REVIEW ARTICLE

Sports Med 2008; 38 (6): 505-525
0112-1642/08/0006-0505/$48.00/0

Anabolic Steroid Use

Patterns of Use and Detection of Doping

Michael R. Graham ,[1] Bruce Davies,[1] Fergal M. Grace ,[1] Andrew Kicman[2] and Julien S. Baker[1]

1 Department of Health and Exercise Science, School of Applied Science, University of Glamorgan, Pontypridd, UK
2 Drug Control Centre, King's College, London, UK

Contents

Abstract

Anabolic-androgenic steroids (AAS) were the first identified doping agents that have ergogenic effects and are being used to increase muscle mass and strength in adult males. Consequently, athletes are still using them to increase physical performance and bodybuilders are using them to improve size and cosmetic appearance. The prevalence of AAS use has risen dramatically over the last two decades and filtered into all aspects of society. Support for AAS users has increased, but not by the medical profession, who will not accept that AAS use dependency is a psychiatric condition. The adverse effects and potential dangers of AAS use have been well documented. AAS are used in sport by individuals who have acquired knowledge of the half-lives of specific drugs and the dosages and cycles required to avoid detection. Conversely, they are used by bodybuilders in extreme dosages with the intention of gaining muscle mass and size, with little or no regard for the consequences. Polypharmacy by self-prescription is prevalent in this sector. Most recently, AAS use has filtered through to 'recreational street

drug' users and is the largest growth of drugs in this subdivision. They are taken to counteract the anorexic and cachectic effects of the illegal psychotropic street drugs. Screening procedures for AAS in World Anti-Doping Agency accredited laboratories are comprehensive and sensitive and are based mainly on gas chromatography-mass spectrometry, although liquid chromatography-mass spectrometry is becoming increasingly more valuable. The use of carbon isotope mass spectrometry is also of increasing importance in the detection of natural androgen administration, particularly to detect testosterone administration. There is a degree of contentiousness in the scenario of AAS drug use, both within and outside sport. AAS and associated doping agents are not illegal *per se*. Possession is not an offence, despite contravening sporting regulations and moral codes. Until AAS are classified in the same capacity as street drugs in the UK, where possession becomes a criminal offence, they will continue to attract those who want to win at any cost. The knowledge acquired by such work can only assist in the education of individuals who use such doping agents, with a view to minimizing health risks and hopefully once again create a level playing field in sport.

1. Background

This article summarizes the classification of anabolic-androgenic steroids (AAS) or anabolic steroids and differentiates between their therapeutic and non-therapeutic use. The distinction between AAS use within and outside sport has been highlighted. This article also discusses the different types of AAS used, the methods of administration and the current strategies for detection procedures employed by authorities, intent on harm reduction.

A literature search was conducted using EMBASE, Entrez-PubMed and MEDLINE. Articles and abstracts have been cited and referenced from 1935 until the present day. The authors have included their own published research and personal communications, and made reference to unpublished data, which are in press.

1.1 What are Anabolic-Androgenic Steroids (AAS)?

AAS are a group of synthetic compounds similar in chemical structure to the natural anabolic steroid testosterone (see figure 1).[1-3] Testosterone, the predominant circulating testicular androgen, is both an active hormone and a prohormone for the formation of a more active androgen, the 5α-reduced steroid dihydrotestosterone (DHT). Physiological studies of steroid hormone metabolism in the postnatal state demonstrated that DHT is formed in target tissues from circulating testosterone and is a more potent androgen than testosterone in several bioassay systems.[4]

Genetic evidence indicates that these two androgens work via a common intracellular receptor. The androgen receptor (AR) is an intracellular ligand-dependent protein that modulates the expression of genes and mediates biological actions of physiological androgens (testosterone and 5α-DHT) in a cell-specific manner.[5]

During embryonic life, androgens cause the formation of the male urogenital tract and hence are responsible for development of the tissues that serve as the major sites of androgen action in postnatal life.

It has been generally assumed that androgens virilize the male foetus by the same mechanisms as in the adult, namely by the conversion of circulating testosterone to DHT in target tissues.

A role for steroid 5α-reduction in androgen action became apparent with the findings in 1968 that DHT, the 5α-reduced derivative of testosterone, is formed in many androgen target tissues where it binds to the AR.[6]

DHT binds to the AR more tightly than testosterone, primarily as a result of stabilization of the AR

complex, and at low concentrations is as effective as testosterone at high concentrations in enhancing the transcription of one response element.[7] This finding clearly indicated that some effects of DHT are the result of amplification of the testosterone signal.

Loss of function mutations of the steroid 5α-reductase 2 gene impairs virilization of the urogenital sinus and external genitalia in males.[8]

In summary, DHT formation acts both as a general amplifier of androgen action and conveys specific function to the androgen-AR complex. The mechanism by which this specific function is mediated is unknown.

The enzyme aromatase controls the androgen/estrogen ratio by catalyzing the conversion of testosterone into estradiol (E2). Therefore, the regulation of E2 synthesis by aromatase is thought to be critical in sexual development and differentiation.[9]

The synthetic version of the testosterone molecule was originally synthesized from cholesterol by the scientist Ruckzika in 1935.[10]

Testosterone is synthesized by the interstitial Leydig cells of the testes, which are primarily under the control of the gonadotrophins, secreted by the pituitary gland. Approximately 95% of circulating testosterone, originates directly from testicular secretion.[10] Following secretion, testosterone is then transported via the blood to target organs and specific receptor sites. The bodily functions that are under direct control of testosterone and that have relevance to the athlete can be divided into two broad classifications: (i) androgenic functions – male hormonal effects (male-producing); and (ii) anabolic functions – constructive or muscle building.

The clinical advantages of a pure anabolic agent were recognized many years ago and work was undertaken by a number of groups and drug companies to modify the testosterone molecule with a view to maximizing the anabolic effect and minimizing the androgenic activity. Some of the structural modifications of testosterone to dissociate the anabolic from the androgenic effects are shown in figure 1. The extent of the dissociation differs depending on the modification, but there is no AAS that has an anabolic effect in an athlete without an androgenic effect.[11]

1.2 Classes of AAS Preparations

There are three major classes of AAS used by athletes, based on the route of administration by the athlete or the carrier solvent:

1. Oral AAS preparations.

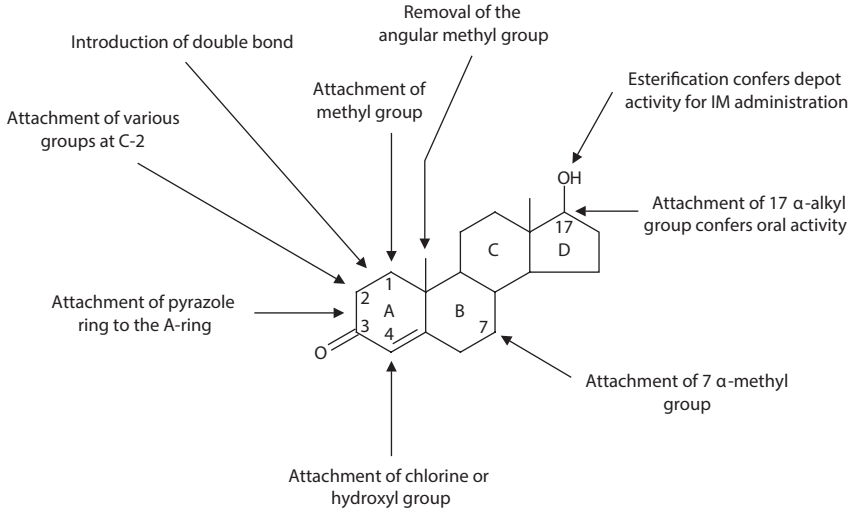

Fig. 1. The structure of testosterone, and structural modifications to the A- and B-rings of this steroid that increase anabolic activi ty; substitution at C-17 confers oral or depot activity (reproduced from Kicman and Gower, [3] with permission from the Royal Society of Medicine). IM = intramuscular.

2. Injectable oil-based AAS preparations.

3. Injectable water-based AAS preparations.

Oral AAS are synthesized in order to offer protection to the molecule when it becomes exposed to the strong acid solutions found in the stomach, and when it contacts the enzymic mechanisms of the liver. Oral activity is conferred by the substitution of a methyl (CH_3) or ethyl (C_2H_5) group for the H attached to the carbon atom (C) on the cyclopentane ring structure, in position 17 (as identified in figure 1). The 17α-alkylated steroids prevent deactivation by the first-pass metabolism by sterically hindering oxidation of the 17β-hydroxyl group. Liver dysfunction has been recorded as a consequence of long-term (>6 months) abuse, but probably in excessive dosages.[11] The treatment of hereditary angioedema patients with therapeutic oral stanozolol or danazol did not cause adverse hepatic changes.[12] Oral activity can also be conferred by attachment of a methyl group at C-1 as in methenolone or mesterolone, but the potency of the steroid is far weaker.

There are weaker formulations of anabolic agents that have the classification of 'nutritional' or 'dietary' supplements and are marketed as 'pro-hormones', particularly dehydroepiandrosterone (DHEA), androstenedione, 19-norandrostenedione, androstenediol and 19-norandrostenediol.[13] These steroids lack the 17α-alkyl moiety and following oral administration are extensively metabolized on first pass through the liver. DHEA and androstenedione bind to the AR with such a weak affinity that it is barely activated, but enzymes convert a proportion to testosterone. Supplements of DHEA or androstenedione may be of little or no benefit to healthy young men who wish to improve their strength and sporting performance if, as would be expected, any anabolic effect is primarily mitigated through peripheral conversion to testosterone. Any contribution from exogenous DHEA or androstenedione will be largely moderated by the large amount of testosterone contributed by the testis. In the young adult female, an increase in performance may be possible following ingestion of these supplements, as circulating testosterone would be expected to increase. The plasma concentration of testosterone in females (0.7–2.6 nmol/L) is approximately one-tenth that found in men and the proportion arising from peripheral conversion is much greater. Even though only 12–14% of androstenedione is converted peripherally to testosterone, this concentration accounts for about one-half of the circulating testosterone in the female.[14,15] As the peripheral contribution to blood testosterone is far greater in the young adult female than the male, ingestion of modest amounts of DHEA, androstenediol or androstenedione is likely to raise circulating testosterone. There are a few studies describing a modest to large increase in circulating testosterone following administration to women.[16-19] An investigation where the androstenedione was mixed and ground with lactose to aid dispersion in the gut showed that the plasma testosterone concentrations increased from ~1 nmol/L to a maximum mean of 25.1 nmol/L at 75 minutes and remained significantly different from control values between 30 minutes and 8 hours post-administration.[16] The mean exposure to testosterone (as determined by the area under the plasma concentration-time curve) was greater than an order of magnitude compared with the control period and the plasma concentrations observed were similar to those encountered in abuse of testosterone for anabolic purposes. A similar profile would be expected with long-term administration, but the risk of virilization precludes such a study.

