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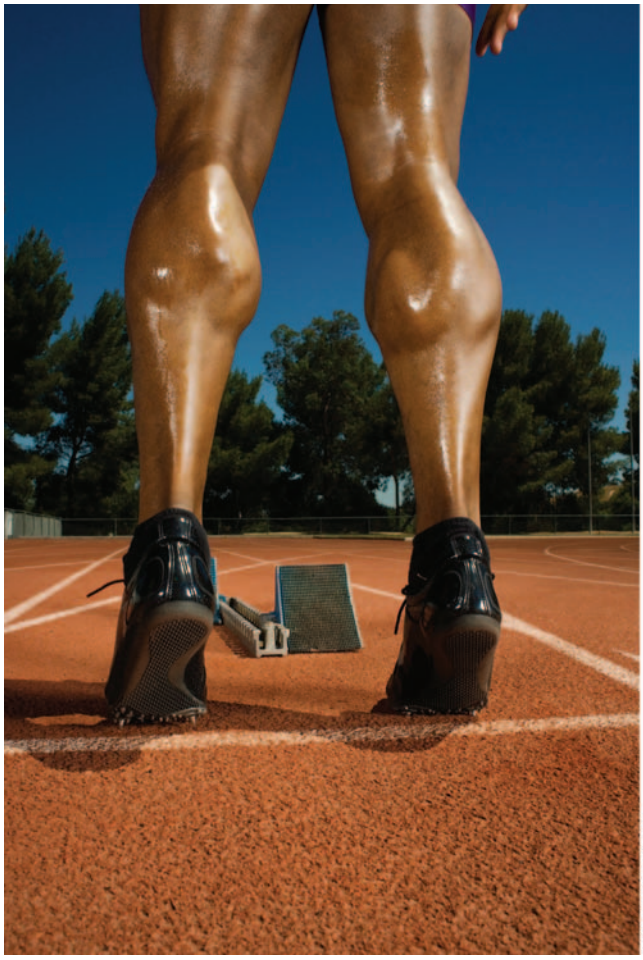
Is science killing sport?

Gene therapy and its possible abuse in doping

More than two thousand years ago, naked athletes competed at the Olympic games in ancient Athens for eternal fame and an olive branch. Today, most athletes run, jump or swim not only for fame and honour but also for money—after all, a gold medal is the ticket to lucrative advertising contracts. Not surprisingly, professional sports now resemble high-tech races in which any technological trick is used to gain milliseconds to set the next record. This involves not only designing faster bobsleds, racing bikes or sharkskin swimsuits but also pushing the physical abilities of athletes by using the latest medical and biological research.



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However, this race to be the best also involves the abuse of biomedical research by athletes and their trainers to gain an unfair advantage; for decades, professional sports have been tainted by doping—that is, the use of substances such as erythropoietin (EPO), steroids or growth hormones, which were originally developed to treat human diseases but have also been used to boost the performance of healthy athletes. Barely a major sporting event goes by without some athletes being banned or stripped of their medals because they were found to be doping themselves.

The abuse of scientific research will surely not stop at the misuse of drugs. Only a few years have passed since the first patients were successfully treated using gene therapy, but scientists and sporting officials are already worried about the illicit use of this highly experimental technology to increase athletes' performance, a process known as gene doping (Schneider & Friedmann, 2006; Haisma & de Hon, 2006). Even without a single incident so far, the World Anti-Doping Agency (WADA; Montreal, Canada) is taking the possibility of gene doping seriously, declaring it illegal in sports, and looking for ways to uncover and prove its use (WADA, 2007). "The techniques to be used in gene therapy are likely to be used in sports," said Theodore Friedmann, Director of the Program in Human Gene Therapy at the University of California (San Diego, USA), and Chair of WADA's gene doping panel. However, there are grey areas between the justified and illicit use of medical technologies, which raises the question of where to draw the line. Furthermore, if gene therapy becomes commonplace, how will this change the nature of sport?

