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Building Better Sportsmen: The Genetic Enhancement of Athletes

In the early 1980s, I was a marathon runner with ambitions to run at world class level, which would have required me to run the 42-km distance in about 2 h and 10 min. In those days genetic testing was not available, so to gauge my potential I volunteered for various kinds of exercise tests, including maximal oxygen uptake assessments, lactate threshold tests, and (painful!) muscle biopsies. After one series of tests, the exercise physiologist gave me the not-so-good news: with the physiological engine I had, the best marathon time I could hope to run was around 2 h and 15 min. Pretty good, but not world class. But, he continued, pointing to a cluster of slow twitch muscle fibers on a slide, I had the potential to excel at longer distances. It turned out he was right. I went on to become a world class 100-km runner, winning several international races at that distance, placing third in the 1992 World 100 km Championships, and setting several national ultra-distance running records along the way. Later, I applied my physiological potential to the world of ultra-distance triathlon (Fig. 2.1), winning races ranging in distance from the double ironman to the ten times ironman—the Decatriathlon. I retired in 1999, after completing Race Across America (RAAM), a non-stop bike race from the west coast to the east coast of the United States, fairly satisfied I had made the most of my genetic potential, although I can't be sure.

Okay, so that's my story. But what about the world-class athletes you see on television? Have the Usain Bolts (Fig. 2.2) and Mo Farahs (Fig. 2.3) of this world maximized the potential laid out by their genes? The genes in the cells that make up Bolt's legs were encoded with special instructions to build up lots of fast-twitch fiber muscles (see later in this paragraph), giving his legs that phenomenal explosive power out of the blocks. Now contrast Bolt's genetic make-up with that of double Olympic Gold Medallist Mo Farah, Britain's top distance runner over 5000 and 10,000 m. Farah's leg muscles, as determined by his genes, are much slower than Bolt's because they are designed for the endurance required to run fast (but not nearly as fast as Bolt) for 26–27 min at a time, with little fatigue. Why the difference between these athletes? It's all down to the muscle fiber types. Your body has two types of muscle fiber: slow-twitch and fast-twitch. The fast-twitch fibers contract faster

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Fig. 2.1 The author competing in Ultraman Hawaii. (Courtesy: Rick Kent)

Fig. 2.2 Usain Bolt competing in the 2012 Olympic Games. (Courtesy: Wikimedia/Nick Webb)

Fig. 2.3 Mo Farah on his way to an Olympic 10,000 m gold medal. (Courtesy: Wikimedia/Al King)

and with more force than the slow-twitch ones, but they also tire quicker. These muscle fiber types can also be subdivided into subcategories depending on contraction speed, force, and fatigue resistance. For example, Type IIB fast-twitch fibers contract faster than Type IIA fast-twitch fibers.

By means of hard training, muscle fibers of one type can be made to perform similarly to the fibers of another type. For example, by running lots and lots of kilometers, you can train the Type IIB fibers to be more fatigue-resistant. But, no matter how hard you train, you can't convert one type to another, so if you're planning on becoming an elite athlete, it pays to choose your parents carefully. Now, if you happen to be an athlete who wants to go to the Olympics and weren't given a favorable roll of the genetic dice, what can you do? Well, until recently, your options were either to train harder or to break the rules and intervene pharmaceutically. With the advent of gene doping and gene manipulation another option has appeared, albeit just as illegal as pharmaceutical intervention. How does it work? To answer that, let's turn the clock back a few years to 1999 and one of the favorite media stories of that year: the Schwarzenegger mice. These mice came about because researchers were trying to raise mice whose muscles didn't deteriorate with age. Why did this lead to muscular mice? Well, one of the limiting characteristics of muscle is how much it grows, because muscle growth is carefully regulated by the body. But muscle size can be easily manipulated thanks to insulin-like growth factor 1 (*IGF1*), a gene that controls muscle growth with help from the myostatin (*MSTN*) gene, which produces the myostatin protein. It was the *IGF1* gene that gave rise to the so-called Schwarzenegger mice. In the late 1990s, H. Lee Sweeney, a molecular physiologist at the University of Pennsylvania, led a team of researchers who used genetic manipulation to create these muscle-

bound mice by injecting them with an extra copy of *IGF1*. The result was a breed of mouse with added muscle 30 % stronger than regular mice.

