

COMMENTARY

Drugs in Sport

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This themed issue of the *British Journal of Pharmacology* has been compiled and edited by Ian McGrath, Regius Professor of Physiology at University of Glasgow and David Cowan, Director of the Drug Control Centre at King's College London. It contains 11 articles covering the mechanisms of action of the major groups of drugs used illicitly in sport. The articles, written by experts in how drugs work, set out where drugs can or cannot affect sporting performance, how this relates to their legitimate medicinal use, their other detrimental effects and how they can be detected. Publication coincides with Olympic year, when sport is highlighted in the public mind and much speculation is made concerning the use of drugs. The articles provide a framework of expert, accurate knowledge to inform and facilitate these debates and to help to overcome the ill-informed and dangerous anecdotal information by which sports men and women are persuaded to misuse drugs in the mistaken belief that this will improve their performance without present or future ill effects. A unique article is included by the Spedding brothers, Mike with a long career in drug discovery and Charlie, the 1984 Los Angeles Olympic Marathon Bronze Medallist and still the English National Marathon record holder. From their unique experience, they describe the insidious and unfair way that drug-assisted performance undermines the ethos of sport and endangers the vital place of sport in maintaining the health of the population.

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The physiological systems that make up the human body have evolved over millions of years and consist of thousands of interacting processes that are finely balanced and regulated. Drugs used for medical purposes change these relationships in a way that is intended to be beneficial but, in recognition that this is a sometimes dangerous balancing act between benefit and harm, regulatory authorities throughout the world insist on careful scientific and clinical assessment of any drug introduced for medical use. However, in the case of drugs used illicitly with the intention of producing an unfair advantage in sport, no such analysis is performed, so that any 'benefit' is usually unproven and the dangers are not properly assessed. In the series of reviews in the present issue of *British Journal of Pharmacology*, emphasis is placed on all of the biological actions of the drugs and not simply on any spurious gain in sports performance, so that their effects for good or ill can be understood.

The first major move to control the misuse of drugs in sport, now more usually referred to as doping, is open to debate. However, in 1967 the International Olympic Com-

mittee's (IOC) published list of 'Banned Substance Classes and Methods' comprised five groups: sympathomimetic amines; stimulants of the central nervous system; analgesic narcotics; anti-depressants; and major tranquillizers. One year later the anti-depressants and major tranquillizers categories were removed. The categories remained virtually unchanged until in 1976, after the Winter Olympic Games in Innsbruck but for the Summer Olympiad in Montreal, anabolic steroids were added as a new group.

In 1984 control of excessive caffeine use, based on a maximum allowed concentration in urine of $15 \mu\text{g mL}^{-1}$, was imposed. At the same time testosterone use was controlled based on a test that measured the ratio of testosterone and epitestosterone levels in urine with a reporting limit of six.

Not only are many substances prohibited as outlined above but the use of pharmacological, chemical and physical manipulations were also controlled in 1988 after athletes discovered that probenecid was effective in reducing the urine concentration of many anabolic steroids that were eliminated in urine as their glucuronic acid conjugates. At the same time, the use of diuretics and blood transfusions were prohibited.

The next major change was in 1989 when the use of a number of protein hormones was banned including human chorionic gonadotropin, ACTH and human growth hormone. Erythropoietin (EPO) was added as a named substance in 1990.

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Subsequently, the IOC made just minor amendments to the list that it published each year rather than changing the major categories. In 1999, the IOC hosted a major international conference inviting leaders from international governments. The result was the formation of the World Anti-Doping Agency (WADA), a body supported equally by sport and by governments. After an interim period where the IOC and WADA worked together, WADA published its first list of prohibited substances in 2004. WADA have stated that they wish to use an evidence-based system to justify their prohibited list. Thus it is timely that the *British Journal of Pharmacology* is now publishing a special edition that covers the pharmacology of the different prohibited classes. To our knowledge this will comprise the most comprehensive up to date review (See Table 1).

As an introduction to why we should be concerned about drug use in sport, Spedding and Spedding (2008) describe how the social and motivational aspects of sport and its benefits for the health and happiness of the individual and society are undermined by the presence of drug cheats in sport. They go on to discuss the physiological basis for beneficial changes in the brain that are induced by exercise and the finely tuned interactions between the body's defence and repair systems, all aspects that can be disrupted by the misuse of drugs.

Kicman (2008) provides a comprehensive review comprising the common anabolic steroids, steroids in dietary supplements, as well as so called designer steroids. He also reviews the mechanisms of action, clinical uses and adverse effects including possible behavioural effects. He considers the separation of myotrophic from androgenic activity and the potential greater specificity of selective androgen receptor modulators. He also focuses on the use of synthetic steroids as performance enhancers in sport.

This is followed by a more specialized review of current thinking on the effects of administered testosterone on skeletal muscle, concluding with why this confers an unnatural and unfair physiological advantage on the abuser (Kadi, 2008).

Elliott (2008), a key research scientist at Amgen who was involved with the development of darbepoetin, reviews the use of recombinant EPO. He considers the ergogenic benefits associated with enhanced oxygen delivery to tissues, how low oxygen tension increases endogenous EPO production and how recombinant EPO and other agents used to enhance oxygen delivery to tissues are used and may be misused. He also reviews the means of detecting the misuse in sport.