Androstenediol (the delta-5 form) has been shown to activate AR target genes in the presence of AR,[20] but this hormone also binds with strong affinity to the estrogen receptor (it is not known whether the delta-4 isomer is a potent estrogen, but it is a distinct possibility). Little research has been done on 19-norandrostenedione and 19-norandrostenediol, but as a consequence of high-profile drug doping offences, in athletes, 19-norandrostenedione was made a controlled drug in the UK (table I).

Oral preparations are characterized by the following:

- They have a structure that acidic gastric secretions of the stomach will not render ineffective by degradation.

Table I. UK/European and US generic and trade names [a] of oral anabolic steroids (reproduced from Kicman and Gower, [3] with permission from the Royal Society of Medicine)

Generic name	UK/Europe trade name	US trade name
Methyltestosterone	Methyltestosterone	Android, Metandren, Arcosterone
Testosterone undecanoate	Restandol, Andriol, Undestor, Pantestone	
Metandienone	Dianabol	Dianabol, Dialone
Fluoxymesterone	Ultandren	Android-F, Halotestin
Oxymetholone	Anapolon, Adroyd	Anadrol 50
Stanozolol	Stromba, Winstrol	Winstrol
Ethylestrenol	Orabolin	Maxibolin
Norethandrolone	Nilevar	Nilevar
Metenolone	Primobolan Depot	
Mesterolone	Pro-Viron	

a The use of trade names is for product identification purposes only and does not imply endorsement.

- They have the capability to be absorbed into the gastrointestinal tract, usually the stomach or the proximal small bowel.
- They are able to withstand total degradation by the liver enzymes.
- They have a short half-life. In order to maintain the appropriate blood concentration the drug must be taken several times a day.
- Following the initial pass through the liver the drug must still retain the capacity to bind with the AR sites present in skeletal muscle.

Parenteral preparations do not require a 17α-alkyl group, but the 17β-hydroxyl group is esterified with an acid moiety to prevent rapid absorption from the oily vehicle, which is usually arachis oil and benzyl alcohol.[21]

Injectable oil-based preparations are characterized by the following:

- They have a much longer half-life than oral or water-based injectable steroids, usually in the order of 1–4 weeks.
- They are normally comprised of a mixture of arachis/sesame seed oil and alcohol, which forms the basis of the oil-based carrier.
- The concentration of AAS esters range from 25 to 250 mg/mL, per injection dosage.
- They have a degree of pain at the injection site.
- They have a slow absorption rate into the blood stream, so that the liver experiences a low concentration of the drug compared with substances taken orally. This may be associated with less incidence of liver disorder than that associated with oral preparations.[22]
- Basic alteration of the steroid ring at the 1β, will prolong the effect of the drug.

Non-pharmaceutical water-based testosterone suspensions for injection are advertised on bodybuilding websites and cheats in sport may find these attractive as, in theory, they should be relatively short acting. Non-pharmaceutical-based preparations, whether oil or water based, may be a particular hazard to health as the contents may not have been prepared under sterile conditions. Injectable water-based steroids are characterized by the following:

- They have a half-life of 1–2 weeks, therefore they require more frequent injections.
- They have less discomfort at the injection site because of a lower viscosity compared with the same oil-based anabolic agent.
- They have a molecular structure that is in most cases identical to oil-based preparations.
- They have the ability to mix with other water-based anabolic steroids or water-based vitamins, e.g. vitamin B_{12}.[23]

Typical injectable anabolic steroids available in the UK, Europe and the US, are presented in table II.

Transdermal formulations are invariably testosterone based, legitimately designed for replacement therapy, and include the patch and hydroalcoholic gels, to be applied on a daily basis. Other short-acting testosterone preparations include those designed to be administered by the sublingual or buc-

Table II. UK/European and US generic and trade names [a] of injectable anabolic steroids

Generic name	UK/Europe trade name	US trade name
Boldenone undecylenate	Vebonol	Equipoise
Drostanolone propionate	Masteron, Masteril, Metormon, Permastril	Drolban
Nandrolone decanoate	Deca-Durabolin	Androlone-D 200, Deca-Durabolin, Hybolin Decanoate, Nandrobolic LA
Nandrolone phenylpropionate	Durabolin	Anabolin, Androlone, Durabolin
Stanozolol	Stromba	Winstrol V
Testosterone enanthate	Primoteston -Depot, Testoviron -Depot	Andro LA 200, Andryl 200, Delatestryl
Testosterone cypionate	Depo-Testosterone	Andro-cyp, Andronaq LA, Andronate, Depotest
Testosterone propionate, phenylpropionate, isocaproate, decanoate	Sustanon	
Testosterone propionate	Testex Leo, Virormone	Androlan, Testex
Trenbolone acetate	Finaject, Finajet	Finajet, Finaplix-H

a The use of trade names is for product identification purposes only and does not imply endorsement.

cal route. Such short-acting formulations are of particular concern in sports subject to anti-doping tests.

AAS are abused by athletes during training and are therefore usually not taken during the actual competitive period, in an attempt to avoid detection. Being aware of the pharmacokinetics of a wide variety of preparations, knowledge of a drug's half-life and detection methods has made it previously possible for some athletes to 'pass the test'.[23] Since transdermal, sublingual and buccal preparations, even in large doses, can be cleared from the body in less than a week following withdrawal, oral preparations between 2–14 days, and water soluble 'injectables' after 4 weeks, it is possible to use these agents during periods of intensive training and test negative.

According to the World Anti-Doping Agency (WADA) statistics (2005), AAS are the most frequent adverse analytical findings in- and out-of-competition. Increased out-of-competition testing helps to combat the cheat who is using short-acting preparations and ceasing administration prior to competition in anticipation of testing.

Finally, there are designer steroids. In the field of drug control in sport, designer drugs can be considered as ones that are manufactured specifically to circumvent the doping tests, i.e. they are supplied in clandestine fashion and are not compounds that are advertised for the bodybuilding market. The attempted use of such has become a covert science in direct competition with advances in detection methods. This indicates a deliberate involvement of quasi-medical and even governmental agencies, in the promotion of drug abuse in sport. With respect to anabolic steroids, there are few known examples to draw on. Classified documents saved after the collapse of the German Democratic Republic revealed that since 1983 a pharmaceutical company had produced parenteral preparations of epitestosterone propionate exclusively for the governmental doping programme.[24] Epitestosterone is a steroid with no anabolic activity, but its administration with testosterone simultaneously or sequentially enables an athlete to manipulate the test for testosterone administration if the test is based solely on determination of a raised testosterone/epitestosterone (T/E) ratio (see section 4). One percent of testosterone is excreted unchanged, apart from conjugation to glucuronic acid, compared with ~30% of epitestosterone, and the T/E ratio approximates unity normally, but is raised in testosterone users. However, administration of these steroids in a ratio of ~30 1; T/E, e.g. as parenteral or oral (undecanoate ester) preparations will elevate plasma testosterone, but will not augment the T/E ratio, although the urinary T/luteinizing hormone (LH) ratio will be raised following testosterone administration.[25-27] More crudely, epitestosterone could simply be swallowed in anticipation of a drug test or even attempts be made to urinate over a finger that surreptitiously has epites-

tosterone residue on the surface. In an effort to counter such strategies, WADA have set a urinary threshold of 200µg/L for epitestosterone.

More recently, the Bay Area Laboratory Co-operative (BALCO) affair, in California, USA, attracted media attention due to the high profile of the athletes involved, not least because of a transdermal preparation ('The Cream') was supplied containing testosterone and epitestosterone, as well as a sublingual preparation of a new anabolic steroid tetrahydrogestrinone (THG), coded as 'The Clear'.[28] Underground chemists recently appear also to be accessing information concerning other steroids that were synthesized several decades ago by pharmaceutical companies, but were never marketed. Such steroids that have been detected to date are norbolethone[29] and madol[30] (madol is also referred to as desoxymethyltestosterone by the WADA-accredited laboratory in Montreal, who detected the administration of this steroid around the same time as the laboratory at the University of California, Los Angeles [UCLA]).

1.3 Therapeutic Use of AAS

Testosterone has potent androgenic as well as anabolic properties, therefore chemical modification of the basic testosterone molecule has formed the basis for the clinical application of synthetic AAS for anabolic purposes. Pharmaceutical companies initially developed these synthetic analogues of testosterone in order to treat catabolic medical conditions. The intention was to alter the chemical structure to maximize the anabolic and minimize the androgenic effect, to avoid virilizing side effects in both women and children in therapeutic doses. Nandrolone (19-nortestosterone) [figure 2] was the first synthetic analogue of testosterone to show a favourable degree of anabolic-androgenic dissociation in animal experiments to allow it to gain a licence for use in catabolic medical conditions.[31] In the UK, nandrolone was originally licensed for use in osteoporosis in post-menopausal women, aplastic anaemia and disseminated carcinoma of the breast. The clinical usefulness of the many synthetic anabolic steroids that were subsequently developed in revers-