Without a doubt, tinkering with an athlete's genes has enormous potential to increase performance—initial results from basic research in this area are impressive. Transgenic mice created in an effort to understand muscle growth and muscle disease were soon baptized 'Schwarzenegger mice' owing to their enormously increased strength and muscle mass (Barton-Davis *et al*, 1998; McPherron *et al*, 1997). Genes such as insulin-like growth factor 1 (IGF1) and myostatin, which regulate muscle mass, are obvious targets to increase performance in sporting disciplines in which sheer strength is required. Similarly, genes that stimulate blood production or increase the oxygen-carrying capacity of blood, as well as those that regulate mitochondrial energy production and energy use, are of interest to endurance athletes. And manipulating pain perception by genetically modifying the release of endorphins in athletes' brains might be the ultimate winning combination.

Irrespective of the gene of interest, the advantages over conventional doping are obvious: as the gene product is the same as the endogenously produced protein, it is much harder to detect by current methods than any injected or ingested substance. Scientists are becoming aware of this potential for abuse. Lee Sweeney, who works on therapies to treat muscular dystrophy by targeting IGF1, at the University of Pennsylvania (Philadelphia, PA, USA), said, "It has made me more aware of the potential abuses of what we are doing. Certainly, we are not designing this for healthy athletes." Indeed, gene doping carries considerable health risks. "This research was designed for very sick people, people that are dying. It's highly experimental," explained Angela Schneider, President of the International Association for the Philosophy of Sport. "It can have an effect on a healthy body as well, increasing its capacity; however, only [in exchange for] very high risk."

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As Hidde Haisma, Professor at the Groningen Centre for Pharmacy in the Netherlands and President of the Dutch Society for Gene Therapy, explained, genetic enhancements would not be as tightly regulated as other endogenous processes. "Once you introduce it to the body, in general it is turned on and so far we don't have a good regulatory system to turn it on and off," he said. "The highest risk for the athlete is overdose. And that is the same for EPO, IGF1 or other target genes." Alain Fischer, who works at the Necker Hospital in Paris, France, and who successfully used gene therapy to treat a severe form of immunodeficiency, agrees. "Only people who are dying would have reasonable grounds for using it," he said. "Using gene therapy for [doping] is ethically unacceptable and scientifically stupid."

However, Haisma sees a realistic danger that gene doping will find its way to athletes and trainers with the help of scientists. "It is nearly impossible to stop people who really want to cheat," he said. "All students with some training in molecular biology can isolate these genes [and] produce them in bacteria as DNA. […] I think if someone really wants starting material for gene doping then it is easy to get." As Sweeney commented, the lure of money is simply too strong: "I think there will always be people who cross ethical lines in return for money. Sport is so lucrative that there is a large profit in it for someone to bring gene doping to the athletes. It is only a matter of time before someone with enough scientific knowledge perfects some kind of gene doping."

WADA reacted proactively by banning all forms of gene doping after scientists warned them about the possibility. "WADA is doing all the right things in trying to be way ahead of the game in gene doping and not trying to catch up like they had to do with steroids," Sweeney said. The challenge, however, is to develop effective ways to prove gene doping. Conventional methods would fail to detect an inserted gene that was isolated from the athlete's own body because its product is indistinguishable from the naturally produced form. WADA has therefore established vigorous research programmes to develop new detection methods.

As Friedmann, who heads one of these projects, explained, detection will probably require a different strategy than just searching for individual compounds. "It is a global approach to characterize doping from the point of view of disturbance of the homeostasis of the system," he said. "And that is a break from previous detection methods—it offers a lot of possibilities for finding things. Especially if you don't know what [way of doping] precisely you are looking for." Such an approach would measure the levels of various proteins and hormones in the blood and compare them with a reference database.

Although this would be quite elaborate and expensive, it promises to be a feasible long-term solution for detection. "The problem now is that we are always running behind the athlete. When there is a new drug developed, we have to set up a new assay to specifically detect that new drug," Haisma commented. "[But] if you do this by profiling and see any change in the profile, you will know that this change is non-physiological and caused by a certain drug or gene and you will have sufficient evidence for doping." Still, even this global approach would not be failsafe. "If you are good enough in designing the gene doping, you may mimic what the body normally does. Unless you longitudinally follow a person and have enough early pre-doping data on them, you may not recognize that the person is anything out of the ordinary other than a highly talented athlete," Sweeney said.

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Regardless of whether and how athletes use gene doping, genetic and genomic research has already changed the nature of sport. For example, DNA and protein profiling could be used to identify specific gene variants to predict and select athletes for certain sports. "We know for sure that there are at least 50 [alleles] that you don't find in the general population," Haisma said. "We are getting more and more insight into what makes a distant runner a distant runner or a sprinter a sprinter."