After creating bulked up "muscle mice," researchers turned their attention to producing "marathon mice." In August 2004, a team of researchers reported they had altered a gene called *PPAR-delta* to enhance its activity in mice, which boosted the performance of the fatigue-resistant slow-twitch muscles. The result of the treatment was that these marathon mice could run twice as far as their couch potato counterparts. The genetic tampering also appeared to make this new breed of mice immune to obesity—even the inactive ones. For the scientists it was a real breakthrough in their understanding of exercise and diet. For athletes looking to gain a performance advantage, the marathon mice were proof that gene manipulation worked, bringing the specter of the genetic doping of elite athletes a small step closer to reality. Of course, there's a sizable gulf between mice and athletes, and the field of gene therapy has yielded mixed results, including the death of a teenager in 1999.

The death of 18-year-old Jesse Gelsinger occurred while he was taking part in a gene therapy study for a rare metabolic disorder he had suffered since birth, as a result of rules of conduct being broken that would probably otherwise have prevented him from participating in the trial. The therapy was presented to his parents as safe and, while Jesse didn't count on personally benefiting from the treatment—he agreed to the treatment mostly to help other youngsters—he didn't expect to die. Gelsinger's death brought to light the dark side of gene therapy, which, in common with so many other experimental treatments, has the power to harm as well as help. The teenager's death came at a bad time for genetic researchers because gene therapy appeared to have been on the verge of delivering on at least some of its unfulfilled promise. But, shortly after Gelsinger's death, the U.S. Food and Drug Administration shut down all gene-therapy research at the University of Pennsylvania, where the therapy trial had been carried out. In short, tampering with genes is not without risk, so you might think athletes wouldn't be crazy enough to risk death in this way. Unfortunately, you'd be wrong, because when the difference between winning and being an also-ran is measured in milliseconds, the quest for that extra edge becomes even more important to athletes, some of whom are willing to risk anything and everything. Not convinced? A frequently-cited 1982 sports survey paints a bleak picture. In the survey, Dr. Bob Goldman, founder of the U.S. National Academy of Sports Medicine, asked 198 elite athletes whether they would take an enhancement that would guarantee them a gold medal but kill them within 5 years. More than half (52 %) said "yes." Personally, I think the athletes who answered "yes" are certifiable. During my years spent training and racing in what is a very tough sport I sometimes wished there was a supplement out there that would have made all the suffer-

ing easier, but not one that would kill me! Incidentally, after the first survey (known as the Goldman Dilemma), Dr. Goldman repeated it every 2 years for the next decade and the results were always the same[1]. Even more shockingly, some of the athletes polled were only 16 years old. Clearly, when it comes to elite athletes, we're dealing with a community of high risk takers, so the fact some athletes are trying to gain a competitive advantage by applying some of the technology that killed Jesse Gelsinger should come as no surprise. In fact, genetic modification may be an arena in which the Goldman Dilemma may prove even more relevant.

Consider the case of 16-year-old Chinese swimmer Ye Shiwen. Ye ignited international debate on what the genetic future holds when she struck gold in the 2012 Olympics. She raised eyebrows—not only in the London Aquatics Centre—when she swam a faster final 50-m split in the women's 400 m individual medley (IM) than 26-year-old American Ryan Lochte—world champion at the time of writing—in the men's event. Ye, a girl from the eastern coastal province of Zhejiang, clocked 4:28.43. Not only did she come from nearly a second behind American Elizabeth Beisel in the final leg, the freestyle, but her 28.93 s clocking in her last 50 m beat Lochte's 29.10 when he blew away the men's 400 m IM field in the first event of the evening. Furthermore, Ye's time was more than six seconds faster than her 4:35.15 clocking at the World Championships when she placed fifth, way behind Beisel's 4:31.78. To put the performance in perspective, Beisel, the event favorite, clocked a personal-best 4:31.27 and was still left trailing behind the Chinese teenager.