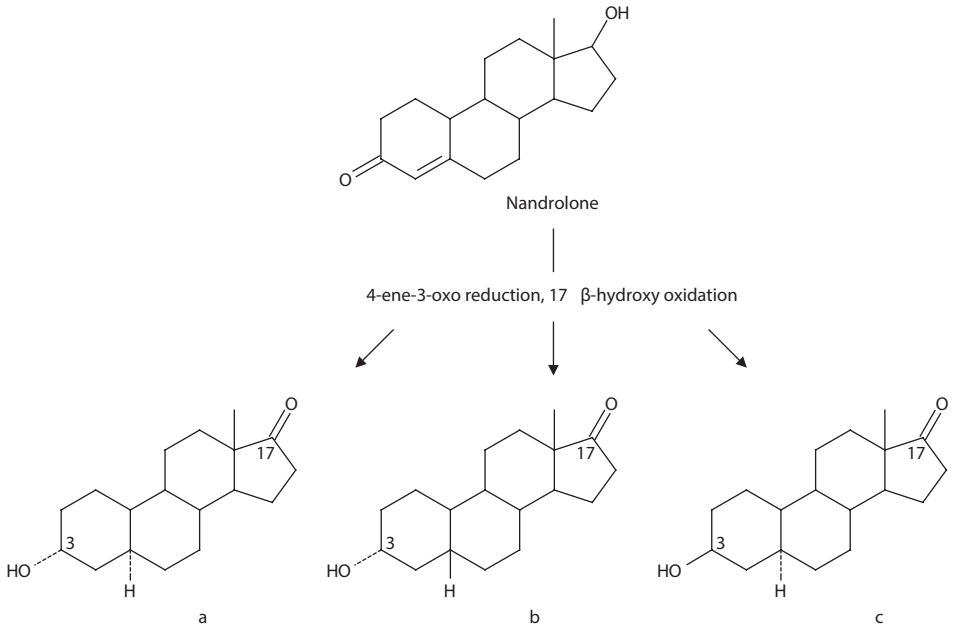

Fig. 2. Structures of the metabolites of nandrolone: (a) 19-norandrosterone (3 α-hydroxy-5 α-estran-17-one); (b) 3 α-hydroxy-5 β-estran-17-one; and (c) 19-norepiandrosterone (3 β-hydroxy-5 α-estran-17-one) [reproduced from Kicman and Gower, [3] with permission from the Ro yal Societ y of Medicine].

ing the catabolic state of patients, such as those with severe burns or wasting diseases, has not been realized based on the conclusions of previous reports. As a result, many anabolic steroids developed in the last century have been withdrawn as licensed products in the UK and numerous countries worldwide. Exceptions within the UK are:

- danazol and gestrinone (progestogens with anabolic-androgenic properties), which are used mainly for the treatment of endometriosis;
- oxymetholone, which has beneficial effects on damaged myocardium;[32]
- stanozolol, used in the treatment of aplastic anaemia;
- testosterone preparations (and also mesterelone but seldom used, if at all) for hormone therapy in male hypogonadism and castrates;[33]
- nandrolone decanoate for osteoporosis (but now not an advocated treatment).[33]

However, consideration of their therapeutic efficacy for anabolic purposes may need to be revisited based on recent reports, especially for the treatment of sarcopenia (loss of muscle mass and strength). Testosterone and synthetic anabolic steroids, such as oxymetholone, appear to be extremely useful in the treatment of HIV-related muscle wasting.[34-38] Nandrolone decanoate has been demonstrated to be effective in countering sarcopenia in patients receiving dialysis.[39,40] Trestolone (7α-methyl-19-norT) may be a promising new androgen therapy, for example in age-related sarcopenia.[41,42] AAS have also been used in catabolic states such as chronic obstructive pulmonary disease[43] and burns.[44]

Observational studies show that blood testosterone concentrations are consistently lower among men with cardiovascular disease, suggesting a possible preventive role for testosterone therapy. Short-term interventional studies show that testosterone produces a modest, but consistent, improvement in cardiac ischaemia comparable with the effects of existing anti-anginal drugs.[45] Such data would indicate that it is the level of androgen present that correlates with the presence of cardiovascular disease, as anabolic steroid abusers who administer excessive amounts over long periods of time have altered serum lipoprotein profiles, as found in groups with an increased risk of developing coronary artery disease (see section 1.5).

1.4 Non-Therapeutic Use of AAS

AAS increase muscle mass and strength.[46] However, no synthetic steroid has completely eliminated the androgenic effect, this is partly due to the fact that the androgenic and anabolic effects differ only in location and not in the mechanism of the steroid hormone action. Also, there is a body of evidence to suggest that there is only one type of active AR.[47] The steroids possessing the most potent anabolic effects are those with the greatest androgenic effects, such as nandrolone, metandienone and stanozolol.[48] A synthetic steroid may differ from the natural androgenic steroid testosterone, by alterations in its basic structure. These alterations include the addition of ethyl, methyl, hydroxyl or benzyl at one or more sites along the synthetic steroid structure.[49] The International Olympic Committee (IOC) Medical Commission was established in 1961, in an attempt to eradicate the use of drugs in sport.[50] In 1974, AAS became a banned class of compounds. It has subsequently been suggested that US track-and-field athletes were abusing AAS at this time.[51] Following the collapse of the Soviet Union and the defection of scientists to the West and with the acquisition of clandestine German Democratic Republic (GDR) government documents, as previously discussed in section 1.2, the GDR had established a systematic doping programme for thousands of athletes from the early 1960s until 1990.[24]

1.5 The Dangers of AAS Use

Psychological effects appear to be the only adverse consequence to an acute overdose of AAS, but long-term administration leads to disturbance in the hypothalamic-pituitary-gonadal axis and the suppression of LH and follicle-stimulating hormone. This can result in infertility, testicular atrophy (in males) and disturbances of the menstrual cycle and secondary amenorrhoea (in females). The severity of adverse effects depends on which steroid or com-

bination of steroids are being abused, the dosage and duration of administration. The adverse effects can be divided into which end organ is affected; the brain and therefore the psyche,[52,53] the skin (cystic acne), the liver (adenoma, carcinoma, peliosis hepatis, cholestatic jaundice), the cardiovascular system (atrial fibrillation and alteration in lipid profile and arterial structure and function)[54-56] and the gonadal systems, including the prostate and testes in males and the ovaries in females.[57]

The main physiological side effects reported by AAS users are presented in figure 3. The main psychological side effects reported by AAS users are presented in figure 4.

In 1994, recreational bodybuilders attending a Welsh needle-exchange clinic completed the 'Buss-Durke Inventory' on feelings of hostility/aggression questionnaire. Between AAS cycles they were AAS free. Subjects reported significantly higher feelings of aggression towards objects, verbal aggression and aggression during training (but not physical aggression towards people), during the 6- to 14-week AAS periods. Other changes during AAS administration periods included significantly higher feelings of alertness, irritability, anxiety, suspiciousness and negativism.[60]

1.6 The Prevalence of AAS Use

A questionnaire study conducted in 1992 in the South Wales area of the UK[61] found that 39% of 160 respondents were regular AAS users.

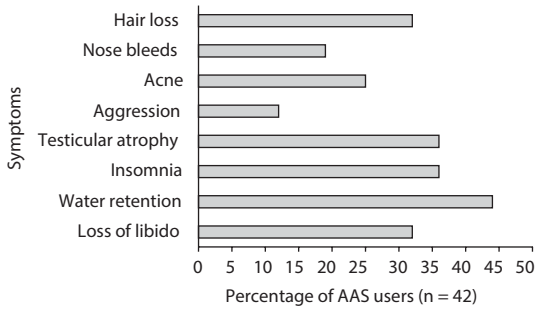

Fig. 3. Physiological side effects reported by anabolic-androgenic steroid (AAS) users (reproduced from Grace et al., [58] with permission from Taylor & Francis Ltd, http://www.tandf.co.uk/journals).

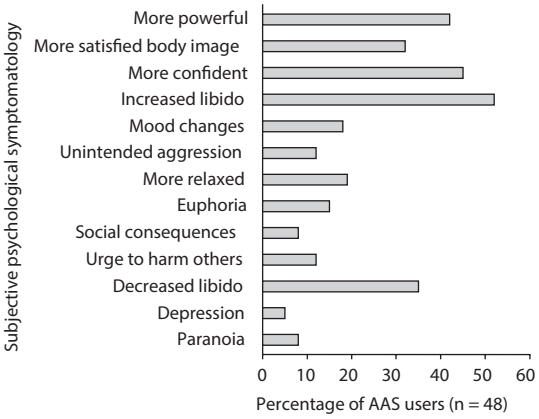

Fig. 4. Psychological side effects reported by anabolic-androgenic steroid (AAS) users (reproduced from Graham et al., [59] with permission).

In 1993, a report investigating use of anabolic steroids in 21 gymnasiums in England, Scotland and Wales found that 119 (9.1%) of the 1310 male respondents to the questionnaire and eight (2.3%) of the 349 female respondents had taken anabolic steroids. The youngest user was aged 16 years. The prevalence of use of anabolic steroids in the gymnasiums ranged from zero (in three gymnasiums) to 46% (28 of 61 respondents). The response rate to the questionnaire was 59% (1677 of 2834).[62]

In the South Wales area in 1996,[63] AAS use was reported in 176 users (171 men and 5 women) and highlighted that 37% of respondents indicated a need for more knowledge among drug workers and a less prejudiced attitude from general practitioners.

In 1996, the Canadian Center for Drug-free Sport estimated that >83 000 11- to 18-year-old Canadians (2.8% of the respondents) were estimated to have used AAS in the year before the survey to improve sport performance. Twenty nine percent reported that they injected them and 29.2% reported sharing.[64]

In another questionnaire study conducted in 1997 in the South Wales area,[65] 100 AAS-using athletes reported high rates of polypharmacy (80%) with a wide array of drug use amongst this sample group. In the South Wales area in 2001, 69% of 107 respondents of hardcore gym weight-lifters, were identified as abusing AAS, highlighting that AAS abuse

was certainly not on the decline.[58] Recent surveys conducted in 2005 in the South Wales area[66] and 2006 online in AAS popular websites,[67] estimate that steroids are being abused by >1 million UK citizens and >3 million Americans, with significant increases in female users.

