

The New Man

By Tom Junod

Se-Jin Lee and Lee Sweeney know how to stop muscular dystrophy. That's great, you say, but what does it have to do with me? Well, their work can also curtail the destructive power of cancer and obesity and, yes, even old age. Interested?

You remember the mice. They were pretty big news when pictures of them went around the world, what was it, seven years ago? Mighty mice, they were called. And indeed, they didn't look like the fruits of sober scientific inquiry so much as they did the figments of some fervid comic-book imagination out to create mice capable of redressing the insult of being, well, mice. They were mice with really big muscles. They seemed unfortunate, in their way, saddled by their creators with ludicrous baggage when they had no say in the matter. Whoever heard of mice with really big muscles?

They were so extreme that you'd be forgiven for thinking that they wouldn't have any application for humanity—for thinking that they had nothing to do with *you*.

ACTUALLY, THERE WERE two groups of mice. The first was revealed to the world in 1997, the second in 1998. The first was the product of the deletion of a gene, the second the product of an addition. The gene that was deleted in the first group was the gene for a protein called myostatin, which inhibits the growth of muscle tissue; the gene that was added in the second group was the gene for IGF-I (insulin-like growth factor), which stimulates muscle growth. It is thought now that myostatin and IGF-I work in tandem to keep muscle cells in the yoke of some homeostatic balance. Or, rather, that they work in opposition to each other . . . that myostatin is an antagonist to IGF-I . . . that they are the yin and yang of muscle growth.

The scientist responsible for the myostatin mice was Se-Jin Lee, a geneticist at Johns Hopkins. The scientist responsible for the IGF-I mice was Lee Sweeney, a physiologist at the University of Pennsylvania working in concert with a scientist at Harvard. In their way, they are as different from each other as their mice are—and as different as their respective ways of arriving at their preferred methods of genetic manipulation. Dr. Lee arrived at his mighty mice almost by accident, and Dr. Sweeney because he had energized his will to pursue the very specific possibility that IGF-I could reverse the wasting of muscle caused by old age. Dr. Lee was shocked by what he had created; the only thing that surprised Dr. Sweeney was how well the intervention worked—how complete it was. Of the two, Dr. Lee is the cautious one, modest not only about his accomplishments but about the biotechnological possibilities his accomplishments raise. When asked if he has ever contemplated manipulating his own myostatin to combat the muscle wasting that comes with old age, he answers, "Well, my muscle is pretty wasted to start with, so I never really thought about it." Dr. Sweeney, by comparison, is openly ambitious and frenetically energetic, with an impossible travel schedule and collaborators on nearly every front of the war to combat disease by enhancing muscle. He's a zealot in a cause that takes on overtones ideological as well as medical. When he testified about the implications of his work to the President's Council on Bioethics, he was approached by a member of the council who suggested that, for his part, he'd be happy to be sitting in a wheelchair when he's ninety. "And when I'm ninety, I'll be happy to push," Dr. Sweeney said.

Dr. Lee was thirty-eight when the world found out about his mice. He's forty-six now. Dr. Sweeney was forty-five when the world found out about his mice. He's fifty-one now.

They're both relatively young men who have been remarkably productive as scientists. Sure, they started with mice. But they have no intention of stopping with mice. Indeed, for all their differences in personality and style, Dr. Lee and Dr. Sweeney are once again ending up in the same place. Because their work has the potential to be elective as well as necessary, and vice versa, they're the guys who will prove that the biotechnological revolution will not be about mice for long. It will be like all great societal changes. It's not about you, until one day it is.

HUMAN BEINGS LIVE in a biological moment as well as a historical one. That's nothing more than a truism—as true, say, three thousand years ago as it is now. But the human beings alive in the year of Our Lord 2004 have the advantage of living in a moment that is *as much* a biological moment as it is a historical one—a moment that history may remember, and judge, for its biology more than for its history, terrorism notwithstanding.

