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NOTRE DAME: A Beast Named 'Gody • BY LUKE WINN

**SPECIAL REPORT**  
**STEROID  
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**STOP  
BLAMING  
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P. 28

# Sports Illustrated

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MARCH 17, 2008

## Hard To Say Goodbye

"I hope people appreciate me, the way I played the game, as much as I appreciate them."

—BRETT FAVRE

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**Sports  
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**STEROIDS  
IN AMERICA  
PART 3**

Think  
performance  
enhancers are  
a problem now?  
Welcome to the era  
of the genetically  
engineered  
superathlete

# The Future

**I**AM ONE of the most avid sports fans you'll find," Se-Jin Lee says. It's true. He'll watch anything. Basketball. Football. Fútbol. Billiards on channel seven-hundred-whatever. As a graduate student in the '80s Lee used to sit in his car in the driveway with the radio on to listen to the games of faraway baseball teams. Even now, in his lab at Johns Hopkins Medical School in Baltimore, he easily rattles off the NCAA basketball tournament winners in order from 1964 to 2007. And, like anyone who values fair competition these days, he's disturbed by the issue of performance-enhancing drugs in sports. ¶ Why, then, is Lee working to usher in technology that will make even today's most inventive doping methods look primitive? A professor of molecular biology and genetics, the 49-year-old Lee studies genes that tell muscles what to do—genes that he knows how to change. As clever as chemists are in altering steroid molecules to avoid detection (recall BALCO's THG, a.k.a. "the Clear"), those designer drugs can be spotted once antidoping agencies know what to look for. Even human growth hormone will be detectable soon, after a valid blood test becomes commercially available. But if athletes develop ways to alter their genes, the



**BY DAVID EPSTEIN**

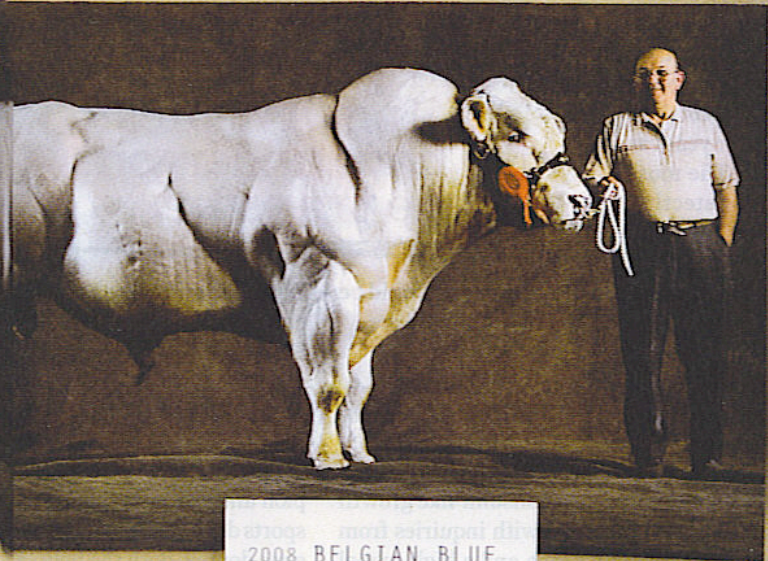
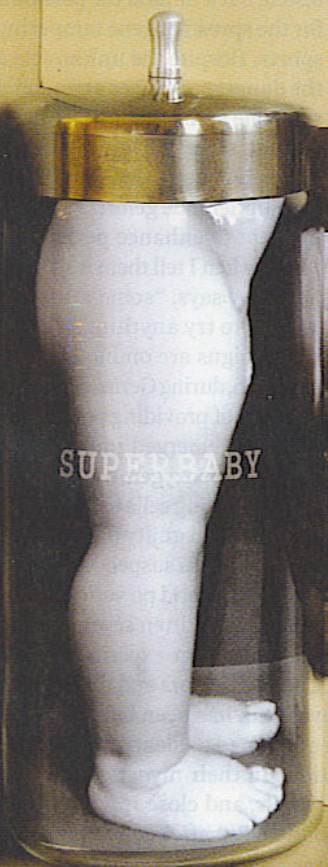
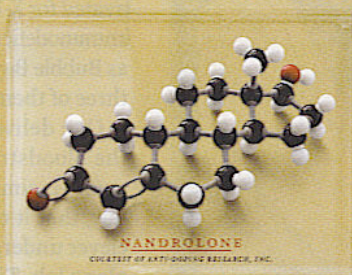
*Illustrations by Doyle Partners*





NORMAL MOUSE

MIGHTY MOUSE



2008 BELGIAN BLUE





very blueprints for their own muscles, there may be no test of blood or urine that can pick that up.

