like those of the upper arm or thigh. With increasing sexual maturity, however, an adolescent body produces more sex hormones, and these hormones ultimately “seal” the growth plates at the conclusion of puberty, so that growth effectively stops and adult height is achieved.

One hypothesis is that as the amount of testosterone generally increases in boys and estradiol increases in girls, wiring patterns in the brain, sculpted by a childhood’s worth of highly personal and individual experiences—nurture, nutrition, fights, flute practice, all sorts of large and small endeavors and behaviors—become more or less permanently fixed. It is as if a neuropsychological circuitry is tentatively mapped out by the experiences of childhood and adolescence, then the reproductive hormones of puberty solder that circuitry in a much more permanent fashion. Not rigidly and irrevocably—otherwise, education would be useless once the ends of our bones fuse—but tentatively. Thus a basic architecture, contributing to a basic probability of neurocognitive tendencies, may well be fixed by the end of adolescence.

This process remains inadequately understood in humans. But researchers have found that in birds, for example, an animal’s flexibility in learning its song system can be extended when testosterone is removed from immature males. Sisk, the Michigan State psychologist, suspects there is a neural equivalent to the way puberty seals bone growth. “I’m betting there is, based on our behavioral data,” she says, “but we don’t yet have empirical evidence for permanent structural changes.”

If her hypothesis is correct, this change would be among the most profound in terms of adult behavior. So while it’s clearly not true that puberty is all in your head, it certainly starts



there, and some of its most lasting effects may be cemented into place there as well. The biology promises to be fascinating but also a little frightening, especially if we find that our “inner teenager” is hardwired into our adult brain. ■

*This story is based on an excerpt from Stephen S. Hall’s upcoming book, *Size Matters*, to be published by Houghton Mifflin in November. Copyright © 2006 by Stephen S. Hall. Used by permission of the Melanie Jackson Agency, LLC.*

→ DOSSIER

1. “The GPR54 Gene as a Regulator of Puberty,” by Stephanie B. Seminara, Sophie Messenger, Emmanouella E. Chatzidaki, Rosemary R. Thresher et al., *New England Journal of Medicine*, Oct. 23, 2003. An account of experiments that showed that a defect in the gene prevents puberty in mice and humans, thus revealing the gene’s pivotal role.
2. “The Adolescent Brain: A Work in Progress,” by Daniel R. Weinberger, Brita Elvevåg and Jay N. Giedd, June 2005 [*The National Campaign to Prevent Teen Pregnancy*]. A highly readable exploration of how the teenage brain undergoes refining and restructuring.