Simply put, humanity has, for the millennia of its checkered existence, been living in, and at the mercy of, biological time—that is, the vast temporalities necessary for nature to further evolution. The mutations we suffer from and sometimes profit by are not of human design. Until now. Because now our ancient and honorable and stumbling and painstaking and agonized inquiry into the origins and nature of our biological existence has finally yielded the possibility of going beyond understanding to intervention. Evolution's timeline is ceding to *our* timeline, for if biological time has the advantage of unfolding exactly as it must, in utter indifference to human wishes, then the human timeline has the advantage of continual acceleration, *in answer* to our wishes. Human change is simply not as patient as biological evolution, and our impatience is starting to bear its first fruits.

CONSIDER HOW LONG it took humanity to figure out the structure of DNA and then how quickly after that humanity mapped its own genome.

Or consider myostatin. It is an evolutionary success story, although its success is counterintuitive. You would think that the gene that creates a protein that does nothing but make muscles *smaller* would have been winnowed out by the ruthless machine of natural selection a few million years ago. But the gene for myostatin is everywhere and in nearly everything. It's in chickens, mice, cows, humans. And not only that, it's pretty much the same, in both form and function, in chickens, mice, cows, humans. It's highly *conserved*, which means that it does something very important—in this case, preventing muscles from chewing up so many calories that the body's other organs and tissues starve to death.

And yet humans didn't know that myostatin existed until 1992, when Se-Jin Lee discovered it. Well, isolated it in his lab. He didn't know what it did. He didn't even have a name for it. He called it GDF-8 to distinguish it from the other genes he'd cloned. He had about thirteen of them, and he didn't know what they did, either. So what he did was conceive litters of mice in which the genes he'd cloned were deleted, or "knocked out," and waited to see what happened. The mice born without GDF-1? They were mirror images of normal mice, with the organs that were supposed to be on the right on the left, and vice versa. They died. The mice born without GDF-11? They were born with eighteen pairs of ribs instead of thirteen, and some were later born with four arms. They died, too. The mice born without GDF-8, though, were the mighty mice. They didn't die. They were normal in every way except in the extent of their musculature and the paucity of their body fat. They were simply advantaged, biologically speaking, by what Dr. Lee had taken out. Se-Jin Lee had discovered both myostatin *and* its function, and when he concluded the paper reporting his lab's findings with the phrase "we will hereafter refer to GDF-8 as myostatin," he coined a brand-new word for good measure.

That was 1997. Right away, Dr. Lee started advertising in muscle magazines, asking bodybuilders to send him blood samples. He was sure that he would find a human being with the same myostatin mutation he had engineered in his mice. He didn't—or hasn't yet—and not from a shortage of bodybuilders eager to account for the miracle of their own development. Nature apparently really likes myostatin, so he put the project aside. Then in the spring of 2003, he received a call from a pediatric neurologist in Berlin named Markus Schuelke. He told Dr. Lee about a little boy he had been called to observe in the neonatal ward of Berlin's Charité hospital. The boy had been jittery at birth, so there was

concern that he was epileptic. His muscles were extremely large and well-defined, so there was concern that he might have a muscle disease that would have made them fibrotic, like Duchenne muscular dystrophy. As it turned out, Dr. Schuelke had sequenced the boy's DNA and found mutations in the gene for myostatin that canceled myostatin's limiting hold on the boy's muscles. Dr. Schuelke sent the sequence to Dr. Lee, who confirmed that the gene produced no myostatin. He also sent the boy's blood to Wyeth Pharmaceuticals, which had retained the rights to all "human therapeutics" derived from Dr. Lee's myostatin work. Wyeth confirmed that the boy's blood was entirely myostatin free, and in the summer of 2004 news of the overly muscled boy's existence went around the world, much as news of Dr. Lee's mice had back in 1997.

It had taken humans the full duration of their existence on earth to chance upon nature's plan to inhibit muscle growth. It then took less than six years for humans to begin deciding whether they *wanted* their muscle growth inhibited. Now, as a spokesman for Wyeth said, "there is more evidence for the hypothesis," the hypothesis being that humans might benefit from myostatin suppression. The boy, though, is more than just evidence. He's a harbinger of sorts, the bridge between one biological era and another, between the epoch of spontaneous mutation and the new age of mutation wrought by human hand. He doesn't represent nature's validation of a method; he is nature's validation of humankind's new design.