Ye's performance prompted John Leonard, the highly respected American director of the World Swimming Coaches Association, to describe the otherworldly performance as "suspicious" and "unbelievable." "Any time someone has looked like superwoman in the history of our sport they have later been found guilty of doping," he added. Leonard is right. Take the story of one Michelle Smith (now De Bruin), arguably the least celebrated triple gold medalist in Olympic history, which is outlined in the sidebar.

[1] In case you're wondering just how different elite athletes are from the general population when it comes to the desire to win, consider this: In 2008, researchers set non-athletes the Goldman Dilemma. In results published in February 2009 in the *British Journal of Sports Medicine*, just two of the 250 people surveyed said they would take a drug that would ensure success and an early death.

The Michelle Smith Story

How do you set an Irish swimming record? Answer: Reach the end of the pool. Until the 1996 Olympic Games in Atlanta, that was the commonly perceived perception of Irish swimmers. Until Michelle Smith came along. Smith, long considered a plodder in the international ranks, looked to be fading towards retirement when, 2 years before Atlanta, she moved to Holland to be with her future husband Eric de Bruin, a Dutch discus thrower serving a 4-year suspension for doping. In Atlanta, at the veteran age—for swimmers—of 26, Smith slashed a jaw-dropping 21 s off her best time in the 400 m medley, taking gold. She won two more gold medals. All of a sudden, a country that didn't even have a 50-m pool owned the best swimmer in the world. Or so it seemed.

Questions about the integrity of her victory led to the April 1997 Sports Illustrated cover featuring an athlete's biceps and a syringe, with the sub-heading, "Irish Gold Medalist Michelle Smith: Did She or Didn't She?" The answer came later that year when the International Swimming Federation banned Smith for 4 years for tampering with her urine sample using alcohol. The ban ended her competitive swimming career.

Leonard went on to suggest that the authorities who tested Ye Shiwen for drug abuse should also check to see "if there is something unusual going on in terms of genetic manipulation." Jiang Zhixue, a Chinese anti-doping official, described Leonard's claims as completely unreasonable and I have to say I agree with Jiang; if someone had accused me of taking something without a shred of evidence, I would have been very upset. Leonard could suggest all he wanted, but the fact remains it was impossible to prove whether Ye's performance was fueled by gene doping or not, because there was no gene test in place for the 2012 Olympics.

So, does gene doping really herald the possibility of an unbeatable master-race of genetically manipulated super-athletes, capable of snatching medal after medal from honest competitors? It may sound like a Hollywood movie, but scientists are taking the threat seriously. After all, the route to systematic gene doping has already been established thanks to research into the human genome, which has identified key genes in our DNA that enhance sporting ability. And, as sure as eggs is eggs, with money and fame as the twin engines driving athletes to take risks, gene doping will no doubt develop rapidly. In fact, once gene doping procedures become refined, it may become just another type of doping, albeit with huge potential.

2.1 Improving the Genetic Blueprint

Despite the success of the marathon and muscle mice, identifying the genes responsible for athletic prowess is a complicated matter. Athletes want to know which genes contribute to athletic performance, but scientists have

