ETHICS

Gene Doping and Sport

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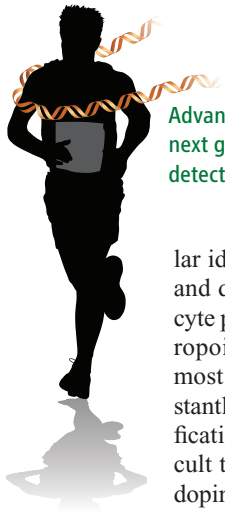

Advances in gene therapy set the stage for the next generation of illegal doping, and doping detection, in sport.

We humans have long sought to enhance ourselves beyond normal through cosmetic surgery and drugs. Science is increasingly becoming humanity's partner and handmaiden in those efforts (*1*) and has added genetic manipulation to our enhancement tool kit. Many forms of human enhancement are becoming more feasible, sought-after, and even justifiable in the quest for healthier, happier, and longer lives.

Around the world, people have been exposed to the notion of human enhancement through sport, as some athletes seek a boost to success, stardom, and financial reward. In the past, doping and cheating in sport have been enabled by advances in pharmacology and physiology. Recently, the successful development of gene therapy has provided the concepts, tools, opportunity, and, for some, justification for genetic modification of functions that affect normal human traits, including athletic performance. This intersection of science and sport raises fundamental ethical and policy issues that neither domain can resolve absent a broader societal conversation (*2*). As science progresses and sport and antidoping authorities express increasing concerns, the time is right to look at how advances in genetics are affecting sport in ways unexpected just a decade ago.

Genetic Manipulation for Doping

Some early experimental studies illustrate the potential of gene therapy for treating diseases (*3*–*8*). Although most gene therapy approaches involve gain-of-function expression of exogenous transgenes, other methods for genetic modification have also emerged (*9*–*15*). A definitive approach to genetic modification for therapy would involve an emerging technology of site-specific sequence correction of disease-causing mutations, as through the use of zinc finger–associated recombinational methods (*16*).

Although highly effective in some models, these gene therapy techniques are imperfect and still highly risky, as demonstrated by severe adverse events such as treatment-induced leukemia, or even deaths (*17*–*19*). Nevertheless, it is inevitable that, as the science and techniques mature, these same methods and concepts will be applied to broader nontherapeutic uses, including gene-based "enhancement" of human traits linked to sport.

Toward that end, genetic methods have been used, for instance, to demonstrate enhanced muscle function from the insulin-like growth factor (IGF-1) or follistatin transgenes (*20*, *21*) and stably increased, regulatable, erythropoietin-enhanced blood production in primates (*22*). One of the most widely discussed transcriptional modulation approaches has involved small molecule modulators of peroxisomal proliferator-activated receptor delta (PPAR-δ), which regulates expression of genes involved in lipid metabolism, energy utilization, and insulin action and that increases the production of slow twitch oxidative energy-efficient muscle fibers. These effects have important implications for therapy of diabetes, obesity, and muscle disease. Furthermore, mice overexpressing a PPAR-δ transgene or treated with a PPAR-δ agonist show enhanced endurance performance (*23*).

Not surprisingly, these scientific approaches are known in sport communities and are coming temptingly close to human doping. A German athletic coach was found attempting to obtain Repoxygen, a gene-transfer vector that induces expression of the erythropoietin gene (*24*). A Chinese genetics laboratory reportedly offered gene-based manipulations before the 2008 Olympic Games in Beijing (*25*). It is not clear whether these or other similar attempts reached the stage of actual use in human athletes, but there seem to be few technical barriers standing in the way.

Genetic Tools for Doping Detection

Traditional approaches to detection of doping in sport have been based on chemical or molecular detection of the doping agent or of markers reflecting the physiological or metabolic effect(s) of the agent (e.g., chemical assays for steroids and stimulants, molecular identification of foreign erythropoietin, and detection of abnormally high erythrocyte production following exogenous erythropoietin exposure). Although this is the most direct approach, new assays are constantly needed to respond to chemical modifications that make some drugs more difficult to detect, and therefore more prone to doping abuse.

