Genetic doping

Super athletes or gene cheats?

P McCrory

The threat of gene transfer technology to elite sport

The International Olympic Committee (IOC) recently released its new list of banned substances and methods. This list will be effective from 1 January 2003 and replaces the 1 September 2001 list. Amongst the important changes, the category of genetic doping as a banned method is listed for the first time. The current list can be easily accessed on both the IOC and World Anti-Doping Agency (WADA) websites (www.wada-ama.org or www.olympic.org)

The use of gene doping or gene transfer technology to improve athletic performance heralds a significant threat to the integrity of anti-doping initiatives. This approach has the potential to improve sporting performance far beyond "traditional" pharmacological means and in ways that make detection of use extremely difficult if not impossible at the present time. It sounds like the ultimate sporting nightmare come true.

There is also another side to gene transfer technology which is a more difficult ethical issue, namely the use of gene mapping in talent identification and the use of tissue engineering in the recovery from injury, such as muscle atrophy following cruciate ligament injury. Once such gene therapy is clinically available then can we deny its benefits to athletes?

HOW MAY GENE DOPING BE USED?

We have known for decades that genetic differences between athletes can result in markedly improved performance.[1] At the 1964 Winter Olympics in Innsbruck, a Finnish competitor Eero Mäntyranta, won two gold medals in cross country skiing. Though his training programme wasn't radically different from his rivals, Mäntyranta had a distinct advantage. He was born with a genetic mutation that increased the oxygen carrying capacity of his red blood cells by 25–50%. Mäntyranta had a mutation in the gene coding for the erythropoeitin (EPO) receptor which prevented the normal feedback control of red blood cell mass.[2] This genetic mutation is exceedingly rare however anyone can boost his or her red blood cells simply by taking exogenous EPO. EPO has been commercially available since 1989 principally for disease states such as for treating the anaemia seen in chronic renal failure. Athletes were quick to exploit the drug, especially in professional cycling, where the scandal at the 1998 Tour de France highlighted this issue when a team employee was caught with a carload of performance enhancing agents, including EPO.

This problem may increase if athletes can insert a gene that results in a similar effect to that which naturally occurred in Mäntyranta. This can be done by coupling the relevant genes to a delivery vector such as an adeno or adeno-associated virus. In 1997, Leiden *et al* used an adenovirus to deliver the EPO gene in mice and monkeys. This boosted the haematocrit from 49 to 81% in the mice and from 40 to 70% in the monkeys. The effects lasted for over a year in the mice and for approximately 12 weeks in the monkeys.[3] Similar findings have been reported in other primate models.[4]

Clearly there are significant safety issues not least from excessive haematocrit levels causing thrombosis as well as some disturbing early reports of unexplained deaths in liver failure patients treated with gene therapy. The fine line of performance and health is highlighted by the fact that in families with EPO gene mutations, early death from stroke and myocardial infarction is often the rule. There is also a theoretical concern that the effect of repeated injections may be less effective because of the immune response against the viral delivery vector. Once these problems are more fully understood, clinical trials of EPO gene transfer in humans will not be far off.

If EPO gene therapy can boost aerobic performance, what about muscle strength? A number of groups around the world are currently working on gene transfer therapy for a variety of chronic muscle diseases as well as for specific problems such as muscle atrophy. To adapt this technology for athletic tissue engineering will be a relatively simple matter.

One of the targets of this research is the protein insulin-like growth factor 1 (IGF-1) and one of its isoforms, mechano-growth factor (MGF) that is turned on by mechanical signals such as stretch or exercise overload. The protein is also important in muscle repair mechanisms such as the muscle damage that may be seen following hard training or competition.

MGF is made in muscle tissue and does not circulate in the blood. This means its effects are localised but more importantly in athletics, blood or urine screening for such agents is unlikely to be useful in detecting use of such agents. One research group from London reported a 20% increase in muscle bulk over a two week period in mice when using MGF gene transfer. IGF-1 itself is made in the liver as well as muscle and has similar anabolic effects with Sweeney *et al* showing a 15% increase in muscle bulk in mice injected with the gene. This was in the absence of any special exercise programme.[5] Such gene therapy is likely to be relatively safe given that the effects seem to be localised to the targeted muscle and is likely that human trials will be relatively soon. It is speculated that combining IGF-1 or MGF with other growth factors or with strength based training programmes may lead to even greater responses in muscle growth.

CAN GENE DOPING BE DETECTED?

Detecting such abuse will not be easy. Engineered genes are likely to look identical with endogenous genes products. Perhaps detection of associated viral particles may be of use but this would involve muscle biopsies. It would be like looking for the proverbial needle in the haystack and would be unlikely to garner much enthusiasm from athletes given the invasive nature of the biopsies.

Many of the muscle based gene technologies are unlikely to be detected by urine or blood testing as is currently done in elite athletes. Even with EPO gene transfer, finding a high haematocrit may be suggestive but separating it from a naturally occurring gene mutation will not be easily and in any case, cyclists have shown that even with injectable EPO use, close medical monitoring ensures that red blood cell parameters can be contained within set levels making it difficult to even be suspicious that illicit gene doping may have occurred.

The labelling of gene transfer products with genetic "bar codes" as has been suggested with GM modified agricultural produce may be another option however this would require the complete cooperation of scientists, ethicists, athletes, sports authorities, medical practitioners, professional societies, pharmaceutical, and biotech industries, and public authorities (including governments) to avert misuse. An unlikely scenario!

