Of Mighty Mice & Super Men

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- Genetically Engineered Animals [1]

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There are mice in Lee Sweeney's laboratory. Cute-looking mice with little ears, tails, fur. Some are black, some white. At first glance, they look like regular mice.

Look again.

Some are beefier than others. Their shoulders and legs ripple with muscle, as much as 40 percent more than normal mice, and they outweigh the others by half. They look like they're on steroids. But they're not.

The mice were genetically engineered in Sweeney's lab at the University of Pennsylvania. The purpose of the experiments: to produce extra muscle. The mice represent hope - for the elderly whose weakening muscles place them in increasing danger of falling as they age, for people suffering the crippling effects of muscle-wasting diseases such as muscular dystrophy. Members of both groups write often and beg Sweeney to let them be his next subjects.

But the majority of those seeking Sweeney's muscles are among the healthiest people on the planet. They come from the world of sports.

In the six years since he published his first set of results, Sweeney has received an average of three e-mails per week from athletes and coaches looking for an edge in their quest to go higher, faster, stronger. The inquiries surge every time another advance is announced.

"Initially, I thought they were jokes," Sweeney said.

No one was kidding. Athletes asked to undergo the procedure. A high school football coach wanted his entire team treated. A college wrestling coach made a similar request.

Sweeney's "mighty mice" herald the next big thing in performance enhancement: the field of gene therapy.

The various techniques used to transfer genes, such as ones that promote muscle growth, are still in the developmental stage. Questions abound regarding safety and effectiveness for use in humans. Researchers hope their work will treat and cure a host of genetic-related diseases. But increasingly they recognize that the potential for abuse by athletes - gene transfer used not for therapy, but for enhancement - not only exists, it is inevitable.

"All that's missing is somebody willing to spend the money and basically set up the gene therapy equivalent of BALCO," said Sweeney, referring to the San Francisco-based nutrition company at the center of one of the worst drug scandals in sports history. "I don't know whether that person exists..."
yet, or that person exists and we don't know about it. But I think given where we are with the technology it's hard for me to imagine someone isn't going to decide to make some money off it."

The only question, experts say, is when. Many believe it's possible a genetically modified athlete will compete in the Beijing Olympics in 2008.

"It's a probability by 2012," said Gary Wadler, a Manhasset-based expert on performance-enhancing drugs and member of the World Anti-Doping Agency (WADA).

Sweeney admitted he could not say for sure no genetically modified athletes competed last summer in Athens. Indeed, some experts believe gene doping is happening already.

"It is either here or so close to here that it makes no difference," said Brian Corrigan, former head of the Australian Sports Drug Agency. "I believe that it's here and that they're already experimenting with it."

U.S. professional sports also are aware gene doping is on the horizon. At Thursday's Congressional hearings on steroid use in baseball, players union chief Don Fehr implored Congress to take up the issue, saying, "That is something which bears the closest scrutiny."

Corrigan calls it the gene genie, and he believes it's out of the bottle. As much as drugs have altered sports, Corrigan said, the fallout from widespread gene doping would be worse.

"Sports will be completely different," Corrigan said. "That's the death of sports as we know it."

Pushing the envelope

In many ways, elite sports already is a science fair. Athletes take dizzying arrays of pills and supplements, relentlessly hone training techniques and test cutting-edge equipment such as altitude tents. They employ psychologists, acupuncturists and nutritionists. They have surgery to improve their eyesight. And those are the athletes playing by the rules.

Others use steroids, erythropoietin (EPO), human growth hormone and other outlawed performance-enhancing drugs. Clean athletes hope their concoctions produce the same benefits received by drug abusers. Sports officials struggle to draw a line between what's allowed and what's not, a line often redrawn as new medical evidence surfaces or attitudes change. Which supplements should be permissible? Which produce a positive drug test and which escape detection? How does one distinguish between substance levels produced naturally by the body and those boosted by artificial means?

In this shadowy world with its slippery ethics and gnawing suspicion of anyone who suddenly looks bigger or performs better than expected, genetic modification looms as the ultimate supplement. Improvement seems guaranteed and permanent, and there is no test to catch users. Gene transfer is banned in Olympic sports and its side effects in humans are unknown, but those hardly will be deterrents. Neither stopped the spread of drugs.