Lee is pushing the frontier of genetic research into muscle building because the same breakthroughs that could boost performance in sports might also bring about a medical revolution. Advances could not only mitigate the effects of diseases like muscular dystrophy but also give senior citizens back their strength—which, often, would amount to giving them back their lives.

In 1995 in his lab on North Wolfe Street, Lee and two colleagues identified the function of myostatin, a protein that tells muscles when to stop growing. It does so, scientists believe, by signaling “satellite cells,” or stem cells that lie dormant around the muscle until they’re needed to build or repair it. Experimenting on mice, Lee inactivated both copies of the gene in the animal that code for myostatin. The result: Over four to six weeks the rodents developed twice their normal muscle mass without a formal exercise regimen. After Lee’s results were published in 1997, he was awash in e-mails from people with muscle-wasting disease (no surprise) offering themselves as subjects for human experiment. He got similar offers (surprise!) from bodybuilders and athletes. Imagine: double the muscle mass. Could he do to them what he had done on the mice?

Some of the athletes barely knew what they were inquiring about. They'd ask Lee where they could purchase some myostatin. "Of course, they didn't want myostatin," he says. "They wanted to block it." But if they could block it with a synthetic gene, the alteration would be a part of their DNA, and it would last for years at the center of their cells. The most straightforward way of detecting the new gene would be to remove a piece of the muscle and probe for it, a procedure most likely too invasive for widescale use. It would be enough to make one long for the simplicity of the steroid era.

**T**HE YEAR after Lee's mice results went public, H. Lee Sweeney, a physiology professor at the University of Pennsylvania, published a paper detailing his own mighty mice, which he had injected with a gene engineered to produce a muscle builder called insulin-like growth factor (IGF-1). Sweeney, too, was inundated with inquiries from athletes. He says a high school football coach and a high school wrestling coach volunteered their entire teams as guinea pigs.

Since the gene genie escaped from the bottle a decade ago, researchers have discovered dozens more genes that appear to affect athletic performance. This is old news in the rodent community. Scientists have created mice whose bodies are flooded

with oxygen-carrying red blood cells, creating greater endurance. Other mice have been engineered to produce extraordinary amounts of growth hormone, while still others have been bred to eat less food. Some mice can metabolize fat and carbs in such a way that they can live on potatoes yet run like marathoners.

Significant safety hurdles remain before gene therapy is widespread for humans. The most efficient means of delivering a synthetic gene is by attaching it to a virus that shuttles it into human cells. Viruses are great at that. They can also trigger the immune system in a way that can lead to fatal results. In 1999 Jesse Gel-

singer, an 18-year-old with a rare liver disease who had volunteered for a gene-therapy trial, died from a massive immune response to the virus used in the treatment. And the dangers extend beyond the immune system. In a gene-therapy trial in France, 12 boys were successfully treated for X-linked severe combined immunodeficiency, commonly known as Bubble Boy syndrome, but at least three of them developed leukemia.

One delivery method—flushing the bloodstream with the desired gene—is simple enough, says Sweeney, that it could be achieved by a clever undergrad in a molecular biology lab. The method is not very efficient and hasn't been thoroughly tested, but it hints at the possibilities for the spread of gene tampering in sports. Despite the unknowns and the dangers, chances are good that someone at the Beijing Olympics in August, someone willing to weigh his or her mortality in gold, will have undergone gene transfer in an attempt to enhance performance. "Even when I tell them it's not safe," Sweeney says, "some athletes are willing to try anything."

The signs are ominous. In January 2006, during German track coach

Thomas Springstein's trial on charges of providing performance-enhancing drugs to minors, evidence emerged indicating that Springstein had attempted to procure Repoxygen, a gene-therapy drug developed to treat anemia by prompting cells to produce EPO and, in turn, red blood cells. (He was found guilty of giving illegal substance to minors and received a 16-month suspended sentence.) In addition, Mauro Di Pasquale, the 1976 world powerlifting champion and an Ontario physician who has written several books on sports doping, says he knows that athletes are experimenting with gene doping, with the help of Chinese doctors and researchers.

Human data relating to myostatin has been hard to come by. Soon after his discovery, Lee attempted to identify potential test subjects with natural mutations in their myostatin genes. He placed an ad in *Muscle and Fitness*, and close to 1,000 muscle-bound men and women responded. But after collecting samples



After discovering how myostatin affects muscle, Lee was flooded with inquiries from athletes.