1.7 Medical Support for AAS Users

Needle-exchange clinics have been established for AAS users, distinct from conventional drug addicts, in an attempt to educate individuals hygienic use of such drugs. Drugs in Sport Clinic and User's Support (DISCUS) was established by a UK general practitioner, but attracted opposition from the medical authorities who believed such drug use was being condoned, rather than the promotion of harm minimization. AAS are now the third most commonly offered drugs to children in the UK, following cannabis and amphetamines.[68]

Clinics have also been established, outside sport, for drug addicts, who are using AAS more frequently. In Massachusetts, USA, prior AAS use appears to be common, but under-recognized, among men entering inpatient substance abuse treatment, especially those with opioid dependence. AAS use may serve as a 'gateway' to opioid abuse in some cases and may also cause morbidity in its own right.[69]

The 'Kaleidoscope project', Wales, UK, under the auspices of the Gwent Specialist Substance Misuse Service (GSSMS), UK, has identified an enormous increase in AAS use in drug addicts, who have turned to AAS as a quick fix for their symptoms of anorexia, following recreational drug use. From the period 2005–6, 700 clients attended from 3000 clients registered with the clinic. Sixty eight percent (478 clients) agreed to answer a questionnaire on injecting AAS and other ergogenic aids. Eighteen percent (185 clients) admitted to injecting AAS. Twelve percent (55 clients) admitted to injecting AAS and growth hormone. The youngest AAS user was 18 and the oldest AAS user was 59 years of age. In this time period, they were supplied with 256 579 needles and syringes, equating to one needle per syringe per day.

2. Methods of Using AAS by Athletes

Personal discussions with users and articles in bodybuilding magazines has highlighted the following non-scientific methods of use:

1. Stacking/blending/shotgunning: using more than one drug at the same time. Individuals frequently use several anabolic steroids simultaneously, mixing oral and/or injectable types, sometimes using drugs such as stimulants or painkillers. The rationale for stacking is a belief, which has not been tested scientifically, that different drugs have a synergistic effect on muscle size.
2. Tapering: gradually decreasing intake.
3. Plateauing: when a drug becomes ineffective at a particular level another drug is taken.
4. Cycling: using different drugs for a fixed period of usually 6–12 weeks, stop administration for the same period of time, and then repeat the cycle.
5. Pyramiding: maximizing dosage within a fixed space of time and then minimizing the drug in the same time frame.

The stacking of AAS preparations has been the most commonly used method by bodybuilders. This concept of using smaller doses of different drugs with similar actions has been well established in the medical field. The overall idea has been to minimize the potential side effects and maximize the effectiveness of the regimes. Taking smaller dosages of multiple drugs may reduce the chance of liver abnormalities when compared with huge dosages of a single drug.[1]

There is also evidence to suggest that there may be an increased liver tolerance to a smaller dose of multiple drugs compared with a large dose of a single anabolic agent. This increased tolerance would allow the liver to increase its degradation of one particular drug, in much lower concentrations. This may also facilitate the administration of multiple anabolic agents for longer periods, minimizing the plateauing effect.[23]

Table III. Typical anabolic-androgenic steroid regime (number of doses) of a first-time user

Drug	Dosage (route of administration)	Week 1	2	3	4	5	6	7	8	9	10	11	12
Sustanon	250 mg/mL/wk (IM)	1	1	1	1								
Metandienone	5 mg tablet/d (PO)	6	6	6	6	6	6	6	6	6	6	6	6
Nandrolone decanoate	100 mg/mL/wk (IM)				2	2	2	2	2				
Stanozolol suspension	50 mg/mL/wk (IM)									3	3	3	3

IM = intramuscular (parenteral); PO = oral.

3. Dosages of AAS Used by Bodybuilders

Bodybuilders are known to misuse enormous dosages of AAS, which have contributed to dyslipoproteinaemia, hyperhomocysteinaemia and premature death.[70] Table III and table IV list examples of the illogical cocktails and current dosages that are being promoted, equating to excessive weekly doses of thousands of milligrams.

4. Detection of AAS

4.1 Sample Collection from Athletes

Urine is the preferred biological fluid for detection of drugs of abuse. Independent sampling officers in the UK must witness a urine sample being delivered into a collection vessel. The sample kits and the chain-of-custody documentation must be able to withstand legal challenges. The athlete must pass urine equally into two coded glass bottles, each assigned a unique code. The samples are designated 'A-sample' approximately 70 mL and 'B-sample' approximately 30 mL for confirmatory analysis. The bottles are sealed using tamper-proof lids and then sent to the laboratory within a sealed shipping container. The independent sampling officer is also required to measure the pH and specific gravity of the urine.

When the samples reach the laboratory, the A-sample seal is broken and the urine analysed. If the A-sample fails a drug test, the B-sample seal is broken at a later date and the analysis repeated. The failed drug sample athlete or sports person has the option to witness this procedure with an independent scientific expert and a legally qualified representative.

Urine specimens are collected from individuals at multiple locations within a country, therefore transport difficulties may lead to delays of several days. Storage of samples in IOC-accredited laboratories is at +4°C or −20°C. In the UK, samples are stored at −20°C. AAS are not thermally labile, but there has been concern about the possibility of microbial production of testosterone at temperatures that can lead to urine degradation causing positive urinary results.[71] Markers of degradation include a pH >8.3 and/or a high level of 5α-androstenedione and free steroids that were originally glucuronidated (androsterone; etiocholanolone). In 2002, it was demonstrated that testosterone can be elevated by inoculation of urine with *Candida albicans*, but the increase was minor and of little evidential value, i.e. samples would not test positive.[72] It has been argued that adding a preservative to urine samples may compromise the test as an adverse finding may be challenged on the basis that failure of the test was because of adulteration with a foreign material. In our opinion, this argument appears to be weak, given the WADA protocol for blood collection, where blood can be drawn into a tube containing a serum separator gel and a clotting activation factor.

4.2 Analysis

In human sports, the IOC Medical Commission introduced anabolic steroids as a banned class in April 1974 following the development of a screen for the 17α-alkylated orally active drugs. The name of this banned class was amended to anabolic agents in the 1990s to incorporate out-of-competition testing for clenbuterol and other β2-agonists, which are also considered to have anabolic activity. In 1999, the WADA was set up as a foundation under the initiative of the IOC with the support and participa-

Table IV. Anabolic-androgenic steroid regime (number of doses) of a current UK champion

Drug	Dosage (route of administration)	Week															
		16	15	14	13	12	11	10	9	8	7	6	5	4	3	2	1
Omnadren	250 mg/mL/wk (IM)	2	2	1	1	1	2										
Testosterone enanthate	250 mg/mL/wk (IM)			1	1	1	1										
Nandrolone decanoate	100 mg/mL/wk (IM)	2	2	2	2	2	2										
Metandienone	5-mg tablet/d (PO)	10	10	10	10	10	8	6	4								
Sustanon	250 mg/mL/wk (IM)					1											
Testosterone propionate	100 mg/mL/wk (IM)													4	4	4	4
Testosterone cypionate	250 mg/mL/wk (IM)								2	2	2	2	6	6	6	6	4
Mesterelone	25 mg tablet/d (PO)											1	1	1	2	2	2
Growth hormone (somatropin)	IU/d (SC)								2.5	2.5	2.5	5	5	10	10	10	
Clomiphene citrate	50-mg tablet/d (PO)								0.5	0.5	0.5	0.5	0.5				
Tamoxifen	20-mg tablet/d (PO)	1	1	1	1	1	1	1	1	1	1	1	1	2	3		
Clenbuterol	20-µg tablet/d (PO)								5	5	5	5	5	5	5	5	5
Stanozolol suspension	50 mg/mL/wk (IM)											3	4	5	4	4	3
Anastrazole	1-mg tablet/d (PO)													1	1	1	1
Methenolone enanthate	100 mg/mL/wk (IM)											3	3	3	3	3	3
Aminoglutethimide	250-mg tablet/d (PO)														1	1	1
Tri-iodothyronine (T_3)	20-µg tablet/d (PO)											2	3	4	2	3	4
Tetra-iodothyronine (T_4)	25-µg tablet/d (PO)											4	6	8	4	6	8
Ephedrine	30-mg tablet/d (PO)							3	3	6	6	8	8	8	8	8	8

IM = intramuscular (parenteral); PO = oral; SC = subcutaneous.

tion of intergovernmental organizations, governments, public authorities and other public and private bodies fighting against doping in human sport. Under WADA, the rules and technical documents concerning anabolic steroids (and other drugs) are constantly evolving and for up-to-date information the reader is strongly advised to access the WADA web site (www.wada-ama.org).

In 1969, the first application of radioimmunoassay (RIA) for the measurement of steroids in biological fluids was published.[73] At that time there were 14 licensed orally active AAS. These steroids had a common 17α-alkyl substituent (12 with a 17α-methyl group and two with a 17α-ethyl group). The method of detection used was to raise immunoglobulins that could target these two alkyl functions.[74] Any presumptive positive samples could then be analysed by gas chromatography-mass spectrometry (GC-MS) for confirmatory identification.[75] A trial test targeting the orally active alkylated steroids was introduced at the Commonwealth Games in New Zealand in February 1974. Nine of 55 samples failed the immunoassay screen and seven samples confirmed positive by GC-MS. In April 1974, the IOC Medical Commission introduced AAS as a banned class of compounds in the Anti-Doping Code. In 1979, RIA screens were developed to detect the presence of nandrolone in urine, this AAS being manufactured for intramuscular injection.[76] Subsequently, RIAs were developed for nandrolone metabolites.[77]

In the early 1980s, improvements in the MS allowed IOC-accredited laboratories to develop specific and comprehensive screens able to detect ≤1 μg/L of an AAS and its metabolite in urine.[78] The radioimmunoassay screening procedures to detect administration of orally active and injectable anabolic steroids were replaced in a few years by analysis employing GC-MS. The introduction of a benchtop quadrupole gas chromatograph-mass spectrometer offered specificity, sensitivity and excellent data handling, together with a reduction in cost compared with previous MS instruments. Increased chromatographic resolution was obtained with the use of superior capillary columns, and increased sensitivity was achieved by using electron impact MS in the selected-ion monitoring mode. In addition, with automated sample injection and short chromatographic run times (typically 20–30 minutes because of oven temperature programming), large sample throughput made GC-MS the preferred analytical tool. Since AAS are often metabolized extensively, with little parent steroid being excreted into the urine, identification of metabolites for drug monitoring purposes is required. It is important to note that the named compounds listed under adverse findings reflect interpretation by the sporting authority WADA, of the steroid that had been probably administered rather than what the laboratory declares, which is often a diagnostic metabolite, e.g. 19-norandrosterone is the chosen diagnostic metabolite of nandrolone (figure 2). For many steroids, there is more than one diagnostic metabolite. The metabolism of many AAS in humans, the chemical synthesis of the major metabolites and their GC retention times and characteristic mass spectrums, was reviewed in 1993 by Schanzer and Donike.[79]

GC-MS continues to be the predominant analytical approach adopted by WADA-accredited laboratories, screening for anabolic steroids it is supplemented by the application of more sophisticated MS (currently using magnetic sector instruments) or MS/MS, [80] and more recently still by liquid chromatography-MS/MS (LC-MS/MS). The developments in LC-MS/MS are encouraging and the use of this technique is proven as a powerful aid to analyse for anabolic steroids, for example, for the potential screening of future unknown designer steroids.[81] In 2004, the designer steroid THG was identified by Catlin et al., [28] of the WADA accredited laboratory within UCLA, and several international athletes tested positive for this drug and were banned from competition. The American nutritional company 'BALCO' has been prosecuted for federal offences for the manufacture of the drug and the illegal supply to athletes. WADA-accredited laboratories rapidly screen for the presence of THG in urine by LC-MS/MS. Even so, currently there is no LC-MS/MS procedure that has been developed to date that can match that of GC-MS for the comprehensive

screening of the numerous anabolic steroids and their metabolites in urine. Primarily, this is because the chromatographic resolution of high-performance liquid chromatography columns is far inferior to that of GC columns. The development of ultra-performance liquid chromatography-MS (UPLC-MS) may possibly help to address this issue, offering the potential advantage of a screening procedure that avoids time-consuming extraction, glucuronide hydrolysis and derivatization steps necessary for analysis by GC-MS.