only a partial answer because a great number of genes are implicated in sporting performance. By 2004, scientists had identified more than 90 genes or chromosomal locations they thought were responsible for determining athletic performance, but less than a decade later that number has risen to 220 genes. This uncertainty hasn't stopped some from trying to exploit what has been learned. Take Atlas Sports Genetics, a company that claims to be able to reveal your athletic predispositions. Well, some of them at any rate. Based in Boulder, Colorado, Atlas Sports Genetics (www.atlasgene.com) began selling a $149 test in December 2008 that could screen for variants of the gene *ACTN3*, which, in elite athletes, is associated with the presence of the protein that helps the body produce fast-twitch muscle fibers. Sounds promising. The only problem is that research hasn't determined exactly how the protein affects muscle function in humans. So, for $149, you're getting limited information about your genetic potential. But it won't be long before more predictive tests are available—after all, we've just scratched the surface in defining what is meant by genetic advantage. As research begins to delve into more refined traits and as gene screening becomes more accurate, athletes (and their parents!) will have a powerful tool that will be able to predict performance.

2.2 Detecting Gene Doping

Predicting performance and manipulating training based on a genetic test is fine, but what about the dark side of all this—the altering of an athlete's genetic profile? As we've already discussed, this is similar to gene therapy in medicine, which, partly owing to the Jesse Gelsinger tragedy, doesn't have the greatest track record. Also, this type of genetic manipulation has never been studied in sports performance, partly because it constitutes a real ethical dark zone and partly because there are medical concerns. Not surprisingly, anti-doping agencies have come out against it, because they know that it's just a matter of time before someone pushes it in the sports world.

Gene manipulation may be the big wild card at the next Olympics in Rio de Janeiro in 2016 because the presence of gene doping is hard to detect with certainty. Many of the tests that might succeed in detecting whether an athlete has gene doped require tissue samples, which means asking athletes to submit to a (painful) muscle biopsy, and there aren't many athletes who will be willing to give tissue samples when they're preparing to compete. Non-invasive tests are no good because evidence of gene manipulation probably won't show up in the blood stream, urine, or saliva. Despite these detection problems, anti-doping officials are upbeat about their chances of detecting the next generation of genetically enhanced super-cheats. For example, Pat-

rick Schamasch, medical director of the International Olympic Committee (IOC), has said the viruses used to smuggle genes into the body leave behind traces that can be detected. There is also the newly introduced biological passport[2], which tracks an athlete's physiological profile, and triggers alarms if anything suspicious occurs, such as a spike in hormone levels. But many scientists question the authorities' confidence in their ability to catch dopers and point out that cheats are already using biological methods to avoid detection.

In addition to the biological passport there is a promising test being developed by scientists at the universities in Tübingen and Mainz in Germany. In 2010, German scientists announced they had developed a direct method of testing that uses conventional blood samples to detect doping via gene transfer and is still effective even if the doping took place up to 56 days before. The test provides a clear "yes" or "no" determination based on whether or not so-called transgenic[3] DNA (tDNA) is present in blood samples. tDNA is a clear indication of doping because it is DNA that is foreign to the athlete being tested. That's because tDNA has to have been transferred into the athlete's body to create a performance-enhancing substance such as the endurance-booster erythropoietin (EPO). As with a lot of genetic research, the efficacy of the procedure was tested in laboratory mice by inserting the foreign genetic material into the muscles. The introduction of this tDNA triggered excess production of a hormone, which prompted the generation of new blood vessels. Two months after the genes had been injected into the muscles, researchers were still able to tell which mice had been subjected to gene doping and which had not.

So, will the biological passport and the German gene-doping test deter dopers? Probably not. Remember, this group of risk-takers has always found all kinds of ways to run faster, jump higher, and hit harder, whether it was French cyclists chugging strychnine at the end of the nineteenth century or erstwhile Hall-of-Fame baseball pitchers using human growth hormone (HGH) to keep their fastballs zinging at the beginning of this century. Some of these athletes have been caught, others have gotten ill, some have died, and some have reached the top of their sport. But one thing they all had in common is that they used a foreign substance to artificially increase performance. And they did it in spite of tough anti-doping controls—just read Tyler Hamil-

[2] The Athlete Biological Passport (ABP) was used at the London Olympics in 2012. One way this system might work to detect whether an athlete is gene doping is to recognize how the body responds to a foreign gene—particularly the defense mechanisms it might deploy.