Sweeney's work has been among the most promising gene therapy experiments. Using a common technique in which a normal copy of a gene is spliced into a carrier such as a virus and then injected into the body, Sweeney injected the muscles of his mice with the gene for insulin-like growth factor-I (IGF-I), a protein that promotes cell growth and cell repair. The mice gained anywhere from 15 to 40 percent more muscle. When Sweeney injected rats doing weight training (they climb ladders carrying weights on their backs), they gained twice as much muscle as rats doing only weight training. Neither the mice nor the rats lost any muscle as time passed. Nor were there any side effects.

Sweeney's latest results became public in June. The news was electrifying: Substantial muscle gain with no exercise, no side effects and no loss of strength over time. Immediately, Sweeney was inundated with requests for treatment from the sick and the elderly, and from athletes and coaches.
"Most of these people are willing to volunteer and say they want to be guinea pigs," Sweeney said. "Every once in a while we get people willing to pay, and pay substantial amounts of money."

Sweeney is not the only researcher attracting the sports-minded.

In London, Geoffrey Goldspink injected mice with the gene for a type of IGF-I called mechano growth factor (MGF) and measured a 30 percent increase in muscle mass in three weeks. Goldspink, who took out a U.S. patent for the procedure, has been contacted by what he calls the athletic counter-culture - Web sites that sell supplements and want to offer MGF.

Se-Jin Lee, a molecular biologist at Johns Hopkins, engineered his own mighty mice by blocking the gene for myostatin, a protein that limits muscle growth. Bombarded with inquiries from sports people, Lee stopped discussing his techniques. But people know he's onto something.

Lee was part of a team last year that examined an unusually muscular 4Â½-year-old German boy able to hold 6.6-pound dumbbells aloft with each arm stretched out horizontally. Most children that age can lift only one pound. Lee discovered the boy had a myostatin mutation. Sweeney believes myostatin inhibitors will be the next big designer drugs in sports; at least one company already markets a supplement it claims will neutralize myostatin.

Last year also marked the debut of "marathon mice." Ronald Evans, a scientist at the Salk Institute in California, created the strain by genetically engineering the switch that burns fat cells so it stayed on all the time in the mice's muscles. That allowed the mice to increase their slow-twitch muscle fiber, the type good for endurance. When Evans put the mice on a treadmill, they ran one hour longer and twice the distance as normal mice.

"These guys just run like the devil," Evans said. "Not only was the muscle engineered but everything adapted to that change - the nerves, circulation, heart - to create a truly fatigue-resistant mouse. That was a surprise."

Evans has been contacted by people who, as he put it, "wanted some increased performance ability."

Despite these successes, the field of gene therapy is not as far along as public perception would indicate. Experts believe approval to use gene transfer in humans in even a limited way is at least five and probably 10 years away. But they acknowledge someone in sports will try gene transfer surreptitiously long before that. That worries many scientists because they still have many questions. Since mice live only three years on average, long-term effects are unknown; researchers such as Sweeney now are testing longer-living dogs. There also are questions about the safety of using gene transfer in human beings and whether the genes, once they are turned on, can ever be turned off.

"The techniques are still very, very immature. They're probably hazardous, probably dangerous," said Theodore Friedmann, director of the Program on Human Gene Therapy at the University of California in San Diego and one of the founding fathers of gene therapy.

It is one thing to try gene transfer on sick people who desperately need treatment, Friedmann said. "But to play with these very immature techniques in healthy young athletes would be irresponsible at best and probably medical malpractice and professional misconduct," Friedmann said. "The animal studies are all sort of pointing in the direction of feasibility, but there's a huge gulf between doing that in animals and in human beings."

That became clear in 1999 when Jesse Gelsinger, an 18-year-old boy with a rare liver disorder that was being treated with diet and drugs, died four days after receiving a genetic injection from James Wilson at the University of Pennsylvania Institute for Gene Therapy. Gelsinger's death, Sweeney said, set the field back at least five years.

Apropos to the current blend of optimism and sober evaluation is a recent gene therapy trial in
France in which 11 infants, all boys, were treated for x-linked severe combined immunodeficiency (X-SCID), the so-called "boy in the bubble" syndrome. All the children but one developed working immune systems and no longer required isolation. But three developed leukemia as a direct result of the gene transfer, which unexpectedly activated a cancer-causing gene. One of the boys died. Earlier this month, the Food and Drug Administration suspended several U.S. gene therapy trials and recommended restricting the X-SCID treatment to children who have no alternatives.