Effective tests for detection of synthetic (foreign) AAS resulted in a large increase in the use of the hormone testosterone over the last 20 years or so, on the assumption that a test could not be produced to detect a substance that the body produces naturally,[82] despite its unfavourable androgenic potency compared with the synthetic drugs. A test based on determining whether a urine concentration of testosterone exceeds the upper limit of a reference range would be insensitive because of the wide variability in excretion associated with a single-pass urine collection. To overcome the problem, in 1979, Brooks et al.,[76] in anticipation of athletes switching to the use of testosterone to evade detection, introduced the concept of the hormone ratio. The use of a ratio was considered to be independent of urinary flow rates. The ratio of testosterone to LH (T/LH) was originally proposed, but this necessitates an immunoassay procedure for LH and, in retrospect, immunoprocedures are generally accepted as not having the discriminatory power of MS for evidential analysis,[83] although it is useful as an ancillary test. In addition, LH secretion will be suppressed in women using oral contraceptives, and therefore the measurement of urinary T/LH is only applicable to men. In 1982, the test adopted by the IOC for detection of testosterone administration was based on the GC-MS determination of the ratio of testosterone to its 17α-epimer, epitestosterone, following glucuronide hydrolysis (often referred to as the T/E ratio).[84] The T/E decision limit was derived empirically from an observed distribution of measurements in specimens collected from a large number of individuals. In healthy men and women, the median T/E ratio approximates unity, but supra-physiological doses of testosterone cause an increase in the ratio as a result of increased excretion of testosterone, the laboratory reporting threshold chosen being recently lowered by WADA from a T/E ratio of 6 to a T/E ratio of 4.

In the case of a T/E ratio >4, a reliable method of detection (e.g. isotope ratio mass spectrometry [IRMS]) has not determined the exogenous source of the substance, further investigations may be conducted to ascertain whether a doping offence has occurred. Usually it is concluded that surreptitious testosterone administration has happened, but occasionally the athlete may have a physiologically increased ratio, being a 'natural biological outlier'.[85-90] In addition, the possibility of a pathological condition, e.g. a T-secreting tumour accounting for an augmented ratio in a sports competitor must not be neglected, although there is no such case report described in the scientific literature (possibly because such tumours are most likely to be of testicular origin and that these also secrete epitestosterone).

With an adverse finding, investigating the T/E results from previous and subsequent tests, i.e. assessing the T/E intra-individual (within-subject) variability, is useful in determining whether an offence has occurred. However, to date, there are very limited data on intra-individual variation of T/E ratios presented in the peer-reviewed literature. In their article on detection of testosterone and xenobiotics, Catlin et al.,[91] have reviewed the data on intra-individual variability. They present their criteria for determining whether testosterone doping has occurred in men, based on T/E ratio data from drug-free males who showed an intra-individual coefficient of variation (CV) of <60% (variation from the collection of three or more samples of urine taken at monthly or greater intervals). In contrast, they report an example of a case of an athlete with an initial T/E ratio of 8.2, and after being sampled four times had a CV of 114%, indicating that testosterone administration had occurred. This pattern was considered to be typical of an individual who is caught and then discontinues testosterone administration. In these authors' experience, most testosterone users who provide three or more urine samples

or no regard for the consequences. Polypharmacy by self-prescription is prevalent in this sector. Most recently, AAS use has filtered through to 'recreational street

have a CV of >60%. In 1997, individuals with a CV <60% and a T/E ratio between 6 and 10, were tentatively classified as 'naturally increased'[91] (the T/E threshold was 6 : 1). WADA in their Technical Document (TD2004EAAS) state that "normal variation of up to 60% may be expected" and that "using appropriate statistical evaluation is found to be significantly different, that will constitute a proof of the administration of a source of testosterone." In the event that previous T/E results are not available, three further unannounced tests should be carried out, preferably within a 3-month period following the report of the suspicious analytical result.

WADA have also adopted the isotope ratio approach as an important tool to aid the determination of natural androgen administration, particularly testosterone.[92-102] The natural abundance of ^{13}C is ~1.11%, the human diet consisting of plant and animal sources, with varying ^{13}C isotope content relative to ^{12}C due to isotopic fractionation in biological systems.[103] Endogenously produced steroids should thus have a $^{13}C/^{12}C$ that reflects an average of that in the carbon sources ingested (figure 5). Testosterone used in pharmaceutical formulations is now generally synthesized from soya-bean stigmasterol, which has a smaller ^{13}C content. Detection of misuse of testosterone and related androgens can therefore be based on assessing whether there is a reduction in the relative carbon isotope content of targeted urinary steroids. The analytical probe used is GC/combustion/IRMS (GC/C/IRMS), with a number of recent articles[92-94] reporting its potential for detecting testosterone administration in human sport. This states that the isotopic ratios ($^{13}C/^{12}C$) of the relevant metabolites of such androgens should whenever possible be measured each time an elevated parameter of the steroid profile is estimated from the Screening Procedure or Confirmation Procedure and reported to the Testing Authority as having been determined.[103] The results of the IRMS analysis and/or of the steroid profile measured by GC-MS shall be used to draw conclusions as to whether a doping violation may have been committed. WADA recommend IRMS analysis on a urine sample with a T/E ratio of >4, or where concentrations of the following androgens exceed concentration limits (in parentheses): testosterone or epitestosterone (200 ng/mL), DHEA (100 ng/mL), androsterone or etiocholanolone (10 000 ng/mL).

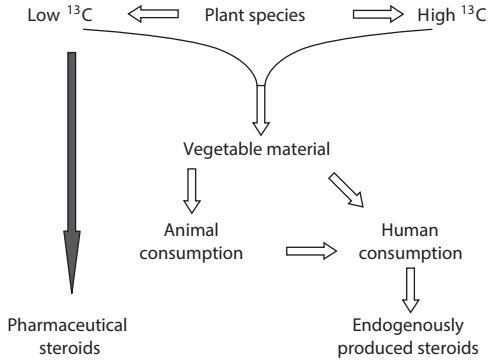

Fig. 5. Endogenously produced steroids have a $^{13}C/^{12}C$ content that reflects an average of that in the carbon sources ingested, whereas testosterone in pharmaceutical formulations are synthesized from soy, which has a smaller ^{13}C content (a more negative delta value). The dark arrow represents the direct route to pharmaceutical steroids containing low levels of ^{13}C (reproduced from Kicman and Gower, [3] with permission from the Royal Society of Medicine).

The lowering of the threshold for the T/E ratio from 6 to 4 has led to intense discussion with the accredited laboratories and raised questions. According to the International Federation of Association Football (FIFA) database 2005, none of the samples with elevated ratios between 4 and 6 showed evidence of exogenous intake in the GC-IRMS tests. Legal difficulties arise in cases where the T/E ratio is between 4 and 6, but GC-IRMS does not verify exogenous intake.[104] The most likely reason for this disparity is because IRMS demands a larger amount of analyte injected compared with standard GC-MS and for this reason metabolites of testosterone are usually targeted for isotopic analysis rather than testosterone itself. Metabolism from an exogenous source of testosterone appears to be similar to that of endogenous testosterone, where a large proportion (~30%) is converted to androsterone and etiocholanolone (figure 2) with only a very minor proportion (~1%) being excreted as testosterone (mainly as glucuronide conjugate). Following glucuronide hydrolysis and extraction procedures, an athlete will have failed a dope test if the GC/C/

of a more active androgen, the 5α-reduced steroid dihydrotestosterone (DHT). Physiological studies of DHT binds to the AR more tightly than testoster one, primarily as a result of stabilization of the AR

IRMS values of androsterone and/or etiocholanolone in a sample are more negative than a chosen cut-off value. Alternatively, a value that is suspiciously negative, but more positive than the chosen cut-off, might require further samples collected on separate occasions also to be measured by IRMS to determine the 'usual' delta value for that individual. The problem with the approach of measuring androsterone and etiocholanolone is that the exogenous portion of these 17-oxosteroid metabolites is diluted by an endogenous source that is not suppressed with testosterone administration. It is well recognized that the clinical assay used for urinary 17-oxosteroids was a poor index of androgenic status, since about two-thirds originates from adrenal steroid metabolism.[105,106] The adrenal steroids secreted that are metabolized to urinary androsterone and etiocholanolone glucuronides are DHEA sulphate and DHEA (which can be peripherally interconverted), and androstenedione. This adrenal contribution will attenuate the sensitivity of the IRMS test for etiocholanolone and androsterone, especially where smaller doses of testosterone are being administered or when the sample collected is on the tail end of the elimination of testosterone. To address this problem, a number of laboratories are now developing methods so that the parent steroid, testosterone itself, can be analysed.