[3] A transgene is a gene that has been transferred naturally, or by genetic engineering, from one organism to another.

ton's book *The Secret Race*[4] if you're not convinced. So, no matter how effective the German test might be, athletes will still try to take advantage of the latest frontier in performance enhancement, whatever that might be.

2.3 Tweaking Genes

Imagine you are an athlete who has made the most of the genetic material you were born with and now you want to take the next step and tweak your genes. How would you do it? First, since scientists aren't yet sure what many of these "sports" genes do, I would suggest—for safety's sake—you modify only those genes with a well-understood function. For example, if you are a football player, you might be interested in the *IGF1* gene, which produces a hormone, the protein IGF-1, that repairs and bulks up muscles. Therapy using the *IGF1* gene is being developed to help people with illnesses, especially degenerative muscle conditions such as Duchenne muscular dystrophy. The protein IGF-1 is made in the liver as well as muscle and has anabolic effects, so it is perfect for football players. The concentration of IGF-1 is related to the concentration of growth hormone (a peptide hormone) and scientists already know the gene gives rise to an increase in muscle bulk in mice injected with it. Extending this treatment to athletes could result in all sorts of advantages. For example, it could lead to a tennis player's shoulder muscles, or a sprinter's calves, being strengthened. And the good news about this particular type of gene therapy is that it is likely to be relatively safe because the effects seem to be localized to the targeted muscle. For those athletes wanting to gain an even greater advantage, there is the possibility of combining IGF-1 with other growth factors, which may lead to even greater responses in muscle growth.

Okay, so increasing muscles may not prove too difficult, but what if you happen to be an endurance athlete looking to augment the oxygen-carrying capacity of your blood? This is the sort of boost that could have dramatically improved my performance as an endurance athlete, because success in running 100 km is all down to the number of red blood cells you have and how efficiently your body utilizes oxygen; the more blood cells, the better the oxygen uptake and utilization. Until quite recently, athletes looking to increase the oxygen-carrying capacity of their blood could either go to altitude or take the illegal route and buy a supply of EPO, which controls red blood cell production. As a sport scientist, I was aware of genetic conditions that

[4] Hamilton was a professional cyclist and Olympic Gold medalist. Like most riders in the 1990s, he used performance enhancing drugs. In The Secret Race, Hamilton lays bare the meticulous regimen of doping in professional cycling, explaining how simple it was to avoid positive tests.

boosted red blood cell mass and I sometimes wished I had been lucky enough to have had that genetic roll of the dice. I remember reading about Finnish Nordic skier Eero Mäntyranta who won two gold medals at the Olympic Games thanks to this sort of genetic advantage; Mäntyranta had a naturally occurring genetic mutation[5] that gave him more red blood cells than other athletes, which meant Mäntyranta's cells carried more oxygen from his lungs to his tissues, thus increasing his endurance. In short, Mäntyranta had what I and every endurance athlete wanted.

The good news for the endurance athletes (and bad news for the anti-doping agencies) is that endurance athletes may be able to alter their genes in a way that mimics the natural mutation that Mäntyranta had. Athletes wishing to take advantage of this gene-tweaking will simply have an additional copy of the gene inserted into them to boost EPO production. EPO will go to work, instructing the athletes' bodies to manufacture new red blood cells, which, in turn, will increase aerobic capacity, enhance oxygenation of tissues, and increase endurance.

The risks? Well, yes, there are risks, but nobody said this would easy. Researchers have already tested this method of EPO delivery in mice and monkeys and the results weren't encouraging if you happen to be a professional cyclist looking for the latest performance advantage. The hematocrit (the proportion of blood volume made up of red blood cells) values of the animals was boosted[6] significantly, as expected, but severe anemia ensued in some animals owing to an autoimmune response to the transgene-derived EPO. While this response hasn't been observed in other studies, there is always a chance it could develop in humans. Because of the unexpected side effects, more trials are needed, so it may be a while before EPO gene therapy can be fully evaluated in clinical studies. This won't stop the endurance athletes though, especially professional cyclists, many of whom have been taking regular EPO for more than a decade.