Chances are good that an athlete at the Beijing Olympics will have undergone gene transfer.



from 150 of them, he has yet to find a single one with the myostatin mutation he had engineered in his mice.

From his study of Belgian Blue cattle, Lee knew the mutation could occur naturally. A cross between the Shorthorn and the Holstein, which have been bred for some 150 years, these massive animals look as if their skin has been stuffed with watermelons. They've. Lee got in touch with Dee Garrels, owner of the Lakeview Belgian Blue Ranch in Stockton, Mo., who sent him samples for testing. Garrels knew Belgian Blues were strong—her 2,500-pound bull once ripped a metal restraining gate off its hinges with its horns to get at a cow in heat—and Lee found out why. He discovered that they had mutations in their myostatin genes.

Lee didn't see the power of a human myostatin mutation until Markus Schuelke contacted him in 2003. A pediatric neurologist in Berlin, Schuelke had been summoned three years earlier to examine a jittery baby in the nursery at Charité hospital in Berlin, where he was taken aback by the newborn's chiseled calves and sculpted quads. By the age of four the boy could hold up a pair of 6.6-pound dumbbells at arm's length. Schuelke had been monitoring the boy's development, and he got in touch with Lee, who confirmed the boy had mutations on both myostatin-coding genes, leaving no detectable amount of the protein in his body.

Apparently it ran in the family. The boy's mother, who was 24 when she gave birth to the "superbaby," had a mutation on one of her two myostatin genes, presumably leaving her less of the protein than normal but not so little that she was as muscle-bound as her son. Nevertheless, she is a testament to the tantalizing temptation of gene-doping. Superbaby's mother, the only adult in the world with a documented myostatin mutation, was a professional sprinter.

**T**HE WORLD ANTI-DOPING AGENCY has banned gene tampering in athletes and spent millions attempting to develop tests to identify it. Such a procedure will require technology unlike any employed by antidoping scientists. The theory, according to Ted Friedmann, the scientist leading WADA's search for gene-doping countermeasures, is to fight genes with genes. If one medical breakthrough is revolutionizing doping, perhaps another can beat it back.

Thanks to the Human Genome Project, someday all of us could carry our entire genetic blueprint on a microchip, which we'd present to doctors during medical treatment. As that technology matures, Friedmann hopes athletes' genomes can be screened, and that gene-doping markers or signatures will emerge.

As pharmaceutical companies race to turn genetic research into medicine, new gene-therapy drugs could

come to market en masse over the coming years. In practical terms it will be impossible to develop specific tests for each of them. "We can keep buying instruments and keep building labs," says pharmacologist Don Catlin, founder of the UCLA Olympic Laboratory, "but [the antidoping] industry isn't like Exxon. There are certain limits."

Perhaps a time will come when there is no longer a need to define those limits—not because of new artillery in the war on doping but because gene therapy will have become so widespread that it will be as controversial as Flintstone chewables. So far Sweeney has aided antidoping officials. "But I've often told WADA my position would change if [gene therapy] is proven to be safe," he says. "Then we're withholding something that would make the athletes healthier."

That would, in turn, raise a new series of questions: What is it we seek to gain from sport? Do we want to see larger-than-life behemoths swatting 600-foot home runs? Or do we prefer to see people more like us pressing the limits of their strength and skill? After all, with their legions of doctors and coaches and cutting-edge equipment, professional athletes, doped or not, are hardly us.

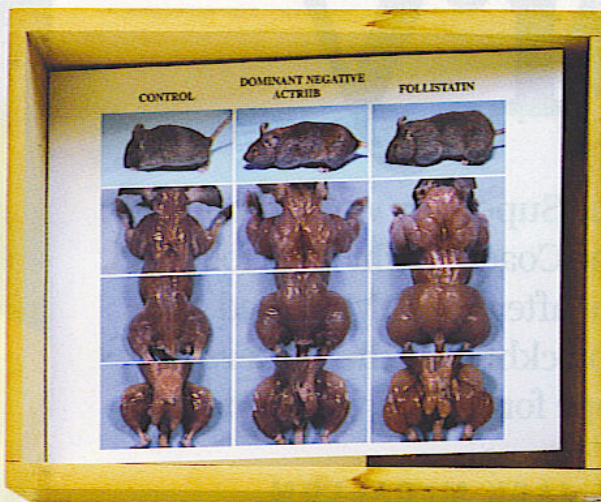
The gravest danger in the debate over gene transfer is not that athletes might taint sport by tampering with their genes. It's that by abusing such treatment, they'll create the same stigma for gene therapy that they have for steroids.

