Dossier de prensa
European Sicencie Open Forum (ESOF 2008)

Dopaje: ¿Hacia la máquina humana perfecta?

En una sociedad donde el éxito deportivo aporta fama, gloria y dinero, conseguir ser al mejor a cualquier precio es una gran tentación que puede llevar a la utilización de sustancias y/o métodos prohibidos. Bajo esta premisa, expertos internacionales de organismos antidopaje, de organizaciones que gestionan los controles, de asociaciones de científicas interesadas en el tema y los propios deportistas, participarán en esta sección científica donde se hablará de la situación del dopaje en el deporte en un momento de máxima actualidad, justo antes de los Juegos Olímpicos de Pekín.

Una visión internacional multidisciplinar

La sesión científica está organizada por el Dr. Jordi Segura y contará con la participación de expertos internacionales en el ámbito del dopaje y del deporte.

Jordi Segura. Director del Laboratorio Antidopaje del Institut Municipal d'Investigació Mèdica (IMIM-Hospital del Mar)

También es coordinador del grupo de investigación en Bioanálisis y Servicios Analíticos del Programa de Investigación en Neuropsicofarmacología del IMIM, miembro de la "Medical Commission Games Group" del Comité Olímpico Internacional (COI) y del Doping Control Review Board de la Federación Internacional de Natación (FINA). Es experto en cromatografía, espectrometría de masas y análisis hormonales. Además, es profesor titular del departamento de Ciencias Experimentales y de la Salud de la Universidad Pompeu Fabra.

El Laboratorio antidopaje del Institut Municipal d'Investigació Mèdica fue creado en 1985 y está acreditado por la norma ISO 17925 y por la Agencia Mundial Antidopaje. Fue el laboratorio responsable del control antidopaje durante los Juegos Olímpicos y Paralímpicos de Barcelona en el año 1992. Posteriormente, el laboratorio ha controlado grandes acontecimientos internacionales como son los Juegos Panamericanos de 1991 y 1995, los Juegos Asiáticos de 1998 y los Campeonatos Mundiales de Natación de 2003, entre otros. El laboratorio recibe diariamente muestras y consultas de todo el mundo.

El Dr. Jordi Segura con el título: "*Doping and Society: towards the perfect human machine*?" que da nombre a toda la sesión científica, nos hará una introducción general sobre el estado actual del dopaje y su control, y ofrecerá un resumen de la previsión para el futuro próximo.

Alain Garnier. Director Médico de la Agencia Mundial Contra el Dopaje (WADA-AMA)

Inicia su relación con la WADA como médico consultor en el año 2000, gracias a su experiencia previa como médico especialista en deporte en diversos hospitales franceses y como jefe del área médica del Ministerio de Juventud y Deportes francés. En el marco de la WADA, fue miembro del grupo que desarrollo el Código Mundial Antidopaje (Code) y uno de los responsables de asegurar la aceptación del código por parte de los diferentes gobiernos. En la actualidad, es el director médico de la WADA, a cargo de todos los aspectos médicos relacionados con el dopaje, especialmente de la supervisión del programa "Therapeutic Use Exemptions" y del proyecto "WADA's Athlete Passport".

Bajo el título: *"Moving from toxicology to biology: the need for a medical approach in the fight against doping*" el Dr. Garnier, con su ponencia, nos hará una aproximación médica a la situación actual de la lucha contra el dopaje. ¿Por qué los médicos deportivos se han de oponer al dopaje? ¿Hay consecuencias a largo plazo para la salud? ¿Se pueden tomar sustancias restringidas en caso de no haber tratamiento farmacológico alternativo? Se hará una especial incidencia en el proceso de la Exención de Uso Terapéutico (TUE) y el concepto de "Pasaporte del Atleta" (Athlete's Passport). Este último pretende hacer un seguimiento longitudinal de los parámetros biológicos del atleta, hecho que permitirá la identificación de perfiles anormales en el uso de sustancias o métodos prohibidos.

Michelle Verroken. Directora-fundadora de Sporting Integrity. La consultora Sporting Integrity se creó en 2004 y es la primera y única de este tipo existente en Reino Unido. Su finalidad es asesorar a sus clientes en la buena práctica deportiva y adoptar y mantener los mejores procedimientos relacionados con la ética y la integridad del deporte.