Until quite recently, taking synthetic EPO was endemic in professional cycling. When EPO first became the drug of choice in endurance sports in the early 1990s, it was being taken in harmful doses. And by harmful I mean deadly, because the same effect that improves endurance performance also

[5] Mäntyranta had primary familial and congenital polycythemia (PFCP), a condition that causes an increase in red blood cell mass and hemoglobin due to a mutation in the erythropoietin receptor gene (EPOR), which was identified following a DNA study performed on several members of Mäntyranta's family. PFCP results in an increase of up to 50 % in the oxygen-carrying capacity of the blood, an advantage that no doubt played a part in the seven Olympic medals the Finnish skier won in his career.

[6] An increase in hematocrit results in a condition known as polycythemia. People with this condition have an increase in hematocrit, hemoglobin, or a red blood cell count above the normal limits, which is why the condition is usually reported in terms of increased hematocrit (greater than 48 % in women and 52 % in men) or hemoglobin (greater than 16.5 g/dL in women and 18.5 g/dL in men).

risks the athlete's health. That is because when an athlete takes EPO, they are increasing the thickness of their blood, thereby increasing the risk of blood clotting, which can in turn block blood vessels, causing a heart attack or stroke. If that wasn't enough of a deterrent, EPO use causes hypertension, seizures, and even congestive heart failure. A normal hematocrit level, the percentage of red blood cells in the blood, is 40–50 % in men, but some cyclists in the 1990s were found to have levels above 60 %. A number of young cyclists died of unexplained heart attacks, probably caused by taking excessive amounts of EPO. Since then, fewer heart attacks have occurred, although in 2009 a young Belgian cyclist, Frederiek Nolf, died in his sleep while competing in the Tour of Qatar. Inevitably, given the reputation of cycling and doping, speculation began immediately as to whether Nolf had died a drug-related death. To some who remembered the beginning of the EPO era, it brought back the thoughts of one cyclist who was quoted as saying: "During the day we live to ride, and at night, we ride to stay alive." The quote was a reference to the cyclists who would set their heart rate monitors to sound an alarm if their heart rate dropped below a certain level. On hearing the alarm, the cyclists would jump onto their bikes and spend 10 min on the rollers in their hotel rooms to jumpstart their circulation.

You might think that with so many cyclists ending up in coffins, athletes might think twice before taking such risks, but cases such as Nolf's, tragic as it was, will do absolutely nothing to stop those intent on doping. Sadly, while injecting synthetic EPO was dangerous, the risks of this approach may pale in comparison to the injection of new genes. In gene therapy, scientists send genes into the body by injecting vectors—DNA molecules used as a vehicle to carry foreign genetic material into another cell—into muscles or blood. Efficient vectors for shuttling genes into a cell are viruses, which act like little syringes and naturally inject their genetic material into the athlete's cells. Risky? It can be, because research has shown that this type of delivery system can result in serious health risks, such as toxicity and inflammation.

Of course, an unmodified virus could be dangerous, so scientists re-engineer them to deliver human genes by cleaning out the harmful parts of the virus before inserting a human gene into the virus's genetic material and then injecting the virus into the body. If scientists can't find a suitable virus they might use a plasmid as a vector instead. Plasmids are rings of bacterial DNA into which human genes can be added. When plasmids are injected into muscles, scientists apply an electric field to the muscle cells to open pores in the cell walls through which the plasmids can enter the cells—a technique known as electroporation—resulting in the muscle cells taking up the plasmids. The successful introduction of new genes is harder than it sounds. For the method to be effective, scientists have to deliver the genes to the right cells—after all,

