Editors' view

Sex, steroids and anabolic androgens in athletics

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The ancient Olympic games were (almost) men only affairs. Successful athletes were highly honoured, and, perhaps for this reason, skulduggery was not unknown. For example, we read in Wikipedia that 'Sotades at the ninety-ninth Festival was victorious in the long race and proclaimed a Cretan, as in fact he was. But at the next Festival he made himself an Ephesian, being bribed to do so by the Ephesian people. For this act he was banished by the Cretans.' With the discovery that drugs may plausibly enhance athletic performance modern athletics associations, perhaps unsurprisingly, have to contend with doping as well as other thorny issues, and the use of drugs in sport is believed to be widespread despite its prohibition [1]. The World Anti-Doping Agency publishes a list of drugs whose use is prohibited either in or out of competition (<http://www.wada-ama.org>). Drug testing involves analysis of blood or urine samples mainly by gas/chromatography/mass spectrometry or radioimmunoassay in approved laboratories according to strictly defined protocols.

Evidence-based doping?

Evidence-based medicine makes an important distinction between statistical significance and clinical relevance: real effects may be too small to be therapeutically useful. This is very important in a clinical context; for example cholinesterase inhibitors have a statistically significant effect on formal measures of cognitive function demonstrable in groups of patients with Alzheimer's disease, yet individually many such patients and their carers do not notice an improvement, and treatment should continue only if worthwhile improvement is noted on an individual basis (<http://www.nice.org.uk/nicemedia/live/13419/53624/53624.pdf>). When drugs are used in sport this situation is stood on its head, since a marginal improvement in performance ($\leq 1\%$), which would be extremely difficult to

detect experimentally even in a randomized controlled trial, could nonetheless make the difference between winning and losing. None of the drugs used in sport (including anabolic agents, erythropoietin, human growth hormone, insulin, β_2 -adrenoceptor agonists and others) have been convincingly demonstrated to enhance athletic performance, but this absence of evidence has not impressed contenders in the past half century and is unlikely to do so in future.

Motherhood goes with gold?

Although male athletes have been assumed to be innately superior to females, such advantage is specific to particular events – a woman, Bilistiche, is mentioned as a winner in an equestrian event in the ancient Olympics (http://en.wikipedia.org/wiki/Ancient_Olympic_Games accessed 11th May 2012). An article in the Huffington Post titled 'Might pregnancy be a boon to female athletes?' used the occasion of Paula Radcliffe's victory in the 2007 New York marathon to discuss the possibility that physiological changes of pregnancy might actually be advantageous (http://www.huffingtonpost.com/eileen-mcdonagh-and-laura-pappano/might-pregnancy-be-a-boon_b_71803.html), and several subsequent notable athletic successes by pregnant women accord with this. Physiological actions of female sex hormones on muscle metabolism, and effects of increased blood volume and oxygen delivery are surely consistent with this possibility – although this is of course a far cry from definitive evidence. Radcliffe herself used the services of two male pacemakers in achieving her 2003 world record breaking time of 2 h 15 min 25 s in the London marathon, a women's world record that was subsequently and contentiously disallowed because of the male involvement though it stands as a world best (<http://www.telegraph.co.uk/sport/othersports/athletics/>

8823417/London-2012-Olympics-Paula-Radcliffe-calls-for-her-marathon-world-record-to-be-reinstated.html).

Exploiting physiology: the example of blood doping

Despite this draconian instance, taking advantage of a natural physiological state such as pregnancy could hardly be called into question whereas an attempt to mimic it by taking exogenous drugs would surely count as cheating. The rules can seem pretty arbitrary – the one about male pacemakers was made and applied retrospectively. 'Blood doping' (reputedly favoured by cyclists) exemplifies the shades of grey, as well as some of the problems of detection: transfusion of heterologous packed blood cells with intent to boost athletic performance rather than to treat intercurrent illness seems eminently unfair (and easy to detect), autologous transfusion of one's own harvested and stored blood seems no better (though harder to detect), injecting oneself with epoietin is cheating (and can be detected through differences in the exogenous and endogenous human hormone), training at high altitude when one's home is say in Ethiopia is hard to find fault with, but how about sleeping in a low oxygen tent at night – and how could this be detected after the event? This raises the semantic question of whether oxygen is a drug, and if so whether lack of oxygen – and hence an inert displacing gas such as nitrogen – is also a drug. If I share my bedroom with the 'wrong end' of an oxygen concentrator which delivers oxygen to a patient with chronic obstructive pulmonary disease in the adjacent room would she be receiving therapy but I am guilty of a lifestyle offence by virtue of the erythropoietin I secrete in response to the partly oxygen-depleted nitrogen I breathe overnight? These are questions probably best left to modern equivalents of the medieval schoolmen who argued about angels and the points of pins, and I shall not in any case be competing athletically in the near future.

Anabolic androgens

The androgen-induced changes that accompany puberty in boys, including increased muscle mass, confer a clear advantage in many sports, but attempts to mimic such changes artificially in order to gain athletic advantage are prohibited. Nevertheless, anabolic androgenic steroids are currently the prohibited substances most commonly detected by accredited anti-doping laboratories around the world. When given in combination with physical training and a high protein diet, androgens increase muscle mass and body weight, but there is little evidence in

healthy people (as opposed to debilitated patients) that they increase muscle strength or improve athletic performance more than training and diet alone. Their effects persist long term, so out-of-competition testing is used to detect them. Some of the drugs in use are endogenous hormones or their metabolites, making it harder to prove that they have been administered illicitly, although sophisticated isotope ratio techniques based on differences in ^{12}C : ^{13}C ratios do enable endogenous and exogenous steroids to be distinguished. Exogenous administration of these drugs does not replicate the complex fluctuating patterns of secretion of endogenous sex hormones, interfering with negative feedback on the hypothalamus and anterior pituitary gland and causing a number of adverse effects including testicular atrophy and loss of libido, as well as aggression, effects on mood, hepatotoxicity, liver and renal tumours, cardiovascular disease including cardiomyopathy, virilizing effects in women, fusion of bony epiphyses and stunted growth in adolescents. Cheating by using these drugs, said to be particularly an issue in weight lifters and participants in field events, does not come without risk but this is not always conveyed to naive youngsters by their trainers or suppliers and the possibility of adverse effects may even be dismissed by less immature contestants who are nonetheless still too young to weigh such risks rationally (the youthful illusion of invulnerability, itself perhaps influenced by androgen secretion). Young people who are not elite athletes may be exposed and vulnerable to illicit androgen use in the setting of gyms or other sports. Detection of such misuse is thus an important health issue.

Genetic factors result in large variations in disposition of testosterone and other anabolic steroids, with consequences for the correct interpretation of analytical doping tests. To correspond with the 2012 Olympic Games, we have therefore invited Anders Rane and Lena Ekström to review these topical aspects, and their account appears in this present issue of the Journal [2].

In conclusion, we wish success to the host of athletes who 'play fair', and to the World Anti-Doping Agency in accurately detecting those who do not, and trust that our readers will enjoy this summer's spectacle.

REFERENCES

- 1 Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. In: Chapter 54 Lifestyle Drugs and Drugs in Sport (Pages 765–769) in Rang and Dale's Pharmacology, 7th edn. Edinburgh: Elsevier Churchill Livingstone, 2012.
- 2 Rane A, Ekström L. Androgens and doping tests: genetic variation and pit-falls. *Br J Clin Pharmacol* 2012; 74: 3–15.