La Sra. Verroken cuenta con dos décadas de experiencia como experta mundial en el campo de la ética y el deporte. Directora de Ética y Antidopaje en UK Sport, fue responsable de diseñar e implementar los estándares internacionalmente aceptados por el control antidopaje, gestión de los resultados y educación. Además, creó la base de datos UK's Drug Information y políticas nacionales antidopaje (en el que se ha basado el Código Antidopaje Mundial).

Con el título: "*Ethics and Doping- ethos, pathos or kudos*?" la Sra. Verroken nos hablará sobre la ética del deporte limpio y la necesidad de que todos seamos conscientes de la importancia de su control. Según Verroken, las reglas del juego deberían ser la propia esencia del deporte. La corrupción del deporte a través del dopaje está destruyendo esta ética única. A menudo, los atletas se convierten en intérpretes que se forman a partir de sistemas de entrenamiento que utilizan las nuevas innovaciones científicas. Dibujar la línea entre lo que es aceptable e inaceptable se está haciendo cada vez más difícil. Este complejo tema se ejemplificará con experiencias concretas y clarificadoras.

Franchek Drobnic. Responsable del Departamento de Fisiología del Centro de Alto Rendimiento (CAR) de Sant Cugat.

Es Doctor en Medicina por la Universidad Autónoma de Barcelona y especialista en Medicina de la Actividad Física y el Deporte. Actualmente es el responsable del Departamento de Fisiología del Deporte del Centro de Alto Rendimiento de Barcelona y responsable de los Servicios Médicos de la Federación Española de Taekwondo. Además de colaborar directamente con diversos deportes en la preparación olímpica.

Su interés investigador en el mundo del deporte es amplio y se orienta hacia la mejora del rendimiento físico deportivo dentro del ámbito de la salud, con especial énfasis en los trastornos y en la adaptación respiratoria al esfuerzo, así como en la fisiología del rendimiento físico y reparadora bajo condiciones especiales, como el propio ejercicio, hiperbaria, hiperoxia, los cambios de temperatura o el estado de hidratación y nutricional.

Su presentación "*Therapeutic Use Exemptions: why and when*?" describirá las posibilidades que existen para administrar productos de la lista prohibida a aquellos deportistas enfermos que lo necesiten. El procedimiento llamado "*Therapeutic Use Exemptions*" permite, en sus dos versiones (convencional y abreviada), suministrar la información médica pertinente que permita el uso de los medicamentos en situaciones patológicas donde no haya otras alternativas. La presentación pondrá un especial énfasis en algunas de las solicitudes de uso terapéutico más comunes como son las relacionadas con los deportistas con asma o el asma inducido por el ejercicio.

Xavier O'Callaghan, ex-jugador de balonmano FC Barcelona y actual gerente de la sección de balonmano del FC Barcelona

Entró en las categorías inferiores del FC Barcelona donde ganó tres campeonatos estatales juveniles y uno júnior. La temporada 1990-91, con 18 años pasó al primer equipo donde jugó 15 temporadas siendo uno de los deportistas que ha ganado más títulos a nivel estatal y europeo (54). Ha sido 87 veces internacional y logró 140 goles, además de ser medalla de bronce en los Juegos Olímpicos de Sydney 2000 y diploma olímpico en Atenas 2005. Al final de la temporada 2005, y después de toda la carrera deportiva en el FC Barcelona, pasó a ocupar el cargo de gerente de la sección de balonmano del FC Barcelona.

Su presentación nos introducirá en la visión del dopaje, tanto desde el punto de vista del deportista como de la responsabilidad de la gestión deportiva. Xavier 0'Callaghan intentará responder, desde su visión personal y en base a su experiencia deportiva, por qué hay deportistas que se dopan y otros que no, y qué factores pueden influir en esta decisión.

Francesco Botrè. Ex-presidente de la Asociación Mundial de Científicos Antidopaje (WAADS) y director científico del Laboratorio Antidopaje de Roma.

El Dr. Botré es profesor asociado de la "Sapienza", Facultat de Medicina de la Universidad de Roma, miembro del grupo de trabajo de Laboratorios de la WADA y pertenece a la Comisión Médica del Comité Internacional de los Juegos del Mediterráneo. También es miembro de diversas sociedades científicas, autor de más de 200 publicaciones científicas, conferencias y trabajos monográficos.