Holt and Sönksen (2008) review the physiology of GH, IGF-I and insulin and explore the myths as well as the facts that give the reader an insight as to why athletes may abuse these substances. They also outline how administration may be detected using the two proposed approaches based on the determination of GH isoforms or the biomarkers IGF-I and type III pro-collagen (P-III-P).

Velloso (2008) reviews current thinking on the physiological mechanisms through which growth hormone and IGF-I act, in particular, to regulate muscle mass. Discussion then centres on whether these actions would necessarily confer any benefit on those attempting to abuse these substances by self administration. It is concluded that some advantages

may be conferred in relation to increased lean body mass but that evidence is very thin for improved performance by such abuse in mature healthy adults. This contrasts with the interesting potential that manipulation of this system may have therapeutically, for example, for restoring deficits in development or those caused by ageing.

Stenman *et al.* (2008) provide an extensive review of the biochemistry of human chorionic gonadotropin and luteinizing hormone, and discusses its measurement in urine and reference and cutoff values for doping control purposes.

Davis *et al.* (2008) make a comprehensive review of current knowledge of the β -adrenergic system; this important system regulates many body functions both in the brain and in the periphery and provides the basis for understanding the actions of several groups of drugs that are abused and, therefore, banned in sport. β -Agonists and β -blockers both act directly on the β -adrenoceptors that mediate the system, though agonists stimulate while blockers 'block', respectively. In addition, many drugs, mainly central nervous system stimulants, release the neurotransmitter noradrena-

Table 1 Substances (S Class) and methods (M Class) are prohibited at all times (in and out of competition) except 'S6 Stimulants', which are prohibited only in competition

WADA class	Agent	Article
S1	Anabolic agents	
S1.1	Anabolic androgenic steroids (AAS)	Kicman (2008), Kadi (2008)
S1.2	Other anabolic agents e.g. clenbuterol	Davis <i>et al.</i> (2008)
S2	Hormones and related substances: The listed substances and their releasing factors, are prohibited	
S2.1	Erythropoietin (EPO)	Elliott (2008)
S2.2	Growth hormone (hGH), insulin-like growth factors (e.g. IGF-I), mechano growth factors (MGFs);	Holt and Sönksen (2008), Velloso (2008)
S2.3	Gonadotrophins (e.g. LH, hCG), prohibited in males only	Stenman <i>et al.</i> (2008), Holt and Sönksen (2008)
S2.4	Insulins	Holt and Sönksen (2008)
S3	β -2 agonists	Davis <i>et al.</i> (2008)
S4	Hormone antagonists and modulators	
S4.1	Aromatase inhibitors	Handelsman (2008)
S4.2	Selective oestrogen receptor modulators (SERMs)	Handelsman (2008)
S4.3	Other anti-oestrogenic substances	Handelsman (2008)
S6	Stimulants	Docherty (2008)
M1	Enhancement of oxygen transfer	Elliott (2008)
M3	Gene doping	Wells (2008)
P2	β -blockers	Davis <i>et al.</i> (2008)

Some substances are prohibited only in certain sports (P Class), e.g. P2 β -blockers. This is not the complete WADA list.

line and therefore activate the β -adrenoceptors indirectly. Although the rationales behind the abuse of these classes of drugs are quite different, Davis *et al.* (2008) discuss how a proper consideration of the β -adrenergic system indicates many pitfalls in the abuse of such drugs that make any conferred advantage quite dubious, and with potential deleterious consequences that would be best avoided.

Handelsman (2008) reviews the clinical pharmacology of oestrogen blockade. He indicates how these agents increase blood testosterone concentrations in men by up to 50%. At the same time, he reports that there are no well established clinical indications for oestrogen blockade in men and hence this should not be used in sport despite the fact that some androgen abusers use them to treat gynaecomastia. He explains that the possibility that oestrogen blocker drugs can increase testosterone in females is less clear. The stimulation of endogenous gonadotrophins produced by short courses of aromatase inhibitors appears to be class-specific and he suggests that this indication is particularly relevant for female athletes to treat the anovulatory infertility caused by the intensive exercise of sport that can cause hypothalamic amenorrhea and ovulatory dysfunction.

The actions of stimulants are comprehensively reviewed by Docherty (2008) who explains how most of them act by similar mechanisms, mainly by interfering with monoamine neurotransmitters in the central nervous system. These transmitters, noradrenaline, dopamine and 5-hydroxytryptamine (serotonin) are all important for the regulation of a myriad of brain function including the control of the cardiovascular, metabolic and other body systems as well as more obvious direct brain functions such as controlling mood and alertness. The 'stimulant' drugs have actions which interfere with the normal functioning of all of these systems, and their actions normally extend to two or even three of the amine transmitters. It is, therefore, important to realize that drugs abused for their central 'stimulant' action

can have widespread deleterious actions on many aspects of body function.

There is currently much interest in the theoretical prospect, rather than the current application, of gene doping. Wells (2008) explains the current state of play and looks forward, from current knowledge, to how this is likely to develop in relation both to legitimate use in medicine and attempts to use such knowledge to gain an unfair physiological advantage in Sports.

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