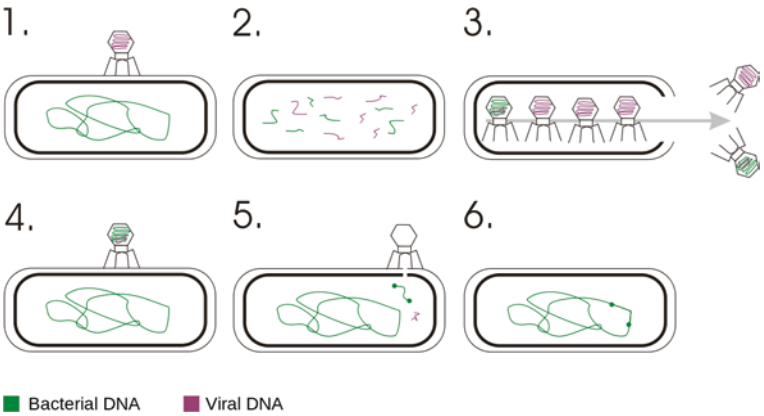

Fig. 2.4 Transduction occurs when fragments of the bacterial chromosome accidentally become packaged into viral progeny produced during a viral infection. These *virions* may infect other bacteria and introduce new genetic arrangements through recombination with the new host cell's DNA. The closer two genes are to one another on a chromosome, the more likely they will be to transduce together. This fact allows geneticists to map genes to a higher degree of precision

it's no good having growth proteins appear in your ears if you want your leg muscles to get bigger! Delivering the right gene to the right place is anything but easy, although scientists can try to steer genes by injecting into muscles, so the genes only enter muscle cells. They can also use a virus that infects only certain body parts, and if that doesn't work they can let the genes enter cells liberally but make them activate only in certain cells. The process of inserting DNA into a cell by means of a virus is known as transduction, and by a non-viral process, transfection. Once the right gene has been put in the right cell, the cell is said to be transduced or transfected. Transducing (Fig. 2.4) a cell is one thing, but transducing an entire body part is something else altogether because there will always be some cells that won't cooperate and these uncooperative cells usually die. If the transduction is successful, the transduced cells will follow the new genetic instructions and make the desired proteins, hopefully—for the athlete—in a way that boosts performance.

Athletes thinking about this form of gene doping may want to consider research studies that boosted mice EPO. That research didn't go so well; the animals' red blood cell production went into overdrive—as expected—but the animals died of stroke. In short, their blood turned thick, like Jell-O. The prospect of death by stroke doesn't deter most athletes from trying this type of gene doping though. Consider the case of German track coach Thomas Springstein. Springstein became a notorious figure in the doping underworld when he tried to get his hands on Repoxygen—an experimental gene therapy for anemia. Developed by Oxford BioMedica to treat anemia, Repoxygen was designed as a viral gene delivery vector carrying the human EPO gene under

the control of a hypoxia response element (HRE)[7]. The way Repoxygen works is very similar to regular EPO; Repoxygen is simply injected into the muscle, EPO synthesized in the tissue, and more red blood cells are produced. In common with regular EPO, the use of Repoxygen isn't without risk because too many red blood cells can result in erythrocytosis, which makes the blood thicker and places more stress on the heart. This scenario isn't hypothetical, because erythrocytosis has been implicated in the deaths of several cyclists.

Springstein recognized Repoxygen's blood cell-boosting benefits and tried to order a supply for the purpose of improving the performance of his athletes. Instead, he was investigated by the police and received a 16-month suspended jail sentence for supplying doping products to unwitting minors. Until Springstein appeared in court Repoxygen was an obscure gene-therapy drug developed to fight anemia, but following Springstein's court case in January 2006, the drug vaulted to notoriety, prompting one columnist to write that the era of genetic doping had arrived. Whether the era of gene doping has arrived or not, the Springstein case reminded everyone just how impatient rogue coaches and athletes are to find new ways to cheat, despite the risks.