Su presentación "*Testing: scientific aspects. Who are the laboratory experts?*" tratará sobre la actividad que realizan los laboratorios antidopaje para la WADA, haciendo un estudio de la evolución que ha llevado a cabo en los últimos años para conseguir ser más efectivos en la lucha contra el dopaje. Dará un especial énfasis a la evolución futura de la ciencia del antidopaje, en pro del "*fair play*", la protección de la salud y el conocimiento por parte de la sociedad de la actividad que se desarrolla en un laboratorio antidopaje.

Josep Guardiola, ex-jugador de fútbol y actual entrenador del primer equipo de fútbol del FC Barcelona.

Ha sido uno de los mediocampistas más importantes del fútbol catalán. Ha jugado 43 veces con la elección española y durante muchos años también ha sido el capitán de la selección catalana. En el año 2001 pasó a ser jugador del Brescia y tan solo dos meses después fue acusado de dopaje por el Comité Olímpico Nacional Italiano. No fue hasta 2007, 6 años después, que el Tribunal de Apelación del Brescia lo absolvió gracias a nuevas evidencias científicas que explicaban el origen natural de los hallazgos. Actualmente es el entrenador del primer equipo del FC Barcelona.

Su participación se realizará mediante una declaración pregrabada, dado que en el momento de la realización de la sesión se encuentra fuera del país, donde nos dará su personal visión del dopaje. Los temas prioritarios que tratará son la visión del dopaje y su control desde el punto de vista deportivo, el papel que puede jugar el entorno más próximo al deportista, su propia experiencia por haber sido considerado sospechoso de dopaje, algunas consideraciones sobre el futuro de la lucha antidopaje y qué papel puede jugar la ciencia en la mejora de este control.

Los orígenes del control antidopaje

La utilización de sustancias o de otros métodos para mejorar el rendimiento es tan antiguo como el propio deporte de competición. Se sabe que los atletas que participaban en las Olimpiadas de la antigua Grecia (IV-VIII a.c), utilizaban dietas especiales y pociones estimulantes para aumentar su capacidad. Asimismo, no fue hasta principios del sigo XX cuando se pensó en la necesidad de controlar el uso de las sustancias dopantes en el deporte. Inicialmente no existían medios para detectar el uso de estas sustancias, pero los avances científicos permitieron instaurar progresivamente el control antidopaje a partir de la década de los años 60 por parte del Comité Olímpico Internacional y las principales federaciones deportivas. Hechos lamentables, como la muerte de algunos ciclistas, destaparon el uso inicial de anfetaminas y narcóticos. Posteriormente, se conoció la utilización cada vez más elevada de la testosterona y derivados (esteroides anabolizantes) como elementos de dopaje. Actualmente la lista de sustancias incluye muchos otros grupos farmacológicos. La revolución biotecnológica en medicina también está comenzando a incidir de forma espectacular en el consumo de sustancias dopantes que tienen una estructura idéntica a las que produce el propio cuerpo humano. La próxima llegada del dopaje genético añadirá complejidad a los aspectos éticos y a la detección del dopaje del futuro.

El dopaje en la actualidad

Productos y métodos dopantes en la actualidad

Cada año, la WADA realiza un listado de sustancias prohibidas que se puede encontrar actualizada en su página web http://www.wada-ama.org. Estas sustancias se presentan englobadas en grandes categorías como pueden ser los agentes anabolizantes, las hormonas y sustancias relacionadas, los estimulantes o los narcóticos por citar algunos ejemplos. Por otra parte, también dispone de un listado de métodos prohibidos que incluyen el aumento del oxígeno por transfusión (doping sanguíneo), la manipulación química o física, es decir, la manipulación o sustitución de muestras o el dopaje genético.

Realizar el control antidopaje de los componentes de la lista es muy complejo técnicamente, caro y sólo pueden realizarlo 34 laboratorios en todo el mundo; los acreditados por la WADA, entre los que está el Laboratorio Antidopaje de Barcelona del Institut Municipal d'Investigació Mèdica (IMIM-Hospital del Mar).

A continuación adjuntamos un cuadro con algunos ejemplos de sustancias prohibidas, con sus efectos en el rendimiento deportivo y sus efectos secundarios a nivel de salud.

