doi:10.1006/mthe.2001.0347, available online at http://www.idealibrary.com on IDEAL

Gene Transfer and Athletics—An Impending Problem

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In an excellent and prescient 1986 article on the ethics of human gene therapy, Leroy Walters describes the broad potential applications for genetic manipulation (preventive, therapeutic, and enhancement) of human traits at both the somatic and germ-line levels (1). By policy at both the U.S. Food and Drug Administration (FDA) and Office of Biotechnology Activities (OBA) of the NIH, gene transfer studies in human subjects and patients in the United States are currently restricted to models of human disease and experiments aimed at modification of nondisease human traits are explicitly *not* being entertained. The reason behind this restriction is the obvious difference between the risk–benefit estimates for serious human disease and those for traits that are cosmetic, minimally burdensome to our society, and, in some cases, possibly even trivial. There are also broader ethical questions regarding the appropriateness and social acceptability of genetic human modification not aimed at disease prevention and treatment. However, despite the governmental lack of receptivity to enhancement studies and our personal ethical uncertainties and reservations, we all know that advancing technology, increased efficacy and safety, and eventual demonstration of true clinical efficacy will eventually lead to the redirection of therapeutic gene transfer methods toward enhancement of human traits. What has not been at all clear, until recently, is the direction from which the first serious challenge to the enhancement issue would come.

Success in several animal gene transfer models and in the use of new classes of vectors suggests one likely source of strong and possibly even irresistible enhancement pressure; i.e., the highly visible, high-pressure, and lucrative world of athletics. Athletic prowess is valued and stunningly well rewarded in our society. Pressures are enormous on athletes, teams, coaches and trainers, and athletic societies and federations to develop and use ever more effective means of improving athletic performance and on winning. This attitude pervades all levels of sport to varying degrees, from professional and "amateur" international and Olympic-level competition to local and sand-lot venues. Pharmacological methods for enhancing athletic performance are epidemic throughout the sports world and have led to the concurrent phenomena of doping and screening. International rejection of pharmacologically engineering athletes coexists with tacit and even enthusiastic acceptance of drug doping, as exemplified by the open, advertised, and even publicly accepted use in American professional baseball of food supplements that are known to contain precursors to anabolic steroids, but which are not regulated by the FDA.

However, drug use for athletic enhancement is not the end of the athletic enhancement story. Athletes, their coaches and trainers, and the well-funded sports associations, all of whom benefit from winning and record-breaking performances, are always looking for more effective, safer, and less detectable methods for altering the athletic physiology. Is it possible that genetic methods will not become increasingly attractive to them? The world of athletics is aware that model gene transfer studies with obvious interest and relevance to athletic performance athletics are reported commonly in the gene therapy literature and form a compelling and now apparently a credible basis for therapeutic trials in human subjects and patients. Such proof-of-principle studies, especially with those dealing with the transgenes such as erythropoietin, growth hormone, and IGF1, are so directly relevant to athletics that it takes very little imagination to envision direct illicit extension, with few if any substantive modifications, to sport. The genes involved in many of these studies are precisely the agents that have, in all probability, already found their place in performance enhancement in sport. In the case of erythropoietin, stable long-term gene expression and resulting long-term increases in red cell numbers have been demonstrated in mouse and monkey studies, using tools virtually identical to those being applied so promisingly in approved clinical studies for diseases such as hemophilia B (2–7). The major difference between these applications is the nature of the transgene. It is no secret that the performance of athletes in several aerobic-intensive sports would improve enormously through an increased oxygen-carrying capacity from an elevation of hematocrit induced by any means, pharmacological or genetic. Envisioning the use of vectors and delivery systems for stable delivery of a performance-enhancing transgene is not difficult.

What pressures currently exist for moving from the world of "traditional" drug enhancement to the world of gene transfer? Why take seriously the possible use of genetic modification of athletic traits when there are still so many unanswered questions of efficacy and safety in the truly therapeutic use of the same gene transfer techniques—the many technical, ethical, and policy concerns that justify the elaborate governmental and institutional review and regulation policies now in place for even dire, life-threatening diseases? What advantages would genetic delivery provide, if any? At first glance, genetic approaches to doping would seem to be even less predictable

1525-0016/01 $35.00

and therefore even less safe than drug doping. Screening methods would still be available as they are now to test for the enhancing gene products and to detect for their physiological effects. However, the attraction to genetics rather than drug delivery is in its potential for producing a desired physiological effect accompanied by authentic physiological regulation of a foreign gene tissue-targeted transgene, in physiological patterns and at lower and therefore safer levels, than periodic drug delivery. Furthermore, under some conditions, gene delivery could be less susceptible to detection than drug delivery.

Is it possible to imagine athletes, trainers, and sports associations irresponsible enough to use the currently highly experimental and imperfect techniques of gene transfer for athletic use? Sadly, yes. As imperfect and immature as they may be, as little as we know about their long-term dangers, current gene transfer methods may prove to be irresistible to the sports world. At a time when we are hearing misguided pronouncements of imminent attempts at another poorly understood and surely unsafe technology with equally weighty ethical and public policy quandaries, i.e., human cloning, the combination of enormous economic pressures and the rewards of athletic glory and alluring genetic technologies suggests that the immature, possibly dangerous, and certainly incompletely understood genetics tools will be applied in athletic settings outside the knowledge or the reach of review and regulatory bodies and responsible athletic bodies. The Lausanne-based World Antidoping Agency (WADA) is planning a workshop this fall at which representatives of the relevant communities—athletes, policy makers, and scientists—will come together to have a first joint look at the nature of this potential problem. It is hoped that other bodies, including athletic associations, the gene therapy community, and review and regulatory agencies, take the issue seriously and begin to plan how they might prevent or respond to premature gene transfer attempts in athletes. In addition, the athletic issue may represent only the first relatively straightforward application of gene transfer methods for enhancement purposes and therefore should catalyze a renewed examination of the broad question of genetic enhancement in other potential applications.

REFERENCES

[1] Walters, L. (1986). The ethics of human gene therapy. *Nature* **320:** 225–227.

[2] Kay, M. A., *et al.* (2000). Evidence for gene transfer and expression of factor IX in haemophilia B patients treated with an AAV vector. *Nat. Genet.* **24:** 257–261.

[3] Rudich, S. M., Zhou, S., Srivastava, R., Escobedo, J. A., Perez, R. V., and Manning, W. C. (2000). Dose response to a single intramuscular injection of recombinant adeno-associated virus-erythropoietin in monkeys. *J. Surg. Res.* **90:** 102–108.

[4] Osada, S., Ebihara, I., Setoguchi, Y., Takahashi, H., Tomino, Y., and Koide, H. (1999). Gene therapy for renal anemia in mice with polycystic kidney using an adenovirus vector encoding the human erythropoietin gene. *Kidney Int.* **55:** 1234–1240.

[5] Bohl, D., Salvetti, A., Moullier, P., and Heard, J. M. (1998). Control of erythropoietin delivery by doxycycline in mice after intramuscular injection of adeno-associated vector. *Blood* **92:** 1512–1517.

[6] Zhou, S., Murphy, J. E., Escobedo, J. A., and Dwarki, V. J. (1998). Adeno-associated virus-mediated delivery of erythropoietin leads to sustained elevation of hematocrit in nonhuman primates. *Gene Ther.* **5:** 665–670.

[7] Snyder, R. O., *et al.* (1997). Efficient and stable adeno-associated virus-mediated transduction in the skeletal muscle of adult immunocompetent mice. *Hum. Gene Ther.* **8:** 1891–1900.