Pat Furlong has felt the effects of that stigma. She is the head of Parent Project Muscular Dystrophy. Her two sons began life happy and healthy, "and then over 10 to 15 years, you watch them go away, helpless," she says. Part of her job is to persuade parents of kids with muscular dystrophy and their doctors that anabolic steroids are beneficial. "I get calls from parents nervous about steroids because of what they've heard," she says. "But the flip side is that steroids have benefits in people who are losing function. In Duchenne muscular dystrophy, it's all we have."

"We know there's no drug that will come without side effects, but steroids are an option to preserve and protect muscle for a few minutes longer, or a few months longer, or a few more years." The local newscasts, and Congress, rarely mention the part about how they can help kids with MD walk longer, which keeps their spines straighter and helps them breathe better.

As he stands at the edge, looking over the gene-doping precipice, Se-Jin Lee has similar concerns. The hysteria that will ensue when an athlete is caught gene-doping, Lee frets, will result in restrictions on gene-therapy drugs, making them hard to obtain by those who truly need them.

"If [an athlete] did cheat, it was his choice," Lee says. "If [the league] turned its back and allowed that to happen, it was their choice. Patients with debilitating diseases did not get there by choice." □



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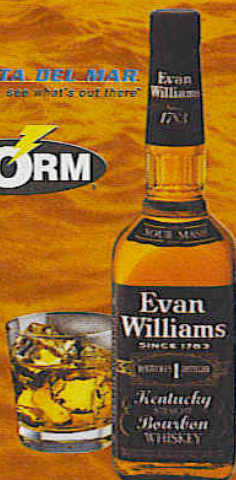


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## Editor's Letter

# Time to Get Real

The steroid debate must go far beyond sports by Terry McDonell

**W**HAT IF the Mitchell Report had been the findings of an investigation into the use of anabolic steroids and human growth hormone not just in baseball but also across America: Steroid Nation.

What if President Bush had looked beyond sports in his 2004 State of the Union address when he said that the use of performance-enhancing drugs sends the wrong message that there are shortcuts to accomplishment and that performance is more important than character.

And what if the medical community's steroids acumen had not lagged a decade behind that of weightlifters and bodybuilders, leaving physicians less educated than their patients, and athletes, young and old, with only doped-up behemoths to answer their questions about those drugs (*The Godfather*, page 38).

In the 1970s and early '80s, as steroids infested the sports world, the idea of enhancement invaded the popular culture on all fronts. *Faster, higher, stronger*, to be sure, but also *smoother, brighter, tighter, longer*. Only in the last dozen years, when the powerful effects of steroids—initially poooh-pooohed by doctors—became undeniable did medical science more actively join the debate about the dangers and benefits of steroids and HGH.

Right now there are two obvious reasons to oppose the use of performance-enhancing drugs: 1) if they are dangerous (as they certainly are for healthy children) and 2) if using them is cheating (as it is in sports). But all of the lines keep moving, redrawn by both research and philosophy.

Some argue that HGH and testosterone are natural substances that need to be replenished when the body's supply runs low, as it does when you grow old. Correcting deficiencies with synthetic hormones, in moderation, isn't just permissible, they say, but therapeutic. But is aging something to be "treated," like a disease? The debate has been slowed by the need for deeper research, but that is on the way—science is catching up and in some cases taking the lead, as with genetic manipulation (*The Future*, page 44).

Athletes have dominated the headlines, but the culture of enhancement has pushed the use of steroids and HGH everywhere. It's not that the emperor has no clothes but that he's juiced. As senior writer Jack McCallum reports (*The Real Dope*, page 28), "Crucial medical questions are being debated by serious medical people, yet we seem determined to hear them only in the limited context of Roger Clemens's injected buttocks." Everyone involved, especially members of Congress, needs a broader view. Sports is about playing fair. Medicine is about enhancing life. These two ideas are braiding quickly, which is why SI has organized an investigative unit to report on the ever more complex issue of drugs and sports.

This team is led by senior editor Larry Burke and supported by senior writers George Dohrmann and L. Jon Wertheim, associate editor Luis Fernando Llosa and writer-reporter David Epstein. Epstein was the lead researcher on the Special Report in this issue, responsible for much of the investigative and scientific reporting. Epstein studied environmental science and astronomy at Columbia (where he was twice All-East as an 800-meter runner), graduating in 2002. He later earned master's degrees in environmental science and journalism from Columbia, then joined SI in '06. "His passion for science is matched by his skill as a writer and doggedness as a reporter," says Burke. "He enjoys taking on the most ambitious stories."

That's where we're going with this.



Epstein brings science expertise to SI's coverage.