SUSTANCIAS PROHIBIDAS (sólo algunos ejemplos)	EFECTOS	EFECTOS SECUNDARIOS
Sustancias que aumentan la cantidad de oxígeno en el músculo		
Eritropoyetina (EPO)	Aumenta los glóbulos rojos y se gana en oxigenación y resistencia	Accidentes cardiovasculares graves
Darbepoetina	De la familia de la EPO, pero perdura más en la sangre	Accidentes cardiovasculares
Insulina	Muy importante por el transporte de nutrientes hacia las células, permitida para los diabéticos	Accidentes cardiovasculares y coma diabético
Transfusión de sangre	Muy eficaz para mejorar el rendimiento de forma rápida	Riesgo de infección en caso de deterioro de la sangre o mala administración
Sustancias que aumentan la masa y la fuerza muscular (anabolizantes)		
Testosterona	Incrementa el desarrollo muscular	Enfermedades hepáticas y crecimiento del pelo en la mujer
Nandrolona	Incrementa la fuerza, la potencia, la agresividad y la velocidad	Problemas hepáticos y descenso del deseo sexual

Estanozolol	Derivado de la testosterona, promueve el desarrollo muscular	Trastornos sexuales importantes
THG	Favorece el desarrollo muscular. Droga sintética que fue diseñada para ser indetectable.	Trastornos sexuales
Clenbuterol	Favorece el incremento muscular y la fuerza	Dolor de cabeza y temblores
Sustancias estimulantes		
Cocaína	Ausencia de fatiga. Aumenta la agresividad	Adición, ansiedad, agresividad, taquicardias, temblores y accidentes cardiovasculares.
Substancias diuréticas		
Hidroclorotiazida	Enmascara la presencia de otros dopantes al eliminarlos por la orina	Fatiga inusual, palpitaciones y ojos amarillentos.

Número de sustancias identificadas en cada grupo de sustancias prohibidas (Información facilitada a la WADA por los laboratorios acreditados). Año 2007. Por ahora los esteroides todavía son las drogas más detectadas por los laboratorios de la WADA a la hora de mejorar el rendimiento de los deportistas.

Substance Group	Number*	% of all *Adverse Analytical Findings*
S1. Anabolic Agents	2,322	47.9%
S6. Stimulants	793	16.4%
S8. Cannabinoids	576	11.9%
S3. Beta-2 Agonists	399	8.2%
S5. Diuretics and Other Masking Agents	359	7.4%
S9. Glucocorticosteroids	288	5.9%
S2. Hormones and Related Substances	41	0.8%
P2. Beta-Blockers	27	0.6%
S7. Narcotics	21	0.4%
S4. Agents with Anti-Estrogenic Activity	18	0.4%
M1. Enhancement of Oxygen Transfer	3	0.1%
M2. Chemical and Physical Manipulation	3	0.1%
TOTAL	**4,850**	

¿Qué circuito sigue la muestra?

Al atleta se le recoge la muestra en dos recipientes, el A y el B. La muestra A sirve para realizar el análisis y la muestra B se reserva por si fuese necesario realizar un contraanálisis. Ambas muestras se envían herméticamente cerradas y precintadas, tan solo con un código numérico al laboratorio que realizará el análisis. En todo momento la muestra es anónima (identificada por un código numérico) y está custodiada para garantizar su seguridad y confidencialidad. Todos los pasos que siguen a la extracción y el análisis de la muestra se anotan y todo el instrumental y procedimientos que se utilizan están acreditados y homologados. El proceso de acreditación de los laboratorios antidopaje es doble, tanto por parte de los organismos aceptados internacionalmente (ISO), como por parte de la WADA. La fiabilidad de los análisis antidopaje está entre las actividades más controladas del mundo científico. Actualmente existen 34 laboratorios antidopaje acreditados en el mundo (consultar página web: http://www.wada-ama.org/en/dynamic.ch2?pageCategory.id=333)

¿Qué organismos pueden solicitar un control antidopaje?

Existen varios: las Federaciones Nacionales e Internacionales en que compite el deportista, el Organismo Nacional Antidopaje (NADO) de los países donde reside o compite el deportista, la Agencia Mundial Antidopaje, los organizadores de grandes competiciones internacionales y el Comité Olímpico Internacional entre otros.