IF YOU WANT IT NOW, you can get it. You can get your myostatin inhibited. Of course, it helps if you're willing to be a guinea pig, which means it helps if you're a student at a university attached to the medical centers where Wyeth is running its first trials of the human antibody it calls MYO-029. This is the first drug that targets myostatin. It has nothing to do with gene therapy. It leaves your genes alone. It allows them to produce all the myostatin protein they're capable of producing. What MYO-029 does is locate and attack the myostatin protein itself in your blood. It was developed by Wyeth to answer the first big question about myostatin's clinical significance. Se-Jin Lee demonstrated that without the impediment of myostatin, mice with muscular dystrophy don't get as weak and mice engineered for obesity don't get as fat. But his mice were genetically engineered to lack myostatin from conception, and the genetic engineering of embryos is, in his words, "off the table" for humans.

What Wyeth proved was that myostatin didn't have to be engineered *out* of a mouse for a mouse to benefit from its absence. It supplied a University of Pennsylvania scientist named Tejvir Khurana with its antibody, and when Khurana injected the antibody into mice with muscular dystrophy, he achieved results as promising as Lee's.

Now Wyeth is testing MYO-029 in human volunteers. The testing is in Phase I, which means that the volunteers are healthy and that MYO-029 is being tested for toxicity rather than effectiveness. Not until testing enters Phase II will Wyeth be expected to show that the MYO-029 works on victims of muscular dystrophy.

Still, Wyeth's participation in a Phase I trial means that someone out there knows what myostatin inhibition feels like. It means that someone has already gotten big muscles from it, because, as Lee Sweeney—who keeps a shrewd eye on all potential commercial applications of muscle-enhancement technology—says, "If that hasn't happened, then it doesn't work."

What does even provisional freedom from myostatin feel like? Is its impact steroidal, without the dark shadings and the testicular backlash? Does it feel . . . good? Wyeth won't say. Like most pharmaceutical companies in the first stages of testing a promising compound, it won't allow its scientists to do interviews, and its spokesman is extremely tight-lipped. The only elaboration the company volunteers is that MYO-029 is delivered intravenously, which means it's not a pill, not yet, although muscle enhancement that comes in pill form is the Holy Grail of biotech companies like Wyeth. So right now you'll have to give up a vein. You'll have to sit there while the bag empties into you. How many times? Well, after four doses, delivered over four weeks, the mice at Penn showed changes that were visible to the eye, and at the end of three months, they exhibited a 25 to 30 percent increase in muscle mass. Of course, they were all sacrificed to science before they got the opportunity to enjoy their new physiques. Humans, though, will have the opportunity to make some decisions. MYO-029 is a drug made by a drug company. It doesn't change your body permanently; you'll have to keep taking it for it to keep

working. If you have muscular dystrophy, you'll keep taking it. If your cancer has conspired to degrade your musculature, you'll keep taking it. If you're getting old, or getting fat . . . well, right now, the only human being known to be myostatin free is a five-year-old boy in Germany. He's not talking. But his doctor is. When Dr. Schuelke first did an ultrasound of the boy's muscles, he expected to find abnormalities. Instead, what he found was a baby who had twice the muscle mass and half the fat of "normal" babies. A baby who was, in Dr. Schuelke's words, "twice as normal."

How many times will you keep on coming back to be twice as normal?

THE INHIBITION OF MYOSTATIN can't cure disease, because myostatin itself does not cause disease. The best that can be hoped for is that it strengthens the weak—that it keeps kids with muscular dystrophy functioning until a cure can be developed. But you have to understand what this rather conditional hope means to those kids and their families: something. As opposed to what they have typically had for the entire duration of the human species: nothing.

It is the other reason why this is all happening, why you will almost certainly gain the power to keep your muscles from decaying before you die: because the power is being developed to help those who are dying much faster. On the one hand, there are those who are terrified by the continual acceleration of human biological inquiry; on the other, there are those who are terrified by its deliberateness—by the terrible fact that it cannot accelerate as fast as the suffering of their children.