Some animal experiments also have been disquieting. In 2003, a team headed by Wilson injected eight rhesus monkeys with a gene that raises levels of EPO, a substance which increases red blood cells and hence the body's ability to store oxygen. EPO is among the most abused banned performance-enhancing drugs because of the benefits it gives athletes in endurance sports such as cycling and cross-country skiing.

Within three weeks of receiving the injections, four of Wilson's monkeys reportedly had higher levels of EPO than the worst abusers in sports. As the monkeys' blood thickened, Wilson's team kept them alive for more than a year by thinning their blood before finally euthanizing them. The bodies of the other four monkeys attacked the EPO as a foreign invader, in the process destroying the EPO produced naturally by the body and creating severe anemia. Within four months, the monkeys were euthanized.

These setbacks likely will do little to dampen enthusiasm among athletes as the technology improves and becomes more widespread.

"There are some guys that are desperate enough that they'll try anything," Mets pitcher Tom Glavine said. "You hate to see stuff get too crazy. You'd love to see guys just go out there and improve themselves the old-fashioned way, by working hard. But it's like everything in life now. Everybody's looking for ways to cut corners."

Rami Zur, a California kayaker who competed in the Olympics in Athens, said many athletes are aware of the looming possibilities of genetic engineering.

"It's the new thing." Zur said. "Every time there's a new thing people talk about it. We're not talking about it in a way where, 'We want to get that, I want to use that,' the people at least that I'm socializing with ... But you never know. People talk one thing and they have a dark side that they do whatever they think is right to get ahead."

Retired baseball slugger Jose Canseco, an admitted steroid user whose recent book alleging widespread steroid use in baseball created a firestorm, says gene doping soon will supplant drugs as an athlete's enhancement of choice.

"I truly believe in three, four, five years steroids will become obsolete because you will be able to interchange genes and become super athletes and it won't be detectable," Canseco told a San Francisco TV station earlier this month.

Gene transfer will infiltrate sports because athletes by nature are risk takers. Those who use illegal drugs do so despite proven long-term side effects. Many athletes face enormous national pressure to win, and the financial rewards can be huge. And, as Canseco noted, genetic manipulation currently is undetectable. Plus, the stigma attached to gene transfer might fade as enhancement (Viagra, Botox, cosmetic surgery) becomes more accepted by society in general.

WADA saw this coming. Unlike its pursuit of drug abusers, a come-from-behind game in which WADA develops a test for an illicit substance only to have athletes move on to the next undetectable drug, the agency has been ahead of the curve on gene doping. Wadler and Friedmann co-chaired a WADA conference on gene therapy in Cold Spring Harbor in 2002, which resulted in a WADA ban. On the other hand, none of the four major North American professional leagues have any rules regarding gene doping.

"I want us to be with or ahead of the curve instead of playing catch-up as we are with drugs," WADA president Richard Pound said. "We're probably with the curve. We're in pretty good shape."
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Staying there will be difficult.

WADA is spending $1.5 million this year researching gene transfer, WADA science director Olivier Rabin said. Developing a test is a "mid- to long-term goal," he said, compared to the need to ferret out human growth hormone and insulin, suspected of being widely abused now.

Some researchers feel greater urgency. Goldspink said he has been contacted by China's anti-doping agency, fearful gene doping will make its debut in Beijing. One track and field gold medalist from Kenya, a country renowned for champion long distance runners, visited Goldspink with more personal concerns.

"They were worried the Kenyans would no longer have that edge, would no longer win the long distance races because anyone could get the extra five percent fatigue resistance they need to win," Goldspink said. "They were very keen to stamp out any misuse."

Armed with two WADA grants, Goldspink is trying to develop a blood test to detect gene doping; a urine test, he said, will be impossible. Testing a blood sample would work, Sweeney said, provided the tester knew which virus had been used to deliver which gene to which muscle in which athlete and picked the corresponding test - a fiendish twist on the needle-in-a-haystack. Even then, Sweeney said, a positive test wouldn't rule out the possibility the athlete had been exposed to the virus naturally.

The only surefire way to test for genetic modification of an athlete's muscles is a muscle biopsy, Sweeney said, which Pound himself conceded would not be allowed because of its invasiveness. But Pound maintains developing a test is going to be easier than anybody thinks. His optimism is rooted in a question he posed to scientists at the Cold Spring Harbor conference three years ago: What if the next Nobel Prize in medicine were guaranteed to go to the person who developed a test to detect gene transfer?

