

Dream Genes

If you can't beat 'em at the Olympics, try manipulating your dna.

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One of the most enduring memories in Canadian Winter Olympic history occurred in 1964 at Innsbruck, Austria, under a gentle snowfall when Canada's unheralded four-man bobsledding team upset the world's best to win the gold medal. Innsbruck was the last Winter Olympics without drug testing, and during that innocent era, when team captain Vic Emery climbed out of his sled he was mobbed by coaches and fans rather than being hustled off to give urine and blood samples. Another star of those Games was a young Finn named Eero Mäntyranta, who won two gold medals in cross-country skiing. Mäntyranta's competitive fire certainly helped, but in research later published in the American medical journal *Blood*, scientists disclosed that he did in fact have a tremendous advantage: a genetic condition known as familial erythrocytosis, which triggers an overproduction of red blood cells, meant he had 45 percent more of the crucial oxygen-carrying cells than most of his competitors.

That an Olympic champion possesses a unique set of genes may seem only natural. But it's scant consolation for the losers in the rarefied world of high-performance sport, where nature is often regarded as an obstacle to be overcome. And increasingly the natural advantage held by people like Mäntyranta is being imitated in laboratories around the world. The genetically engineered athlete, long an imagined creature, is slowly starting to emerge. Such athletes may already be here, and the sporting world appears ready to embrace them. Witness the experiment conducted by Dr. Lee Sweeney, a physiologist at the University of Pennsylvania, who started working on a cure for muscular dystrophy in the late 1990s. To reverse the disease's muscle-wasting effects, he injected the gene that tells the body to grow new muscles into a single leg of his lab rats and put them on a weight-training regimen. Soon each rat had one leg that was nearly twice as big as the other.

When word of Sweeney's rats spread in 2003, athletes, undeterred by

the experimental nature of the science, came forward asking to serve as guinea pigs, leading Sweeney to predict that the superhuman of fiction was about to step onto the playing field. "The world," he warned two months prior to the Athens Olympics in 2004, "may be about to watch one of its last Olympic Games without genetically enhanced athletes."

The reception area outside the offices of the Montreal-based World Anti-Doping Agency (wada) is decorated with Dick Pound's personal collection of Olympic torch replicas. Pound, once vice-president of the International Olympic Committee, is now chairman of wada, which will help administer 1,200 drug tests during the Olympic Games in Turin, Italy, next month. Pound's broad shoulders hint at his past as a swimmer who represented Canada at the 1960 Olympic Games in Rome. And in 2003, perhaps fearing that an athlete genetically morphed to have extremely long arms might one day dominate the Olympic pool, Pound added the "non-therapeutic use of cells, genes, [and] genetic elements" to WADA's official list of prohibited substances and methods. "I want gold medals given to athletes, not to their gene engineers," maintains Pound.

Sweeney's experiments are still being talked about in training camps around the world because of the relative ease with which he boosted the size of the leg muscles in his lab rats. He had injected them with the gene that triggers production of the insulin-like growth factor, igf-i. Before injecting it, Sweeney attached the gene to a harmless virus capable of moving through cell walls to deliver the gene to the targeted muscles. In effect, Sweeney gave the rats a genetic infection that took hold, producing a group of super-rats.

Now imagine the gruelling thirty kilometre cross-country ski race at the Turin Olympics. The winner, moving on genetically enhanced legs, wins by a wide margin, but a subsequent drug test fails to turn up any trace of a steroid or other performance-enhancing drug. wada officials, clearly concerned that such an incident could become a reality, are spending more than \$4 million to develop a test for gene doping and have assembled a panel of eminent geneticists to oversee the project. Sweeney joined the panel, but he admitted that it may be

difficult to catch gene-doped athletes. “If we [geneticists] do our jobs properly,” he said, “it [gene doping] will be impossible to detect.”

Pound’s attempt to stamp out gene doping at the Olympics will likely prove futile because for each medical breakthrough in gene therapy there seems to be an athletic application. Genetic science may soon advance beyond changing musculature and bloodoxygen levels to altering everything from limb proportion and heart size. Consider Lance Armstrong, the seventime winner of the Tour de France, whose heart is 30 percent larger than the average human’s and who produces one-third the usual amount of lactic acid under exertion, enabling his muscles to absorb oxygen at an extraordinary rate. Or the size seventeen feet of Australian Olympic swimmer Ian Thorpe, which act like flippers in the pool.

While athletes can’t train for genetic advantages, medical science may soon be able to create them. “You can deliver the [gene] to neonatal animals or in utero,” says Dr. Jeffrey Medin, a biochemist who runs a gene-therapy lab at the Ontario Cancer Institute in Toronto. “As the animal ages, that [gene] gets distributed very nicely. If you wanted to provide long-term gene doping, that would be the time to start.”