TEN YEARS AGO, Lee Sweeney had nothing. He told Pat Furlong that, and she still wouldn't leave his office. She wasn't used to scientists telling her to get out of their offices. She had two boys who were dying of Duchenne muscular dystrophy; she was head of Parent Project Muscular Dystrophy; she—or her organization—had money to spend. Those facts alone usually allowed her to stay awhile, even though half the time she'd come uninvited. That's what she was doing in those desperate days: telling security guards at medical libraries that she was a doctor so that she could sneak in and read the literature; visiting the offices of any scientist whose work seemed to have a bearing on Duchenne, which of all the muscular dystrophies is the most common and the most catastrophic; promising them money if they promised something that would help. Most of them took it, or tried to, telling her how close they were to a cure. Dr. Sweeney told her that he had nothing, that he would have nothing, that a cure was twenty years away.

"I have money," she said.

"I don't want your money. I want you to get out."

"But my sons . . ."

"Look, if you really want to help your boys, go home and have them checked for heart abnormalities. That's what's going to kill them."

She left, and after lying down on the floor of a bathroom at the University of Pennsylvania and weeping for three hours, she went home and asked her sons' doctor to check their hearts. There's nothing wrong with their hearts, he said. Check, she said.

Within two years, both her sons were dead of heart abnormalities. Patrick was fifteen. Christopher was seventeen. She called Dr. Sweeney back and thanked him for his honesty—for being, in fact, the only scientist who told her the truth. He was impressed, because most people who watch their sons die of Duchenne want nothing more to do with the disease. But now Pat Furlong was talking about saving the next generation of boys with Duchenne. We've lost this generation, she said. The boys who are just being diagnosed now, the ones who are four and five, those are the ones we have to do something for. But they don't have twenty years. They don't even have ten.

"All right," he said. "But you have to grow up. If you're going to do this, you have to educate yourself. You can't allow yourself to get *taken advantage of*. . . ."

It wasn't that Dr. Sweeney was averse to putting personal causes at the heart of his research. His own scientific interest at the time was not in Duchenne muscular dystrophy but rather in gene therapy for the elderly, and it was motivated by the experience of watching his grandmother lose muscle and mobility until she was a mind-trapped in a body that could no longer walk or perform any of the functions that brought her peace and pleasure. What he was averse to, however, was the idea of pursuing half measures—something less than a cure—in order to palliate the desperation of parents who were watching time run out on their sons. "God forbid, if someone should put a dying kid in front of me," he says now, quoting his concerns back then. "I'll lose my *objectivity*. . . ."

He has talked to the parents of a lot of dying kids since then, and he has seen a lot of kids die. He has nothing to offer to the generation that Pat Furlong wanted to save, and so the genetic mutations they were born with still take their inevitable course: Their genes still didn't produce the dystrophin protein their muscles needed to absorb the shocks of movement, the shocks still inflicted damage that can't be repaired, damaged muscle cells were still taken over by fiber and fat. The boys still begin falling at four or five and still began losing their ability to walk by the time they were ten. Although they tend not to die as early as Pat Furlong's sons did, they are in wheelchairs if they are in their midteens, or on ventilators.

It is the *next* generation—the generation of boys being diagnosed with Duchenne right now—that stands to benefit most from Dr. Sweeney's ardent pursuit of the necessary half measure, his determination to offer something instead of nothing. In the spring, a compound he developed with a small biotech company called PTC Therapeutics will enter clinical trials; it stops the dystrophin gene from prematurely stopping the production of the dystrophin protein and offers the chance of something like a cure for about 15 to 20 percent of the boys with Duchenne as well kids with genetic diseases like cystic fibrosis. He is also planning to test a kind of therapy best known for use in cancer and AIDS patients—protease inhibitors—in boys with Duchenne, because protease inhibitors have shown the potential to slow muscle damage to such an extent that Dr. Sweeney has seen the potential for their use in preventing muscle atrophy in everyone from people who are bedridden to astronauts on a manned mission to Mars. And although he dedicated the paper that made his name in scientific circles back in 1998—the paper reporting the success of IGF-I in restoring muscle in elderly mice—to his grandmother, he has since devoted himself to finding ways of using IGF-I in gene therapy, primarily with muscular dystrophy in mind. Indeed, he has gone from kicking Pat Furlong out of his office to serving on scientific-review boards for both the Muscular Dystrophy Association and the Parent Project.