5. Non-Steroidal Hormones, Human Chorionic Gonadotrophin and Human Growth Hormone

Athletes abusing drugs up to the time of competition have used human chorionic gonadotrophin (hCG). hCG is a polypeptide glycoprotein hormone produced by the female placenta, having the action of pituitary LH and has been used by bodybuilders in an attempt to prevent testicular atrophy during prolonged administration of AAS. In 1987, identification of hCG in sports samples led to its banning by the IOC Medical Commission.[107]

The use of hCG results in an elevation of testosterone and epitestosterone, since the testis contributes approximately 95% of the pool of urinary testosterone and epitestosterone glucuronide in eugonadal males. Consequently, there is an equal stimulation of urinary testosterone and epitestosterone and the T/E ratio remains relatively unaltered.[108] The rise in serum testosterone is modest, being only 2- to 3-fold in healthy eugonadal men. More insidiously, hCG co-administered with testosterone can suppress the urinary T/E ratio elevation by stimulating epitestosterone production and may confound the testing procedure in comparison to taking testosterone alone.[109] A validated immunoassay is required to detect and quantitate hCG. For confirmation, a second different immunoassay of hCG is required, which may lead to variance in results due to difference in immunoglobulin specificity between kit manufacturers. A recommended detection limit of 10 IU/L in ultrafiltered urine samples, above which a sample is positive was recommended using the Serono MAIAclone assay.[110] Currently there is no reporting threshold set by WADA, but there is a required performance limit where all the accredited laboratories must be able to detect a minimum of 5 IU/L. If methods based on MS for endpoint measurement are to achieve the same sensitivity associated with immunoassays for protein hormones, then they may be adopted for confirmatory analysis.[80] The diagnostic capability of MS has been shown by the enzymal lysis of hCG, using matrix-assisted laser desorption ionization time of flight (MALDI-TOF)/MS.[111] Subsequently, methods for the detection of low concentrations of urinary hCG by LC-MS have been developed based on analysis of trypsin digests of extracts from immunoaffinity trapping and analysis.[112] Following on from this work,[113] a limit of detection corresponding to that of 5 IU/L of urinary hCG has been achieved. The approach of immunoaffinity trapping and concentration of digested sample extract prior to MS analysis can demonstrate similar analytical sensitivity to that of immunoassay. Although such an approach confers the huge advantage of informative data, a major disadvantage is that it is relatively slow and labour intensive.

Blood testing is required to identify the abuse of human growth hormone (hGH), which is a protein hormone with anabolic properties. In growth hor-

substitution at C-17 confers oral or depot activity (reproduced from Kicman and Gower, Medicine). IM = intramuscular.

[3] with permission from the Royal Society of

mone deficiency, recombinant hGH is a potent anabolic hormone that stimulates the intracellular transport of amino acids and causes nitrogen retention and anabolism.[114] In fit young men and women, however, current research has demonstrated no statistically significant increase in muscle size or strength with recombinant hGH administration.[115,116] It is possible that larger doses over a longer time may achieve the 'desired effect', but it is much more likely that such a regime would be detrimental to health and athletic performance because of the manifestation of symptoms expected with 'iatrogenic' acromegaly. To date, rhGH is the most difficult drug to detect using established drug testing protocols,[117] despite using sophisticated logarithmic calculations of insulin-like growth factor-I and N-terminal extension peptide of procollagen type III,[118] both of which are increased markedly in response to growth hormone administration and are claiming 86% chance of success in males and 60% in females. However, this is assuming individuals are using supraphysiological doses of growth hormone, leaving a minimum window of opportunity of 14%.

6. Recommendations in Detection Procedures

The existing arrangements have proven successful, some offenders have been deterred, and prosecuted, but there is still potential for evasion with some anabolic agents.[119] In 1991, Voy [120] suggested that the following principles could be incorporated into a more sophisticated drug testing regime:

- Testing must be independent, sampling must be carried out by the appropriate officers, independent of governing bodies and trained in IOC procedures. This would ensure that sample collections are above suspicion.
- Testing should be more effective, rigorous and entirely random. The selection of individuals to be tested must be varied and unpredictable, including the possibility of 100% testing during competition. During the training phase, athletes should be regularly called upon for testing. The system used should be effective and efficient, inspiring confidence and respect.
- Competitors in all sports must be required to make a personal declaration of willingness to undertake tests during training and competition. Athletes who fail to comply should not receive support or grant aid from the Sports Council, the Sports Aid Foundation, the British Olympic Association and the National Coaching Foundation. In addition, drug users should not be allowed to represent their country.
- Penalties for taking drugs should be effective and consistent.
- The role of the drug advisory groups should be enhanced.
- There should be wide publicity relating to legal actions taken against offenders, and greater information available outlining the different offences that are committed by athletes. Education and prevention may be key strategies.

7. Current World Anti-Doping Agency Out-of-Competition Testing Programme

WADA tested 3114 athletes in 2005, compared with 1848 athletes in 2004. They conducted blood and urine testing according to the 2005 list. In addition, World Championships in sports such as athletics, aquatics and weight-lifting meant that testing was also increased in these sports compared with previous years.

In 2005, there were a total of 61 adverse analytical findings (AAFs) and two other anti-doping rule violations (ADRVs), as compared with 19 AAFs and four other ADRVs in 2004.

The 2005 figures include several elevated T/E ratios of >4, which were not reported in previous years when the threshold was 6, partially accounting for the increased number of AAFs in 2005. However, there is a significant increase in other AAFs, such as those for steroids. WADA's primary goals are to establish a level playing field for athletes worldwide, to ensure that all athletes are subject to the same anti-doping protocols.

Rather than using random selection to pick all athletes to be tested, WADA has adopted a scientific

ments, as circulating testosterone would be expected to increase. The plasma concentration of testosterone will not render ineffective by degradation.

approach and selects a significant proportion of athletes based on several key factors, including their recent performance, history of doping and vulnerability to the temptation to take performance-enhancing substances. WADA does not have its own sample collection personnel, but works in partnership with selected sample collection authorities worldwide. Samples are always sent to WADA-accredited laboratories. In 2005, WADA out-of-competition testing covered 40 sports. Athletes from 119 countries were tested, and testing was conducted in 70 countries.[121]

8. Conclusions

Implementing testing procedures is difficult since few national sporting bodies have the financial resources available to make the programmes effective. It has not extended into competitive bodybuilding, which has remained largely immune compared with sports such as athletics, in which the sports council has spent significant sums on testing programmes.

It is possible that past surveys have been skewed by the concentration on hard-core gymnasia. Alternatively, with the prosecution of high-profile athletes and the administration of lighter sentences to obtain co-operation in identifying sources of drug use and drug users, the extent of such abuse is only just becoming apparent.

A controversial solution that has been called for; the introduction of a chemical level playing field, such as an Olympic Games where athletes use doping agents freely, under medical supervision. Such a controlled environment could contribute to scientific research and minimize the risks to the athletes.[122,123]

This has been fiercely contested by anti-doping supporters, citing that the main stakeholders, i.e. the pharmaceutical companies, appear to be indifferent to the misuse of their performance-enhancing products by athletes for non-medical purposes.[124]

The war against drug abuse within sport continues.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this manuscript. The authors would like to thank Mr Gary Biddiscombe from the Kaleidoscope Project, Wales, UK, and Mr Mike Mallett from the Gwent Specialist Substance Misuse Service (GSSMS), Wales, UK, for their data on AAS use by drug addicts.

References

1. Haupt HA, Rovere GD. Anabolic steroids: a review of the literature. Am J Sports Med 1984; 12: 469-84
2. Shahidi NT. A review of the chemistry, biological action, and clinical applications of anabolic-androgenic steroids. Clin Ther 2001; 23: 1355-90
3. Kicman AT, Gower DB. Anabolic steroids in sport: biochemical, clinical and analytical perspectives. Ann Clin Biochem 2003; 40: 321-56
4. Wilson JD, Leihy MW, Shaw G, et al. Androgen physiology: unsolved problems at the millennium. Mol Cell Endocrinol 2002; 198: 1-5
5. Janne OA, Palvimo JJ, Kallio P, et al. Androgen receptor and mechanism of androgen action. Ann Med 1993; 25: 83-9
6. Bruchovsky N, Wilson JD. The conversion of testosterone to 5-alpha-androstan-17-beta-ol-3-one by rat prostate in vivo and in vitro. J Biol Chem 1968; 243: 2012-21
7. Deslypere JP, Young M, Wilson JD, et al. Testosterone and 5 alpha-dihydrotestosterone interact differently with the androgen receptor to enhance transcription of the MMTV-CAT reporter gene. Mol Cell Endocrinol 1992; 88: 15-22
8. Wilson JD, Griffin JE, Russell DW. Steroid 5 alpha-reductase 2 deficiency. Endocr Rev 1993; 14: 577-93
9. Kroon FJ, Munday PL, Westcott DA, et al. Aromatase pathway mediates sex change in each direction. Proc Biol Sci 2005; 272: 1399-405
10. Ruckzika L, Wettstein A, Kaegi H, et al. Sexual hormone VIII Darstellung von Testosterone unter Anwendung gemischter Ester. Helv Chim Acta 1935; 18: 1478
11. Di Pasquale MG. Anabolic steroid side-effects: facts, fiction and treatment. Warkworth (ON): MGD Press, 1990
12. Cicardi M, Bergamischini L, Tucci A, et al. Morphological evaluation of the liver in hereditary angioedema patients on long-term treatment with androgen derivatives. J Allergy Clin Immunol 1983; 72: 294-8
13. Van Eenoo P, Delbeke FT. Metabolism and excretion of anabolic steroids in doping control: new steroids and new insights. J Steroid Biochem Mol Biol 2006; 101: 161-78
14. Bardin CW, Lipsett MB. Testosterone and androstenedione blood production rates in normal women and women with idiopathic hirsutism or polycystic ovaries. J Clin Invest 1967; 46: 891-902
15. Horton R, Tait JF. Androstenedione production and interconversion rates measured in peripheral blood and studies on the possible site of its conversion to testosterone. J Clin Invest 1966; 45: 301-13
16. Bassindale T, Cowan DA. Effects of oral administration of androstenedione on plasma androgens in young women using hormonal contraception. J Clin Endocrinol Metab 2004; 89: 6030-8