In 2002, WADA held the "Genetic Enhancement of Athletic Performance" conference, at the Banbury Center of the Cold Spring Harbor Laboratory on Long

Island. This meeting brought together international experts and leaders in biology and genetics, sports medicine, policy makers, legal experts, representatives of the Olympic Movement, and athletes to explore the science, technology, and ethical issues facing the sports community as a consequence of gene transfer technology. The outcome from this conference was that a combination of regulation, education, and research was thought to be the best current method for addressing the prospect of gene doping in sport from becoming a reality.

THE OTHER SIDE OF THE COIN

Although gene doping and the use of gene transfer technologies are of major concern in sport, much of this work is ultimately based on our more complete understanding of the human genome. As a human map of performance related genes and health related fitness phenotypes is drawn up so our understanding of the role of various genes in targeting athletic performance increases and also the potential targets for gene doping similarly expands.[6 7] Currently there are over 100 chromosomal loci, including nuclear and mitochondrial DNA, involved in human performance with more genes discovered each year.

For many years, most countries have had talent identification programmes of one sort or another. Typically these involve sports such as rowing, where young athletes are identified on the basis of anthromorphic characteristics and subjected to intensive training programmes with the expectation that their ultimate performance will be in the elite range. Whilst few people would have a problem with this approach, what if the same potential can be detected using a genetic blood test instead of a tape measure?

The physical performance phenotypes for which genetic data are currently available include cardio-respiratory endurance, elite endurance athlete status, muscle strength, other muscle performance traits, training response, and exercise intolerance to varying degrees. The phenotypes for health related fitness include exercise heart rate, blood pressure, heart morphology, exercise related cardiac arrhythmias, anthropometry, body composition, insulin and glucose metabolism and blood, lipoprotein, and haemostatic factors. Although this seems a wide variety of exercise phenotypes, the human fitness and performance gene map is still in its infancy. With advances in technology such as genome-wide scans followed by intensive positional cloning, new candidate genes will be rapidly identified.[6]

As described above, as more and more candidate genes are identified so the potential problems with gene doping will increase. With more potential gene targets available, once the gene transfer technology is safe for human use, then a Pandora's box of applicable uses in sporting performance will be available. Unless innovative, non-invasive, and as yet unknown means of detecting gene transfer use are developed then the future of elite sport may be a race of tissue-engineered supermen and superwomen.

Br J Sports Med 2003;**37**:192–193

Author's affiliation

P McCrory, Centre for Sports Medicine Research and Education and the Brain Research Institute, University of Melbourne, Melbourne, Australia

Correspondence to: Dr McCrory, PO Box 93, Shoreham, Victoria 3916, Australia; pmccrory@compuserve.com

REFERENCES

1 **Nazarov I**, Woods D, Montgomery H. The angiotensin coverting enzyme I/D polymorphism in Russian athletes. *Eur J Hum Genetics* 2001;**9**:797–801.
2 **Aschwanden C**. Gene cheats. *New Scientist* 15 January 2000:24–9.
3 **Svensson E**, Black H, Dugger D, *et al*. Long term erythropoeitin expression in rodents and non-human primates following intramuscular injestion of a replication-defective adenoviral vector. *Hum Gene Ther* 1997;**8**:1797–806.
4 **Zhou S**, Murphy J, Escobedo J, *et al*. Adeno-associated virus-mediated delivery of erythropoietin leads to sustained elevation of haematocrit in non-human primates. *Gene Ther* 1998;**5**:665–70.
5 **Barton-Davis E**, Shoturma D, Musaro A, *et al*. Viral mediated expression of insulin like growth factor 1 blocks the ageing-related loss of skeletal muscle function. *Proc Nat Acad Sci* 1998;**95**:15603–7.
6 **Rankinen T**, Perusse L, Rauramaa R, *et al*. The human gene map for performance and health-related fitness phenotypes: the 2001 update. *Med Sci Sports Exerc* 2002;**34**:1219–33.
7 **Rankinen T**, Perusse L, Rauramaa R, *et al*. The human gene map for performance and health- related fitness phenotypes. *Med Sci Sports Exerc* 2001;**33**:855–67.

New BASEM office

BASEM is pleased to announce that it has now opened an administrative office in Leeds. It is open on weekdays from 1.00pm to 5.00pm. Contact may be by telephone: +44 (0)113 263 5014; email: basemoffice@compuserve.com or by Royal Mail at PO Box 148, Chelsea Close, Amberley Road, Leeds LS12 4WW, UK. It will be run by Sobia Rafiq, who will redirect all queries to the relevant Executive Member.

Expression of concern about content of which Dr Paul McCrory is a single author

This paper is authored by Dr Paul McCrory. During 2021 and 2022 there was an investigation by BJSM and BMJ which found that some of his work was the product of publication misconduct. Such misconduct includes plagiarism, duplicate publication, misquotation and misrepresentation in publications in respect of which he was listed as the sole author.[1] We are placing a notice to readers on all content in relation to which he is identified as the sole author to alert them to the conclusions of our investigation.

Br J Sports Med 2022;**0**:1. doi:10.1136/bjsports-2022-106408eoc

REFERENCE

1 Macdonald H, Ragavooloo S, Abbasi K. Update into the investigation of former BJSM editor-in-chief Paul McCrory. *Br J Sports Med* 2022.