And because he has seen what his therapies can accomplish for victims of disease as well as victims of the natural biological timetable, he was amazed when he wrote a story on muscle enhancement for *Scientific American* and the editors insisted he make it a story about gene doping in sports.

YOU'LL PROBABLY be able to get it on the black market soon. You'll probably be able to get it in Mexico or Belgium or any of the other places where sports doping has become a popular science. And we're not talking about muscle-enhancing antibodies, either; we're not talking about protease inhibitors, although they may well come into common use to allay muscle loss resulting from injury. We're not talking about drugs at all or anything that's detectable in a blood test. We're talking about the real thing—gene therapy.

Of course, it's been talked about for a long time—so long, in fact, that you might think it doesn't work. Didn't somebody die from it a while back? Somebody did, at the University of Pennsylvania, in 1999. His name was Jesse Gelsinger, and he had a fatal immune reaction to the virus that vectored the foreign gene into his body. Since then, there has been a different virus developed for what is called the "delivery" of the therapeutic agent, and though many scientists—including Dr. Sweeney—are working to improve the process, it still presents formidable difficulties.

It's strange, then, that not only might there be a way to get around some of the problems but that it turns out to be kind of *easy*. The trick in gene therapy is getting the targeted cells to absorb the new gene into their own machinery, which is why viruses, so

adroit at cellular invasion, have been the vector of choice. Last summer, however, Jon Wolff and his colleagues at the University of Wisconsin published a paper that offered "a facile nonviral method for delivering genes . . . to skeletal muscle of mammalian limbs," and what Dr. Wolff did was facile indeed. Instead of pinpointing cells with viruses, he tied off limbs with a blood-pressure collar and dumped naked DNA into a vein. That's it. The DNA was for dystrophin, the missing protein in Duchenne muscular dystrophy, and about 30 percent of the targeted muscle cells absorbed and expressed it. The results were the same in mice, dogs, and monkeys. It is not a method that can be used right now in torso muscles, so it will not be able to get boys with Duchenne up and walking. But it could be used to cancel myostatin genes, and Dr. Sweeney has already contacted Dr. Wolff about the method's particular promise for pumping up limbs with IGF-I.

Dr. Wolff and Dr. Sweeney agree that if gene therapy goes to the black market, the naked-DNA method could be the preferred means of delivery, not just because it is so easy but because it is so cheap. Viruses are expensive, but you can mix up *vats* of DNA for a fraction of the cost. "I've been waiting for this for twenty years," Wolff says. "I never thought it would be this easy."

OKAY: BIOTECHNOLOGY is here. The changes it might effect are not, at least by the standards of a German boy, unnatural. They might be easier to implement on the human organism than previously thought. Cheaper, too. Sounds promising, right? Wrong. Lee Sweeney has encountered a reflexive resistance spoken in the name of human purity by people who endorse the application of his work to muscular-dystrophy patients. Strangers have asked him to stop. They've said, "How can you keep doing what you're doing, knowing what it's going to do to the Olympics?"

Richard Pound, head of the World Anti-Doping Agency has asked him to tag the genes for IGF-I with some kind of marker, so that WADA could find out who's using gene therapy to cheat. Leon Kass, chairman of the President's Council on Bioethics, has spelled out his eloquent philosophical concerns about the consequences of elective biotechnological enhancement, based on what he sees as the dignity of human performance and the integrity of a life cycle that includes infirmity as part of aging and death as part of life.

"What would it mean if there really came a time when the son could never surpass his father in strength?" Kass asks. "Under these circumstances, the only thing meaningful about growing old would be pretending not to be. It's easy to see how one would be tempted to choose this technology. But if one asks oneself what society might be like, the aggregate choices might usher in a society no one would prefer."

"It's a matter of technology versus humanism, I guess," Richard Pound says. "A lot of people might say, 'Who gives a shit about eight guys in the Olympic final?' But very few people think of the downward multiplier. For every eight athletes in the Olympics, there are eight hundred million dreaming of getting there. Do we really want to tell them that they need these drugs in order to compete?"