"Someone in this room would win it, wouldn't they?" Pound said. "They laughed ... Then they said, well, yeah."

Whether he really is confident or blowing smoke to deter athletes is unclear.

WADA has other issues. Penalties, for example. WADA-prescribed bans for substances such as steroids typically are two years for first-time offenders. But the benefits of genetic modification don't go away in two years.

"We honestly don't know how long the viruses would last in humans," Sweeney said. "People have injected monkeys to see how long it would last. It's 10 years and counting."

In other words, a gene-doped athlete returning to competition after a two-year ban still would be doped-up and still would have an unfair advantage, unless scientists figure out a way to turn off the gene or destroy it. Barring that, Rabin said, the sanction for gene doping will be a lifetime ban. Add the unknown risk factor and that's why some scientists say gene doping will be seen first in horse racing, a business with big stakes and fewer regulations.

"I got contacted by people in the horse business. I was told horses are privately owned, you can do what you want," Evans said.

"Gene therapy may well be used in race horses well before humans, because if someone kills a horse they're not going to go to prison for life," Goldspink said. "The risks are less. The potential gains are probably even greater."

Robotic runners

Not even WADA was as far ahead of the curve as Isaac Asimov. In a 1982 short story called "The Super Runners," Asimov wrote about genetically modified athletes who could run at speeds up to 50...
miles per hour, faster than their jet-powered hover cars. These "Runners" had huge rib cages containing enormous lungs, holes in their sides to exhale immense quantities of carbon dioxide, and tubes in their lungs where the air lost water and gained heat to keep their bodies cooled and hydrated.

The degree to which gene therapy will affect elite sports is uncertain because many factors - nutrition, coaching, facilities, equipment - influence performance. Sweeney thinks IGF-1 injections would dramatically affect middle-aged athletes by allowing them to continue competing at a high level. Age group world records for 40- and 50-year-olds, for example, might tumble by the dozen.

"It's certainly going to push back the calendar in events like sprinting," Sweeney said. "The real interest someday is going to be in the professional sports where an injured superstar is a huge financial issue. To be able to keep someone healthy and playing is going to be incredibly compelling to professional teams."

Already, a professional rugby team in Australia is genetically testing its players in order to design individual training programs based on what each player's DNA reveals about the nature of his muscles and the way his body responds to stress, exercise and inflammation.

Gene transfer combined with genetic testing could have a profound impact on pro sports. Longevity records likely would be endangered. Barry Bonds' assault on Hank Aaron's home run record could become a quaint anecdote as healthy, bulked-up sluggers mash baseballs through their 40s and, who knows, even past 50. Unless, that is, gene-modified pitchers keep throwing 100 mile-per-hour fastballs in their 40s and 50s.

The prospect of genetic modification also has led to speculation about so-called designer babies, where parents pick genes - blond hair, blue eyes, proficiency at music - for their offspring. Why stop there? Why not rippling muscles, or thick bundles of fast-twitch fibers? Why not naturally high levels of EPO? Why not six feet, eight inches, 350 pounds of pass-rushing fury? Already, an Australian company has announced a test where parents can find out if their child would be better suited to speed and power events, or to endurance events.

All of which has sparked a philosophical firestorm over ethics. Some experts view gene therapy as the next logical intersection of science and sport. Sweeney says the only ethical consideration is safety. "If it's not safe," Sweeney said, "it should not be done."

Pound, a lawyer, opts for a legal interpretation: If it's against the rules it's against the rules, and therefore unethical. Rules, of course, can be changed.

More compelling is the argument made by many bioethicists that gene transfer is the ethical equivalent of performance-enhancing drugs: Each subverts the essence of sport and what it means to be human.

"We certainly admire superior athletic performance but I don't think we would want it by becoming mere creatures of our chemists or turning ourselves into bionic tools to win and achieve by non-human ways," said Leon Kass, chairman of the President's Council on Bioethics. "To alter the athlete is to change the character of athletics.

"You could engineer a human being to run on four legs like a cheetah but that wouldn't be human running," Kass said. "You can build this android who can hit a baseball 800 feet but would you want to see it? Isn't Barry Bonds a third of the way there?"