A potentially more powerful detection method has emerged, based on the concept that chemical, biological, or genetic doping agents are likely to produce broad metabolic, genetic, and proteomic changes. These changes are now detectable by techniques such as microarray- or sequence-based transcriptional profiling and proteomic and metabolomic analyses that can define molecular "signatures" of exposure to specific doping agents, or families of drugs, or methods. Such signatures may be used to identify perturbed physiological systems, even in the absence of knowledge of, or assays for, specific doping agents. This approach is similar to that commonly used in searches for molecular signatures of oncogenesis, developmental disorders, and so on (*26*, *27*).

Highly concerned by the risk of gene doping, the World Anti-Doping Agency (WADA) (*28*), which has retained gene doping in its list of prohibited substances and methods since 2004, has sponsored international research teams with early results providing growing credence to the utility of molecular signatures in doping detection. For instance, exposure of murine myoblasts to IGF-1 has been shown to induce transcriptional and proteomic changes that may eventually constitute a "signature" specific for exogenous IGF-1 exposure (*29*, *30*). Of course, the application of these kinds of global assays would require rigorous validation of a connection with specific doping agents or methods.

Marketing Gene Doping

The challenges posed to sports organizations concerned with gene doping are compounded by the ubiquity of the Internet, relatively unconstrained by geographical boundaries, which, when fueled with private commercial interests, creates a powerful marketing tool for promotion and distribution of performance-enhancing agents. An industry has emerged to cater to the desire of athletes and

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their coaches to find a competitive edge.

Athletes are an especially vulnerable population in the marketing of performance enhancement (*31*). Reputable athletes or coaches with little knowledge of genetics are at a disadvantage in assessing "scientific" claims that appear in advertisements. Marketing is particularly worrisome when the science is still a work in progress, when a person's health can be adversely affected, and when consumer knowledge about genetics is low. Although advertisements promoting products that promise to enhance athletic performance have pervaded the Internet for many years, recently it has become home for advertisements that promote products to "alter muscle genes…by activating your genetic machinery" (*32*), or that state "your genetic limitations are a thing of the past!" (*33*) or "Finally, every bodybuilder can be genetically gifted!" (*34*).

Conclusion

The stakes are high in competitive sport. Enter the science of genetics and the increasing ability to modify genes for medical and performance enhancement purposes. As a result, the former chairman of WADA proclaimed that "You would have to be blind not to see that the next generation of doping will be genetic" (*35*). As others have observed, "What is clear … is just how impatient some coaches and athletes are to find new and ingenious ways to cheat. First it was steroids, then EPO [erythropoietin], then human growth hormone—and now the illicit grail seems to be gene therapy" (*36*). The global marketplace is ready to meet the demand in ways that will inevitably include untested, and perhaps unregulated, products and exaggerated claims. Although commercial Web sites may be "biased, and unreliable by rigorous scientific standards, they are a principal source of information for many athletes and should be monitored when looking for evidence of developing trends in doping" (*37*).

Accompanying those developments is the emergence of a community that alleges shortcomings in the testing process and blames the antidoping effort for stimulating "an arms race between regulators and the cheats" (*38*). Others question why certain enhancement technologies are banned while others remain legal and argue that athletes should be free to use virtually any enhancing agents that science makes available to them (*39*). Scientists are not mere bystanders in these matters. The 2010 Winter Olympic Games and other major sport events present good opportunities for researchers to reaffirm their responsibilities to conduct and report their work by means consistent with international ethics codes of clinical research. They also must be aware that some athletes and coaches will be tempted, prematurely and unwisely, to take advantage of results packaged by some as performance enhancement "breakthroughs," even if they are untested in humans and the only "breakthrough" is faster or stronger mice (*40*, *41*).

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2. There have long been divergent views of sport doping and the value of antidoping regulation (*41*). Some commentators have addressed how the use of performance-enhancing drugs in sports and their regulation have adversely affected fair competition (*42*). Others have suggested that drug- or gene-based doping causes little or no harm to athletes, sport, and public policy and that the controversies surrounding doping could readily be obviated by simply carrying out doping under medical supervision (*43*).
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