La legislación actual

La creación en el año 1998 de la Agencia Mundial Antidopaje (WADA en inglés), fue iniciada por Josep Antoni Samaranch cuando todavía era presidente del COI. Éste fue un primer paso en la lucha contra el dopaje, pero el impulso definitivo se dio con la implicación política y económica de la comunidad internacional y también con la redacción del Código Mundial Antidopaje, que comenzó a tener forma en la II Conferencia Mundial Antidopaje que se celebró en Copenhague en el año 2003. El código es una norma universal en la lucha contra las sustancias prohibidas que nació con el apoyo de 72 países y que en la actualidad ya cuenta con 191 gobiernos adheridos. Más recientemente, la Convención de la UNESCO y la III Conferencia Mundial Antidopaje celebrada en noviembre de 2007 en Madrid, le han dado el impulso definitivo.

A nivel español, la entrada en vigor de la Ley Orgánica contra del doping y a favor de la salud de febrero de 2007, mucho más severa que la precedente, define como delito la inducción y la colaboración en los casos de dopaje. Asimismo, el Real Decreto 811/2007, de 22 de junio, constituye la nueva Comisión de Control y Seguimiento de la Salud y la Lucha contra el Dopaje en el Deporte.

Los peligros del dopaje

Algunas de las sustancias más utilizadas son los esteroides, la hormona del crecimiento y la EPO. Las tres tienen importantes peligros inherentes a su uso, que destacamos a continuación:

Los efectos secundarios más peligrosos de los esteroides que se han descrito en la literatura médica incluyen anormalidades en la función renal y tumores en el riñón, disfunciones endocrinas y reproductivas, atrofia testicular, efectos cardiacos, en los lípidos y síntomas psiquiátricos. Estas consecuencias se han exagerado con las prácticas dopantes comunes utilizando 10 veces o más la dosis médica recomendada, y en combinación con otras drogas, como los esteroides, EPO o la hormona del crecimiento.

Utilizar la hormona del crecimiento puede causar riesgos importantes, especialmente si tenemos en cuenta que algunos informes estiman que los atletas que utilizan la hormona del crecimiento para mejorar el rendimiento están tomando una dosis 10 superior a la terapéutica. Algunos efectos secundarios de la hormona del crecimiento son el crecimiento anormal de los huesos, la hipertensión, enfermedades cardiovasculares, cardiomiopatía, intolerancia a la glucosa, pólipos en el colon, disminución de la esperanza de vida y cáncer.

Como los esteroides y la hormona del crecimiento, el dopaje con EPO a menudo se inyecta en dosis superiores a las normales, por lo que puede causar un incremento en la viscosidad de la sangre, trombosis venosas coronarias, trombosis cerebrales, embolias pulmonares, arritmias, infartos cerebrales y muerte. Se estima que un buen número de ciclistas europeos han podido morir debido a un abuso de EPO, convirtiéndola en uno de los agentes dopantes más peligrosos.

Retos de futuro

Gracias a la iniciativa de la WADA, algunas agencias antidopaje estatales (ej. USADA) y a programas de investigación nacional, existen múltiples líneas de investigación enfocadas a la detección de las nuevas sustancias dopantes.

Respecto al Laboratorio Antidopaje del Institut Municipal d'Investigació Mèdica (IMIM-Hospital del Mar) de Barcelona, alguna de las líneas de investigación se enfocan a:

- **Detección del aumento de disponibilidad de oxígeno:** eritropoyetina, terapia génica, transfusiones sanguíneas

  Eritropoyetina: En la actualidad se está trabajando en algunas sustancias endógenas que la industria farmacéutica produce mediante la recombinación, especialmente eritropoyetinas de 1ª, 2ª y 3ª generación, con el objetivo de caracterizar sus diferencias respecto a la hormona producida de forma endógena.

  También estamos intentando desarrollar anticuerpos monoclonales contra el ácido N-glicolilneuramínico, un monosacárido presente únicamente en el material recombinado, con el objetivo de desarrollar una técnica de alta sensibilidad. Los planes futuros se basan en el desarrollo de metodologías instrumentales para detectar la presencia de modificaciones en la glicosilación de proteínas (es la adicción de un carbohidrato a una molécula), que son los factores responsables de las diferencias entre la EPO endógena y la exógena.