And yet, Americans are ambivalent about their sports heroes. Bonds remains popular, despite suspicions he has used steroids and his own admission in leaked BALCO grand jury testimony that he used substances described by others as steroids. Applauding home runs but not caring whether they are aided by drugs or genetic engineering deeply troubles Kass and fellow bioethicists such as Thomas Murray, president of the upstate bioethics institute The Hastings Center and a member of WADA's Ethical Issues and Review Panel.
"If we stop caring about the means that people use to achieve these performances then I think sports will certainly have lost most of its beauty and everything that's admirable about it," Murray said. "People who bluster right now about not caring might end up feeling lost. I'm not wise enough to know where we will end up."

In Asimov's story it wound up in the Supreme Court, which issued a decision that belied public opinion: Genetically modified athletes, the Court said, were people.

No turning back

The inevitability of athletic abuse hasn't made scientists question or stop what they're doing. The potential medical benefits of their work are extraordinary. But the history of sports doping follows a disquieting pattern: Legitimate advances in medicine are hijacked by rogues who take something intended as therapy for the sick and use it as enhancement for healthy athletes.

Steroids were developed for starvation victims and people suffering from kidney failure. EPO was a treatment for anemia. Human growth hormone is given to children with dwarfism.

Sweeney said researchers are seeking authorization to start human trials using IGF-I for ALS patients. Success could mean approval of IGF-I injections for ALS and muscular dystrophy victims within five years, Sweeney said. It would take another 10 years of animal data, he said, to get authorization to treat the elderly.

"That's a long way from treating an 18-year-old, but they'll be treated long before I see an elderly person because someone will make it available to them outside the regulatory agencies," Sweeney said.

Surprisingly, the biology is not that difficult. A molecular biologist with standard graduate school training could make the viruses and isolate the genes, Friedmann said, and there are tens of thousands of such people in the United States alone. As for cost, Sweeney said hypothetically speaking he could treat both legs of an athlete for about $50,000, half of the expense just a few years ago.

"If I were interested in being a rogue ... a million dollars would buy a terribly well-equipped lab," Friedmann said. "You're not talking about real money. You're talking about sort of peanut money in an area where there's certain to be rogues and people who are interested in illicit use. There are BALCO kinds of people running around quite capable of doing foolish things at the genetic level as there are at the drug level. It doesn't take an enormously sophisticated shop to do the biology."

Where is that first shop likely to open? Sweeney says the old East German sports machine, which systematically forced its athletes to take large amounts of steroids, surely would have tried gene doping by now were it still intact. Other experts point to entrepreneur-friendly laissez-faire Russia, or a third-world country with flimsy regulations and lax oversight.

The gene genie is bearing down on sports. Sooner or later, it's going to make it to the starting line.

Staff writer David Lennon contributed to this story.

Better, stronger, faster

Greater athletic performance could be cooked up in the lab. Here are two ways:

1) VECTOR - An enhanced gene is placed inside a delivery agent called a vector.

2) ALTERED CELL - Cell is removed from a patient and then spliced with a vector. The new, genetically altered cell is then injected back into the patient.
In both of these methods, the body is instructed to create more muscle.

SOURCE: PROGRAM ON HUMAN GENE THERAPY, UNIVERSITY OF CALIFORNIA (SAN DIEGO)

GLOSSARY OF TERMS

Following is a glossary of terms that appear in this package:

BALCO - The Bay Area Laboratory Co-Operative, a nutrition company in the San Francisco area, is at the center of one of the worst drug scandals in sports history. Company officials have been accused of designing and selling illegal drugs to elite athletes in baseball, football and track and field.

- Erythropoietin (EPO) is a hormonal substance formed especially in the kidney that stimulates red blood cell formation and thus increases the body's ability to store oxygen. Artificial EPO is used illegally by such athletes as cyclists and long-distance runners to boost endurance.

HGH - Human growth hormone is a hormone that occurs naturally in the body but also is genetically engineered and used to treat children with growth hormone deficiencies. It also is used illegally by athletes to increase muscle mass.

IGF-I - Insulin-like growth factor I (one) is a protein that promotes cell growth and cell repair.

MGF - Mechano growth factor (MGF) is a form of IGF-I.

Myostatin - A naturally-produced protein that limits muscle growth.

WADA - Short for the World Anti-Doping Agency, the organization that polices illegal drug use in international and Olympic sports. WADA maintains a list of prohibited substances and techniques; national agencies such as the U.S. Anti-Doping Agency test athletes and levy penalties.

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