2.4 Ethics

As genetic manipulation becomes more advanced, it is possible that sport will enter a high-tech arms race between cheaters and testers, and drawing the line between acceptable and unsporting training methods will become more and more difficult. The potential scenarios of such an arms race are disturbing. For example, taken to an extreme, the search for optimized athletic performance might lead to the breeding of a class of superathletes. This might be achieved by embryos generated through in vitro fertilization subjected to genetic tests for athletic traits—the "best" embryos would then be brought to term. If this technology becomes successful, future athletes may be born and not made, which would make it necessary to redefine what it means to be an athlete. It sounds like a sporting nightmare, but the technology to realize this scenario could happen. After all, scientists are working to perfect gene therapies to treat genetic diseases and it is only a matter of time before unscrupulous athletes may begin to use these therapies to re-engineer their bodies for better performance. While this re-engineering may make for some entertaining sporting contests, there will be a penalty to pay because whenever a new champion is cheered on the podium, we'll be left wondering whether the medal won was the result of doping or of genuine athletic ability.

[7] HRE is claimed to sense low oxygen concentrations and to switch a gene on in response.

Another point to consider is the potential possibility of cancer. A DNA fragment, after being inserted into the body, can cause a change in the genome, which can have fatal results. In addition to the risk of cancer, there is the potential threat arising from the lack of control of gene expression connected with the fact that it is currently not possible to guarantee that the gene is inserted at a particular site in the genome. For example, cyclists looking to boost production of EPO might be given an EPO-coding gene only to discover the process can't be stopped—their hematocrit would continue to increase until their blood became like sludge. Then there is the risk of the autoimmunologic response of the body when you start tampering with all these genes. For example, a risk factor that is most frequent in gene therapy is an immune response by the body to the vector used for gene introduction. And, since most vectors are viruses with the pathogen removed, introducing them to the body provokes a natural response by the immune system; in extreme cases this reaction can cause severe organ dysfunction and perhaps even death. The action of the genes could also cause problems. For example, the genes that encode for human growth hormone and IGF-1 tell cells to divide; if they get into the wrong cells, cells can divide uncontrollably and form tumors. And what about the long-term effects? What happens to athletes who try gene doping at age 20 when they get old? Scientists don't know. No one has followed gene therapy patients that long. Ultimately though, one of the greatest problems in applying gene doping is the lack of procedures that could stop any undesirable and/or lethal effects.

But would athletes really try something that is so risky and unproven? Absolutely. Remember the muscle mice? When gene therapy was first used to create these mice, researchers were swamped by e-mail messages from athletes wanting to use the discovery to improve athletic performance, including one enquiry from a high-school football player who wanted to inject the kids on his team. It doesn't matter to those athletes seeking an edge that scientists are still years away from testing this technology on humans; given the millions of dollars at stake for those competing for Olympic gold, the fact that gene therapy is still unproven is of little concern.

There are those who argue that this sort of genetic manipulation will be a good thing. Remember Eero Mäntyranta? He was suspected of blood doping after winning two gold medals because he had too many red blood cells in his system but was later cleared when researchers found that he and many of his family members had a genetic abnormality. So, the question is: Is it wrong for athletes without Mäntyranta's natural capacity to want to level the playing field? Why can't other athletes have the genetic advantages conferred naturally upon athletes like Mäntyranta?

Sooner or later, the world of sports will be faced with the phenomenon of gene doping to improve athletic performance. How long this will take is anybody's guess, but it is likely to happen by the 2016 Olympic Games. Many genes that potentially have an effect on athletic performance are already available for gene therapy, evaluated in clinical trials for the treatment of illnesses. Gradually, more and more of the gene therapy vectors used in clinical studies will find their way to athletes and their medical support staff. In tandem with this development, illegal laboratories may be set up to produce gene transfer vectors for the purpose of creating a new breed of genetically modified athlete. The question then becomes: Are we on the verge of creating people for sports, instead of the other way around?

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