  La terapia génica está avanzando como una de las terapias más importantes del siglo XXI. La idea de la técnica del dopaje genético parece relativamente sencilla: en lugar de inyectar una sustancia en el cuerpo del atleta, se enriquecen sus músculos con el gen que produce la sustancia. El resultado es el mismo, pero la detección resulta más complicada ya que aparece en los análisis como una sustancia generada por el propio cuerpo. En el ámbito del deporte, la detección diagnóstica de la aplicación de la terapia génica (dopaje génico) podría utilizarse para impedir la mala práctica de una herramienta médica tan importante. El proyecto de investigación está dirigido a aprender más sobre esta capacidad de diagnóstico, en coordinación con los principales grupos de genética e imagen del Parc de Recerca Biomèdica de Barcelona. Asimismo, actualmente todavía no se tiene constancia de la utilización de este método como un procedimiento de dopaje en humanos, pese a que se cree que puede ser realidad en futuro muy cercano.

  En lo que respecta al abuso sanguíneo, el objetivo consiste en desarrollar métodos para detectar el abuso de las transfusiones sanguíneas en los deportistas. Se estudiarán dos enfoques: el primero se basa en la detección de los agentes contaminantes presentes en las bolsas para almacenar sangre o concentrados de leucocitos; las concentraciones de estos agentes contaminantes y sus metabolitos deberían ser más elevadas en los fluidos corporales de individuos sujetos a transfusiones, en comparación con los sujetos que no reciben transfusiones. El segundo enfoque se basa en la detección de marcadores de envejecimiento de leucocitos por el almacenamiento de sangre en sujetos que reciben transfusiones.

- **Detección de factores de crecimiento:** hormona de crecimiento, secretagogos de la hormona de crecimiento, gonadotropina coriónica, esteroides, terapia génica y glicoconjugados.

  La Hormona de crecimiento (GH) es una de las hormonas más propensas a ser objeto de abuso tanto por parte de los deportistas como por padres de niños que presentan una talla baja idiopática. Un mejor conocimiento de su detección y de sus parámetros estructurales resulta realmente útil para evitar su abuso, especialmente si se tiene en cuenta la complejidad de su estructura a causa de las múltiples isoformas (directas, unidas y proteolíticamente derivadas) presentes en el cuerpo humano. En cuanto a la detección, resulta interesante el desarrollo de una herramienta analítica para medir la proporción entre las dos isoformas de la hormona de crecimiento endógenas más abundantes (20 y 22kDa). El uso ilícito de un fármaco con una única

isoforma alteraría esta proporción mediante un mecanismo de reacción, y esto, a su vez, constituiría un indicador de abuso.

El posible abuso de la terapia génica de la GH también es una posibilidad que ha de evitarse en el futuro y está desarrollando un proyecto con un protocolo similar al citado anteriormente para la eritropoyetina.

Otro método alternativo futuro para producir concentraciones elevadas de GH es la aplicación de secretagogos de la hormona de crecimiento (análogos de Ghrelina). Se está desarrollando un proyecto para estudiar la detección de los secretagogos de GH mediante un único protocolo de criba.

Información complementaria:

http://www.wada.org

http://www.imim.es/programesrecerca/neuropsicofarmarcologia/grbsa.html

http://www.imim.es/ofertadeserveis/en_laboratoriantidopatge.htm

WORLD ANTI-DOPING AGENCY
play true

Moving from toxicology to biology: the need for a medical approach in the Fight against Doping

Dr. Alain Garnier
Medical Director
World Anti-Doping Agency

The intent of the presentation is to highlight the need for a medical approach in the fight against doping today. Two main reasons can be developed to support this view.

In a first hand there is an ethical reason and we will try to demonstrate why it is the duty of physicians to oppose doping by all means and not to medically assist or support doping as proposed by some authors. In the current social context of performance and drug addiction, doping is not only cheating but mainly drug misuse. The primary role of physician is to protect mental and physical integrity of athletes, far beyond supporting or enhancing their sport performance. As quoted by Prof. Frontera, President of FIMS: “all sport physicians have the duty and responsibility to oppose the use of doping practices in sports based on moral, ethical and physiological grounds.” To accept medical doping results in accepting the use of medicine for other purposes than health; this is certainly not legitimate and potentially source of danger for the society. Sport reasons today could become economic reasons tomorrow in improving human performance to the detriment of health.