taken orally. This may be associated with less

signed to be administered by the sublingual or buc-

17. Brown GA, Dewey JC, Brunkhorst JA, et al. Changes in serum testosterone and estradiol concentrations following acute androstenedione ingestion in young women. Horm Metab Res 2004; 36: 62-6
18. Kicman AT, Bassindale T, Cowan DA, et al. Effect of androstenedione ingestion on plasma testosterone in young women; a dietary supplement with potential health risks. Clin Chem 2003; 49: 167-9
19. Leder BZ, Leblanc KM, Longcope C, et al. Effects of oral androstenedione administration on serum testosterone and estradiol levels in postmenopausal women. J Clin Endocrinol Metab 2002; 87: 5449-54
20. Miyamoto H, Yeh S, Lardy H, et al. Delta 5-androstenediol is a natural hormone with androgenic activity in human prostate cancer cells. Proc Natl Acad Sci USA 1998; 95: 11083-8
21. Van der Vies J. Pharmacokinetics of anabolic steroids. Wien Med Wochenschr 1993; 143: 366-8
22. Hartgens F, Rietjens G, Keizer HA, et al. Effects of androgenic-anabolic steroids on apolipoproteins and lipoprotein (a). Br J Sports Med 2004; 38: 253-9
23. Taylor WN. Anabolic steroids and the athlete. Jefferson (NC): Mcfarland, 1982
24. Franke WW, Berendonk B. Hormonal doping and androgenization of athletes: a secret program of the German Democratic Republic government. Clin Chem 1997; 43: 1262-79
25. Kicman AT, Brooks RV, Collyer SC, et al. Criteria to indicate testosterone administration. Br J Sports Med 1990; 24: 253-64
26. Dehennin L. Detection of simultaneous self-administration of testosterone and epitestosterone in healthy men. Clin Chem 1994; 40: 106-9
27. Perry PJ, MacIndoe JH, Yates WR, et al. Detection of anabolic steroid administration: ratio of urinary testosterone to epitestosterone vs the ratio of urinary testosterone to luteinizing hormone. Clin Chem 1997; 43: 731-5
28. Catlin DH, Sekera MH, Ahrens BD, et al. Tetrahydrogestrinone: discovery, synthesis, and detection in urine. Rapid Commun Mass Spectrom 2004; 18: 1245-9
29. Catlin DH, Ahrens BD, et al. Detection of norbolethone, an anabolic steroid never marketed, in athletes' urine. Rapid Commun Mass Spectrom 2002; 16: 1273-5
30. Sekera MH, Ahrens BD, Chang YC. Another designer steroid: discovery, synthesis, and detection of 'madol' in urine. Rapid Commun Mass Spectrom 2005; 19: 781-4
31. Hershberger LG, Shipley EG, Meyer RK. Myotrophic activity of 19-nortestosterone and other steroids determined by modified levator ani muscle method. Proc Soc Exp Biol Med 1953; 83: 175-80
32. Tomoda H. Effect of oxymetholone on left ventricular dimensions in heart failure secondary to idiopathic dilated cardiomyopathy or to mitral or aortic regurgitation. Am J Cardiol 1999; 83: 123-5
33. British National Formulary. A joint publication of the British Medical Association and the Royal Pharmaceutical Society of Great Britain. BMJ Group and RPS Publishing, 2007 [online]. Available from URL: http://www.bnf.org [Accessed 2008 Apr 23]
34. Hengge UR, Baumann M, Maleba R, et al. Oxymetholone promotes weight gain in patients with advanced human immunodeficiency virus (HIV-1) infection. Br J Nutr 1996; 75: 129-38
35. Bhasin S, Javanbakht M. Can androgen therapy replete lean body mass and improve muscle function in wasting associated with human immunodeficiency virus infection? J Parenter Enteral Nutr 1999; 23: 195-201
36. Bogin V, Shaw-Stiffel T. Androgenic anabolic steroids and other therapies for HIV-related wasting. J Clin Ligand Assay 1999; 22: 268-78
37. Bhasin S, Storer TW, Javanbakht M, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. JAMA 2000; 283: 763-70
38. Gold J, Batterham MJ, Rekers H, et al. Effects of nandrolone decanoate compared with placebo or testosterone on HIV-associated wasting. HIV Med 2006; 7: 146-55
39. Johansen KL, Mulligan K, Schambelan M. Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. JAMA 1999; 281: 1275-81
40. Johansen KL, Painter PL, Sakkas GK, et al. Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: a randomized, controlled trial. J Am Soc Nephrol 2006; 17: 2307-14
41. Bhasin S, Calof OM, Storer TW, et al. Drug insight: testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. Nat Clin Pract Endocrinol Metab 2006; 2: 146-59
42. Solomon AM, Bouloux PMG. Modifying muscle mass: the endocrine perspective. J Endocrinol 2006; 191: 349-60
43. Ferreira IM, Verreschi IT, Nery LE, et al. The influence of 6 months of oral AAS on body mass and respiratory muscles in undernourished COPD patients. Chest 1998; 114: 19-28
44. Demling RH. The role of anabolic hormones for wound healing in catabolic states. J Burn Wounds 2005; 4: 2
45. Liu PY, Death AK, Handelsman DJ. Androgens and cardiovascular disease. Endocr Rev 2003; 24: 313-40
46. Bhasin M, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996; 335: 1-7
47. Mooradian AD, Morley JE, Korenman SG. Biological actions of androgens. Endocr Rev 1987; 8: 1-28
48. Windsor RE, Dumitru D. Anabolic steroid use by athletes. Postgrad Med 1988; 84: 37-49
49. Hickson RC, Ball KL, Falduto HT. Adverse effects of anabolic steroids. Med Toxicol Adverse Drug Exp 1989; 4: 254-68
50. Ulmark R, Blonstein JL. The dangers of doping. J Sports Med Phys Fitness 1963; 44: 248-9
51. Todd T. Anabolic steroids: the gremlins of sport. J Sport History 1987; 14: 87-107
52. Pope Jr HG, Katz DL. Affective and psychotic symptoms associated with anabolic steroid use. Am J Psychiatry 1988; 145: 487-90
53. Pope Jr HG, Katz DL. Homicide and near-homicide by anabolic steroid users. J Clin Psychiatry 1990; 51: 28-31
54. Sullivan ML, Martinez CM, Gallagher EJ. Atrial fibrillation and anabolic steroids. J Emerg Med 1999; 17: 851-7
55. Kuipers H, Wijnen JA, Hartgens F, et al. Influence of anabolic steroids on body composition, blood pressure, lipid profile and liver functions in body-builders. Int J Sports Med 1991; 12: 413-8
56. Sader MA, Griffiths KA, McCredie RJ, et al. Androgenic-anabolic steroids and arterial structure and function in male body-builders. J Am Coll Cardiol 2001; 37: 224-30
57. Lloyd FH, Powell P, Murdoch AP. Anabolic steroid abuse by body builders and male subfertility. BMJ 1996; 313: 100-1

tempted use of such has become a covert science in urinate over a finger that surreptitiously has epites-