There are currently 1,100 human case studies chronicling the medical use of gene therapy. The first clinical trial was held in 1989 at the National Institute of Health in Bethesda, Maryland, and the first major success came in 2000 when eleven boys suffering from Severe Combined Immunodeficiency (“bubble boy” disease) underwent gene therapy at the Necker Children’s Hospital in Paris. This illness occurs when the body fails to produce a protein called interleukin-2, a critical component of the body’s immune-response system. In an experiment similar to Sweeney’s, the eleven children at Necker were injected with the interleukin-2 gene. The gene caught hold in nine of them and restored their immune systems to the point where they were able to lead almost normal lives.

When three of the nine children subsequently developed leukemia (one later died) the French government temporarily suspended all

similar gene therapy trials. In the United States, the Food and Drug Administration had already shut down human trials at a gene therapy lab when a young man in treatment for a liver disorder died after his immune system failed. But despite the setbacks, gene therapy has produced far more successes than failures. “Gene therapy really hasn’t had that many negative effects,” notes Medin. “You look at bone-marrow- transplant patients in the 1970s, and until they figured it out everybody died. Here, we’ve had two or three patients out of 1,100 that have had severe consequences. If you’re looking at a new cancer drug, that’s an acceptable risk for a lot of people.”

Theodore Friedmann, who directs the gene therapy program at the University of California at San Diego and heads wada’s panel of genetics experts, believes it won’t be long before clandestine gene doping occurs — if it hasn’t already. Athletes will be attracted not only by the fact that it is hard to detect but also because it is far more effective and less dangerous than steroids. While steroids tend to bulk up the whole body, gene doping will allow athletes to target specific muscle groups — stronger shoulders for the shot put, more powerful back muscles for rowing, or bigger calves for the starting block. A team of South Korean and American researchers has developed a “marathon mouse” that can run twice as far as a normal mouse after being injected with a gene that boosts production of slow-twitch muscles. Athletes are taking notice.

And what of Mäntyranta’s natural genetic advantage? Genes are responsible for producing oxygen-carrying red blood cells, via the protein hormone erythropoietin, or epo. Some athletes have already been caught taking a synthetic version of erythropoietin, which causes the body to produce more red blood cells. (It is the drug Lance Armstrong was accused of taking.) Gene doping could provide a permanent boost in oxygen levels and would be virtually undetectable. “You can inject an epo vector [gene] into the skin and turn it on or off at will with a small molecule,” explains Friedmann. “The result of that is increased red blood cell production, which is stable over a very long period of time. You can see that would be an attractive genetic approach to athletic doping.”

Will gene doping ultimately be impossible to detect, as Sweeney

suggests? Unlike virtually every other drug on wada's list, gene doping doesn't produce synthetic copies of hormones, which leave telltale markers. The only evidence of doping lies hidden in muscle cells themselves, where the virus that was used to carry the gene into the body would linger. But these messengers would be difficult to trace without a biopsy, something athletes are unlikely to submit to. "You would have to know where the virus was put," says Friedmann, "and you'd have to look in that muscle itself."

Surprisingly, unlike the universally condemned use of steroids, ethicists are divided over whether gene doping should be outlawed. Thomas Murray, chair of wada's ethics panel, believes that like steroids and other performanceenhancing drugs, gene doping gives an athlete an unfair advantage. "What's chilling about the prospect of gene doping is that it arguably changes a person's natural abilities," says Murray. "It violates our understanding of what should make for success in sports."

Many in the sports world consider Murray's perspective naive. Athletes will inevitably exploit genetic advances intended to benefit society as a whole. The entire concept of athletic competition may change. "The notion of the natural, unmodified human has been defunct for decades, yet sport remains caught in this notion that athletes are different," says Dr. Andy Miah, a bioethicist at the University of Paisley in Scotland and author of the book *Genetically Modified Athletes*. "It is probable that we will soon find ourselves in a world where many people are created through genetic technology. Within the world of sport, we still lack a rigorous form of ethical debate." Miah maintains there is a tangible difference between gene doping and more traditional performanceenhancing drugs. "Our concern about steroids derives from a concern about the abuse of drugs and their harmful consequences," he observes. "We don't have such concerns about gene-transfer technology. If these new forms of enhancement are sufficiently safe, why ban them? If they make the performance much more exciting and interesting, we will have good reason for using them."

In the end, it will be up to athletes to decide whether they want to

increase their chances of winning by doctoring their genes. Canadian sprint cyclist Curt Harnett, one of Canada's most celebrated Olympians, says athletes who used illegal steroids in the past will probably turn to gene therapy. "Body alteration is part of sport," he says. "The question is how far you can push it before it becomes unfair?" He believes certain physical attributes will always predispose athletes to perform certain sports. "That's part of what this is all about," says Harnett. "When I first started out, I wanted to ride the Tour de France, I didn't want to be a sprinter. But that's what my body turned out to be geared for. Even with doping, you really can't turn a donkey into a racehorse." Still, soon enough some geneticists just might want to try. If they succeed, will the world applaud them for making a scientific breakthrough or condemn them for creating a new way for athletes to cheat?

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