The second reason is more technical and based on efficiency. Effectively the classic and current approach of antidoping is mainly based on direct detection of prohibited substances in bodily specimen. Consequently it is more and more difficult to detect modern doping methods by using the traditional toxicological approach adapted to old techniques of doping.

The limits of the system have been reached if one considers the new substances used by cheats and the highly sophisticated protocols for doping abuse of EPO, blood manipulations or other growth factors use. The arrival of biotechnologies and gene therapy will certainly increase this trend. It is the responsibility of antidoping community to adapt the strategies and to

anticipate future trends if we do not want the progress of science operate only in favor of cheats. Consequently the recourse to a more biological and medical approach should be very useful. In that context the use of indirect markers of doping and its monitoring along time, as it is common in medical practice, must bring interesting results. The study of metabolic effects on the body subsequent to xenobiotic intake is known as metabonomic which is already producing encouraging results in veterinary medicine.

The presentation will develop the WADA proposed approach of the athlete passport and its principles.

Ethics and Doping: Ethos, Pathos or Kudos?

Michele Verroken

Director of Sporting Integrity, UK,
Anti-Doping Adviser to PGA European Tour
Secretary of the Medical Commission of the Commonwealth Games Federation
Formerly Director of Ethics and Anti-Doping, UK Sport

Abstract

Playing by the rules should be the very essence of sport. Important lessons for life are meant to be learned through playing sport; fair play, right from wrong, what is allowed and what is not allowed, winning and losing. However sport is struggling to maintain its level playing field. Corruption of sport through doping is destroying its unique ethos. Athletes, once pure performers, are now manufactured through scientifically driven training systems, using scientifically developed equipment. Drawing the line between what is acceptable and unacceptable is becoming more difficult.

This presentation will look at the principle of playing by the new rules of sport, the anti-doping rules contained in the World Anti-Doping Code. Principally designed to reinforce the fairness of sport, anti-doping rules have become caught up in this sporting rhetoric and are now contributing to a new ethical dimension of sport. In the tragedy of sporting competition, athletes are often cast as the victims of sporting systems, vulnerable to evil scientists and malevolent coaches. Fear of doping and cheating the doping system is driving the agenda, with increasing emphasis on control systems as the evidence gathering mechanisms to verify the drug-free athlete. Yet evidence gathered from anti-doping programmes to date does not always stand up to independent examination. Analysis of thousands of urine samples still indicates a small percentage of findings and not all of these are determined to be doping offences. What is the truth behind the doping problem as defined by the Code?

Athletes are challenging our faith in sport ever being drug –free, they lie and deny. A new breed of athlete is emerging, the ‘doping celebrity’. Consideration will be given to how far anti-doping systems need to go before sport has any credibility again.

The Anti-Doping Challenge: The Human Factor

How to be (or to become) an "Anti-Doping Scientist"

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Abstract

This presentation gives a general overview on the activity of the anti-doping laboratories accredited by the World Anti-Doping Agency (WADA), outlining the evolution, over the last four decades, of the strategy followed by the Anti-Doping Scientists to improve the effectiveness of the fight against doping in sport.

In particular, the focus is on the people facing their daily challenges in the laboratories to detect and deter the abuse of performance-enhancing drugs and methods by the athletes, on their scientific background, on their specific training, on their interaction with colleagues belonging to the same international scientific network (the World Association of Anti-Doping Scientists, WAADS), and, perhaps most importantly, on their constant transfer of knowledge to new generations of anti-doping scientists.

Special emphasis is given to the future evolution of the anti-doping science, as seen from the perspective of a laboratory scientist, in the wider context of fair play, health protection, and perception of the activity of the anti-doping laboratories by the general public.

Doping under the point of view of a former professional handball player. Incentives vs. punishments.

Xavier O'Callaghan

1990-2005 FC Barcelona Handball player.
Sydney 2000 and Athens 2004 Olympic athlete.
Since 2006 FC Barcelona Handball Team responsible.