For his part, Dr. Sweeney believes that there are precisely two ethical questions that he needs to ask about any biotechnological or biopharmaceutical intervention he authors: Does it work, and is it safe? Once he is able to answer those questions, he says, "I live in my own world, where I presume that if people suffer, you want to stop it."

He is stunned that people don't automatically share his presumptions. He is particularly stunned by how many people seem to think that the main issue of these biological advances is not suffering but sport.

But then so is Se-Jin Lee, who says, "The idea that sick people won't get this technology because a few bozos might abuse it is ludicrous."

So is Pat Furlong. So is Jon Wolff. But the culture's anxiety about the biotechnological contamination of athletics is just its way of voicing a larger anxiety about humanity's move into the biotechnological era; it has simply chosen sports as its nagging conscience. What myostatin is to muscle, sports is to the debate on myostatin inhibition. It is an expression of our limits, or our nostalgia for limits, which is not a nostalgia that Dr. Sweeney shares.

Last year, he spoke at a scientific conference sponsored by WADA. After Sweeney described his research, Richard Pound asked him if there was anything he could or would do to make it possible for WADA to keep doing its job once "the genie was out of the bottle" and gene therapy became commonplace.

"I kept asking Dr. Sweeney, 'Is there anything you can do?' " Richard Pound remembers. "He was very pleasant about it. But his answer, basically, was, Nah—you guys are fucked."

FUCKED? A future in which sick boys don't die, people with cancer stay whole, old people keep walking, the once morbidly obese are no longer fat, Jerry Lewis benefits from the treatments developed for Jerry's Kids, and, oh yeah, Barry Bonds keeps hitting home runs until he's, like, fifty. Yeah, we're fucked, all right.

YOU MIGHT be able to shoot the works, you know. Myostatin, IGF-I, protease inhibitors. That should do it, right? That should make us twice as normal in no time. Anyway, that's the idea behind the decision of Se-Jin Lee and Lee Sweeney to join forces, along with clinician Kenneth Fischbeck and Kathryn Wagner, who was a researcher in Dr. Lee's lab before she became the head of the center on muscular diseases at Johns Hopkins. The four of them have recently applied for a grant that would get them the funding to establish Hopkins as one of the federal government's designated muscular-dystrophy-research centers. There are three such centers now; two of them focus on using gene therapy to deliver dystrophin to boys with Duchenne, an approach that would essentially offer a cure. The Hopkins approach assumes that no cure will be found, at least for the time being. "Our idea is basically to accept that muscle is degrading and then to try to slow the process down," says Dr. Lee. Of course, once there is a cure, you won't need the combination myostatin/IGF-I/protease inhibitor therapy to compensate for your muscular dystrophy, because you won't have muscular dystrophy. You'll only need it if your muscles are degrading by the usual means—or if you want them to get really, really big.

What will you look like, stripped of myostatin, amped with insulinlike growth factor, and given protease inhibitors as a prophylaxis against muscle decay? Will you look . . . natural? Will you even look human? Assuming such a therapy works, the answer might depend on what your definition of what natural is—and what human is. The German boy born without myostatin is natural. His mutation occurred naturally, and although he is, strictly speaking, a "mutant," he is obviously no more or less human than you are. Pat Furlong's two sons were natural in the same way. They were fully human, although heirs to spontaneous mutations that caused them to suffer and to die. Which is why neither Dr. Lee nor Dr. Sweeney spend too much time thinking about whether their work is natural or not. And why they don't worry about asking nature for permission. "Nature does a lot of horrible things," Dr. Sweeney says. "People talk about evolution. Well, evolution doesn't *care* about kids with muscular dystrophy. It doesn't care about old people. That's our job. That's why we have to take care of them."

Technology versus humanism? You have to understand: From the viewpoint of the scientists creating it, technology *is* humanism. It's all we have. It's all we've ever had. And so when the time comes to choose whether to reject the technology or use it to improve upon the body your ancestors gave you, you're going to have to rely on the knowledge that connects you to those ancestors as surely as your myostatin and IGF-I genes do. You're going to have to rely on what they could have told you the moment some lucky mutation enabled them to recognize the terrible fact of being human in the natural world:

Hey man, you're on your own.