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In fact, there are some people who have mutations that turn them into natural athletes. For example, Finnish Nordic skier and 1964 Olympic gold medallist Eero Mäntyranta had unusually high amounts of red blood cells, and a boy born with a myostatin dysfunction has larger than normal weight-lifting capacities (Schuelke *et al*, 2004). However, if gene doping were to be banned, would such people still be allowed to compete in sports? "I don't see any reason why somebody with a myostatin mutation should be excluded from any kind of competition," commented Se-Jin Lee, from Johns Hopkins University (Baltimore, MD, USA), one of the researchers who described the myostatin case.

If gene therapy becomes sufficiently safe to be used not only as a medical treatment but also for normal enhancement purposes, it will raise the question of whether gene doping should remain forbidden. There is already a grey zone of performance enhancements that are legally used in sports because they are accepted as standard medical treatments. Professional golfers, for example, have subjected themselves to laser eye surgery to enhance their vision. Although some feel that this amounts to doping, Michael Knorz, founder of the FreeVis LASIK Centre in Mannheim, Germany, commented that this does not, in his view, go against the spirit of sport: "Refractive surgery is detectable and does not need to be considered as [a]


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new form of doping. It simply replaces contact lenses. A perfectly normal eye with good vision cannot be enhanced."

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Sweeney believes that in the future, genetic enhancement will also be used not only to treat disease but also to increase fitness. "For me, gene doping will someday be possible and a reality," he said. "The phase that we are in now is when it is potentially extremely dangerous. So it is important that we make sure that the athletes do not do it and do not get access to it. Then there may some day be a phase when certain types of gene doping are desirable from the normal population standpoint and then they will be integrated into the athletic world." As Schneider pointed out: "Sport is cutting edge, because technological advancements will get experimented with there first."

Schneider also sees a further role for the technology as a sort of equalizer. "Why don't we use it as an ability enhancer to allow people with disabilities to be able to compete at a higher level? How can we deny them that?" she asked. "Why should an athlete be denied state-of-the-art technology? Just because he is an athlete?"

Ethicists have already envisaged future scenarios in which genetic enhancementwould be common. "Gene transfer methods were developed for therapeutic use, but there are further uses now," said Claudio Tamburrini, a specialist on sports ethics in the international EU-funded Enhance project. "Genetic technology has the potential of going beyond or bringing us further towards some kind of transhumanism or posthumanism. […] We will have human beings who will live longer with enhanced capacities."

The examples of LASIK (laser-assisted *in situ* keratomileusis) or therapeutic muscle treatment show how grey zones might eventually become slippery slopes that question values of fair play and joy in sport. Tamburrini therefore believes that competition will shift further towards technology. "Suppose one hundred years from now, most of us, perhaps all of us, as a standard procedure will get genetically enhanced," he asked. The logical consequence is that athletes would also use the latest gene technology to get an edge in the game. "It will just be a continuation of what we have now," Tamburrini said. It would be like a Formula One car race, only with a team of biologists instead of mechanics in the background.

In the end, it depends on how strongly athletes and trainers believe in the Olympic principles irrespective of other competitors—as Schneider did when she participated in the 1984 Olympic games as a member of the Canadian rowing team. "[I]t was very clear that the Eastern Bloc women's teams were using steroids. They dominated because of that and I accepted that these were the conditions under which I was competing," she said. "But I was not willing to pay the price of taking steroids." She eventually returned home with an Olympic silver medal.

"Sport is becoming a perversion and a circus," Schneider said. "It is entertainment but it has no meaning. Do we want to celebrate technological advancements and surgeries on bodies that we create to do maximum performances or do we want to celebrate the human will overcoming obstacles?" It is up to society to define whether it wants to see a high-tech race in which the best genetic designers win or the original Olympic ethos of individuals competing with each other in their natural state. To this end, Schneider, Friedmann and Haisma all feel that more education is needed to stress the original idea of sports. "It is the positive model that we support. If we use that criteria we cannot possibly support designing people for sport," Schneider said. "We are treating human beings like pieces of meat. We create them for this activity. If commercialism pushes this so strongly, we lose the core values about celebrating human effort and the joy of the effort and the love of the game."

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