58. Grace FM, Baker JS, Davies B. Anabolic androgenic steroid (AAS) use in recreational gym users: a regional sample of the Mid-Glamorgan area. J Subst Use 2001; 6: 189-95
59. Graham MR, Davies B, Kicman A, et al. Recombinant human growth hormone in abstinent androgenic-anabolic steroid use: psychological, endocrine and trophic factor effects. Curr Neurovasc Res 2007; 4 (1): 9-18
60. Parrott AC, Choi PY, Davies M. Anabolic steroid use by amateur athletes: effects upon psychological mood states. J Sports Med Phys Fitness 1994; 34: 292-8
61. Perry H, Littlepage B. Dying to be big: a review of anabolic steroid use. Br J Sports Med 1992; 4: 259-61
62. Korkia P, Stimson GV. Anabolic steroid use in Great Britain: an exploratory investigation. London: The Centre for Research on Drugs and Health Behaviour, 1993
63. Pates R, Barry C. Steroid use in Cardiff: a problem for whom? J Perform Enhanc Drugs 1996; 1: 92-7
64. Melia P, Pipe A, Greenberg L. The use of anabolic-androgenic steroids by Canadian students. Clin J Sport Med 1996; 6: 9-14
65. Evans N. Gym and tonic: a profile of 100 male steroid users. Br J Sports Med 1997; 31: 54-8
66. Baker JS, Graham MR, Davies B. 'Steroid' and prescription medicine abuse in the health and fitness community: a regional study. Eur J Int Med 2006; 17: 479-84
67. Parkinson AB, Evans NA. Anabolic androgenic steroids: a survey of 500 users. Med Sci Sports Exerc 2006; 38: 644-51
68. Dawson RT. Drugs in sport: the role of the physician. J Endocrinol 2001; 170: 55-61
69. Kanayama G, Cohane GH, Weiss RD, et al. Past anabolic-androgenic steroid use among men admitted for substance abuse treatment: an under recognized problem. J Clin Psychiatry 2003; 64: 156-60
70. Graham MR, Grace FM, Boobier W, et al. Homocysteine induced cardiovascular events: a consequence of long-term anabolic-androgenic steroid (AAS) abuse. Br J Sports Med 2006; 40: 644-8
71. Bilton RF. Microbial production of testosterone [letter]. Lancet 1995; 345: 1186-7
72. Kicman AT, Fallon JK, Cowan DA, et al. Candida albicans can produce testosterone: impact on the T/E sports drug test. Clin Chem 2002; 10: 1799-801
73. Abraham GE. Solid-phase radioimmunoassay of estradiol-17β. J Clin Endocrinol Metab 1969; 29: 866-70
74. Brooks RV, Firth RG, Sumner NA. Detection of anabolic steroids by radioimmunoassay. Br J Sports Med 1975; 9: 89-92
75. Ward RJ, Shackleton CH, Lawson AM. Gas chromatographic-mass spectrometric methods for the detection and identification of anabolic steroid drugs. Br J Sports Med 1975; 9: 93-7
76. Brooks RV, Jeremiah G, Webb WA, et al. Detection of anabolic steroid administration to athletes. J Steroid Biochem 1979; 11: 913-7
77. Kicman AT, Brooks RV. Radioimmunoassay for nandrolone metabolites. J Pharm Biomed Anal 1988; 6: 473-83
78. Catlin DH, Kammerer RC, Hatton CK, et al. Analytical chemistry at the Games of the XXIIIrd Olympiad in Los Angeles, 1984. Clin Chem 1987; 33: 319-27
79. Schanzer W, Donike M. Metabolism of anabolic steroids in man: synthesis and use of reference substances for identification of anabolic steroid metabolites. Anal Chim Acta 1993; 275: 23-48
80. Bowers LD. Analytical advances in detection of performance-enhancing compounds. Clin Chem 1997; 43: 1299-304
81. Thevis M, Geyer H, Mareck U, et al. Screening for unknown synthetic steroids in human urine by liquid chromatography-tandem mass spectrometry. J Mass Spectrom 2005; 40: 955-62
82. Becket A. Anecdotal evidence of drug abuse: drug abuse in sport. London: The Sports Council, 1985
83. Cowan DA, Kicman AT. Doping in sport: misuse, analytical tests, and legal aspects [editorial]. Clin Chem 1997; 43: 1110-3
84. Donike M, Barwald KR, Klosterman K, et al. Detection of exogenous testosterone [in Dutch]. In: Heck H, Hollman W, Liesen H, et al., editors. Sport: Leistung und Gesundheit, Kongressbd. Dtsch. Sportarztekongress. Koln: Deutscher Artze-Verlag, 1983: 293-8
85. Oftebro H. Evaluating an abnormal urinary steroid profile. Lancet 1992; 339: 941-2
86. Kicman AT, Oftebro H, Walker C, et al. Potential use of ketoconazole in a dynamic endocrine test to differentiate between biological outliers and testosterone use by athletes. Clin Chem 1993; 39: 1798-803
87. Raynaud E, Audran M, Pages JC, et al. Study of urinary-excretion of testosterone and epitestosterone glucuronides in children and adolescents. Pathol Biol (Paris) 1993; 41: 159-63
88. Raynaud E, Audran M, Pages JC, et al. Determination of urinary testosterone and epitestosterone during pubertal development: a cross-sectional study in 141 normal-male subjects. Clin Endocrinol 1993; 38: 353-9
89. Oftebro H, Jensen J, Mowinckel P, et al. Establishing a ketoconazole suppression test for verifying testosterone administration in the doping control of athletes. J Clin Endocrinol Metab 1994; 78: 973-7
90. Garle M, Ocka R, Palonek E, et al. Increased urinary testosterone epitestosterone ratios found in Swedish athletes in connection with a national control programme: evaluation of 28 cases. J Chromatogr 1996; 687: 55-9
91. Catlin DH, Hatton CK, Starcevic SH. Issues in detecting abuse of xenobiotic anabolic steroids and testosterone by analysis of athletes' urine. Clin Chem 1997; 43: 1280-8
92. Becchi M, Aguilera R, Farizon Y, et al. Gas chromatography/combustion/isotope-ratio mass spectrometry analysis of urinary steroids to detect misuse of testosterone in sport. Rapid Commun Mass Spectrom 1994; 8: 304-8
93. Aguilera R, Becchi M, Casabianca H, et al. Improved method of detection of testosterone abuse by gas chromatography/combustion/isotope ratio mass spectrometry analysis of urinary steroids. J Mass Spectrom 1996; 31: 169-76
94. Aguilera R, Becchi M, Grenot C, et al. Detection of testosterone misuse: comparison of two chromatographic sample preparation methods for gas chromatographic-combustion/isotope ratio mass spectrometric analysis. J Chromatogr B 1996; 687: 43-53
95. Horning S, Geyer H, Schanzer W, et al. Detection of exogenous testosterone by 13C/12C analysis. In: Schanzer W, Geyer H, Gotzmann A, et al., editors. Recent advances in doping analysis: Proceedings of the 14th Cologne Workshop on Dope Analysis; 1996 Mar 17-22; Cologne. Cologne: Sport und Buch Strauss, 1997: 275-83
96. Shackleton CH, Phillips A, Chang T, et al. Confirming testosterone administration by isotope ratio mass spectrometric analysis of urinary androstanediols. Steroids 1997; 62: 379-87
97. Horning S, Geyer H, Schanzer W, et al. Detection of exogenous steroids by 13C/12C analysis. In: Schanzer W, Geyer H, Gotzmann A, et al., editors. Recent advances in doping analysis: Proceedings of the 15th Cologne Workshop on Dope Analysis; 1997 Feb 23-28; Cologne. Cologne: Sport und Buch Strauss, 1998: 135-48

n-17-one; and (c) 19-norepiandrosterone (3β-hydroxy-5α-estran-17-one) [reproduced from Kicman and Gower, [5] with permission from the Royal Society of Medicine].

98. Aguilera R, Catlin DH, Becchi M, et al. Screening urine for exogenous testosterone by isotope ratio mass spectrometric analysis of one pregnanediol and two androstanediols. J Chromatogr B Analyt Technol Biomed Life Sci 1999; 727: 95-105
99. Aguilera R, Chapman TE, Catlin DH. A rapid screening assay for measuring urinary androsterone and etiocholanolone delta (13)C (per thousand) values by gas chromatography/combustion/isotope ratio mass spectrometry. Rapid Commun Mass Spectrom 2000; 14: 2294-9
100. Aguilera R, Chapman TE, Starcevic B, et al. Performance characteristics of a carbon isotope ratio method for detecting doping with testosterone based on urine diols: controls and athletes with elevated testosterone/epitestosterone ratios. Clin Chem 2001; 47: 292-300
101. Ayotte C, Goudreault D, Levesque JF, et al. GC/C/IRMS and GC/MS in 'natural' steroids testing. Proceedings of the Manfred Donike Workshop – Recent Advances in Doping Analysis (9); 1996 Mar 17-22; Cologne. Cologne: Sport und Buch Strauss, 2001
102. de la Torre X, Gonzalez JC, Pichini S, et al. 13C/12C isotope ratio MS analysis of testosterone, in chemicals and pharmaceutical preparations. J Pharm Biomed Anal 2001; 24: 645-50
103. Trout GJ, Kazlauskas R. Sports drug testing: an analysts perspective. Chem Soc Rev 2004; 33: 1-13
104. Kaufman KR. Modafinil in sports: ethical considerations. Br J Sports Med 2005; 39: 241-4
105. Bethune JE. The adrenal cortex: a scope monograph. Kalamazoo (MI): The Upjohn Company, 1975
106. Grant JK, Beastall GH. Clinical biochemistry of steroid hormones. London: Croom Helm Ltd, 1983
107. Brooks RV, Collyer SP, Kicman AT, et al. HCG doping in sport and methods for its detection. In: Bellotti P, Benzi G, Ljungqvist A, editors. IInd International Athletic Foundation World Symposium on Doping in Sport: Official Proceedings; 1989 Jun 5-7; Monte Carlo. Monte Carlo: International Athletic Foundation (IAF), 1990: 37-45
108. Cowan DA, Kicman AT, Walker CJ, et al. Effect of administration of human chorionic gonadotrophin on criteria used to assess testosterone administration in athletes. J Endocrinol 1991; 131: 147-54
109. De Boer D, De Jong EG, Van Rossum JM, et al. Doping control of testosterone and human chorionic gonadotrophin: a case study [published erratum appears in Int J Sports Med 1991; 12: 430]. Int J Sports Med 1991; 12: 46-51
110. Laidler P, Cowan DA, Hider RC, et al. New decision limits and quality-control material for detecting human chorionic gonadotrophin misuse in sports. Clin Chem 1994; 40: 1306-11
111. Laidler P, Cowan DA, Hider RC, et al. Tryptic mapping of human chorionic gonadotrophin by matrix-assisted laser desorption/ionization mass spectrometry. Rapid Commun Mass Spectrom 1995; 9: 1021-6
112. Liu CL, Bowers LD. Immunoaffinity trapping of urinary human chorionic gonadotropin and its high-performance liquid chromatographic-mass spectrometric confirmation. J Chromatogr B 1996; 687: 213-20
113. Gam LH, Tham SY, Latiff A. Immunoaffinity extraction and tandem mass spectrometric analysis of human chorionic gonadotropin in doping analysis. J Chromatogr B Analyt Technol Biomed Life Sci 2003; 792: 187-96
114. Götherström G, Bengtsson BA, Sunnerhagen KS, et al. The effects of five-year growth hormone replacement therapy on muscle strength in elderly hypopituitary patients. Clin Endocrinol (Oxf) 2005; 62: 105-13
115. Healy ML, Gibney J, Russell-Jones DL, et al. High dose growth hormone exerts an anabolic effect at rest and during exercise in endurance-trained athletes. J Clin Endocrinol Metab 2003; 11: 5221-6
116. Berggren A, Ehrnborg C, Rosen T, et al. Short-term administration of supraphysiological recombinant human growth hormone (GH) does not increase maximum endurance exercise capacity in healthy, active young men and women with normal GH-insulin-like growth factor I axes. J Clin Endocrinol Metab 2005; 90: 3268-73
117. Wu Z, Bidlingmaier M, Dall R, et al. Detection of doping with human growth hormone. Lancet 1999; 353: 895
118. Powrie JK, Bassett EE, Rosen T, et al., on behalf of the GH-2000 Project Study Group. Detection of growth hormone abuse in sport. Growth Horm IGF Res 2007; 17: 220-6
119. Saugy M, Robinson N, Saudan C, et al. Human growth hormone doping in sport. Br J Sports Med 2006; 40: 35-9
120. Voy R. Drugs, sport and politics. Champaign (IL): Leisure Press, 1991
121. World Anti-Doping Agency (WADA). Prohibited list of substances in 2005 [online]. Available from URL: http://www.wada-ama.org/rtecontent/document/2005_Annual_Report_En.pdf [Accessed 2006 May 8]
122. Savulescu J, Foddy B, Clayton M. Why we should allow performance-enhancing drugs in sport. Br J Sports Med 2004; 38: 666-70
123. Kayser B, Mauron A, Miah A. Viewpoint: legalisation of performance-enhancing drugs. Lancet 2005; 366 Suppl. 1: S21
124. Noakes TD. Should we allow performance-enhancing drugs in sport? A rebuttal to the article by Savulescu and colleagues. Int J Sports Sci Coach 2006; 4: 289-316

Correspondence: Prof. Julien S. Baker, Department of Health and Exercise Science, School of Applied Science, University of Glamorgan, CF37 1DL Pontypridd, Wales.
E-mail: jsbaker@glam.ac.uk