The intention of my presentation will try to understand the doping under the fact of incentives and punishment. All athletes have been tempted to use doping, even for a second; may be by themselves, by their coaches or by their doctors. But the question is: why there are athletes who use doping and others no? Under my point of view the relation between incentives and punishments decides this election. We have to observe incentives under a wide list of items, not just money and fame. Everybody has different incentives and takes decisions under different parameters. But at the end the election, even if is not taken rationally, is based under the balance between incentives and punishments.

Even more, this is the reason because there are differences between individual and collective sports in the doping issue. The incentive as the fastest man in the world will be more evident if you compete alone than if you are part of a team. Doping goes related to the improvement of physical conditions, which are less relevant in collective sports than in individual sports.

As a final statement I would like to express my worry as I believe incentives to commit doping grow up in the sport world as we know it today. That's the reason because all actors in this market have to act in their best way to fight against the sport's worst enemy.

El Laboratorio de Control Antidopaje Barcelona. Instituto Municipal de Investigación Médica (IMIM-Hospital del Mar)

El **Laboratorio de Control Antidopaje de Barcelona** es uno de los 34 laboratorios acreditados actualmente por el Agencia Mundial Antidopaje, WADA, en el mundo.

Desde su acreditación en 1985 realiza controles antidopaje en atletas en competiciones deportivas y en períodos de entrenamiento, tanto a nivel nacional como internacional.

También realiza controles antidopaje en competiciones deportivas de animales.

El Laboratorio está acreditado por la Entidad Nacional de Acreditación, ENAC, según la Norma Internacional ISO/IEC 17025, y la Association of Official Racing Chemists (AORC).

El principal objetivo del **Laboratorio de Control Antidopaje de Barcelona** es ofrecer servicios de alta calidad y fiabilidad, por eso su actividad se centra también en el desarrollo de la investigación y de la formación continuada.

El **Laboratorio** ha realizado el control antidopaje en importantes acontecimientos deportivos: los Juegos Olímpicos y Paralímpicos celebrados en Barcelona en 1992; los Juegos Panamericanos celebrados en la Habana en 1991, Buenos Aires 1995, Juegos Panasiáticos de Bangkok 1999, Mundiales de Natación de Barcelona 2003, son algunos ejemplos.

Ámbitos de actuación

- Acontecimientos deportivos
- Participación en comisiones deportivas / antidopaje
- Experiencia Docente / investigación a nivel Internacional
- Software IMLIMS de gestión de laboratorios antidopaje

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Neurol Clin 26 (2008) 149–167

NEUROLOGIC
CLINICS

Enhancement Drugs and the Athlete

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Performance-enhancing drugs: a (brief) historical overview

The use of performance-enhancing drugs (PEDs) is perhaps as old as sport itself. The ingestion of plant and animal extracts to improve sport performance dates back to the origins of competitive sport, when Greek athletes competed in the ancient Olympics. Later, Roman gladiators had special potions prepared using a wide variety of natural products, including mushrooms, roots, and wines [1,2], to attempt to supplement performance. The use of PEDs became more systematic, no longer based on sorcery and alchemy but instead biochemistry and pharmacology, during the twentieth century, when the Olympic Games were reinvented after the recovery and promotion of the Olympic spirit heralded by Baron Pierre de Coubertin.

To compare the lifespan of the ancient Olympics with that of the modern Olympic Games, the first ancient Olympic Games took place in 776 BC and the last one was held in 393 AD, when, although the Games already had degenerated, they officially were abolished by the Roman emperor Theodosius, who, as a Christian, was against the heathen spirit of the Games [3,4]. The modern Olympic Games, the first edition of which took place in Athens in 1896, celebrates their 112th anniversary in Beijing in August 2008. It follows that the history of the ancient Olympics, spanning more than 11 centuries, is approximately 10 times longer than that of the modern Olympic Games.

This work was supported in part by Grants from the Italian Department of Health ("Commissione per la Vigilanza sul Doping e la Tutela Sanitaria delle Attività Sportive").

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doi:10.1016/j.ncl.2007.12.003

The history of PED use strictly follows the history of scientific development that took place at the time of the ancient and the modern Olympic Games; although the drugs used by athletes competing in the first ancient Olympic Games approximately were the same of those used 1 millennium later by their colleagues or by Roman gladiators, the illicit pharmacologic support to sport performance proceeded at a much faster pace in the twentieth century, with a further dramatic increase from the early 1960s to the present.

The problem of drug abuse in sport first was tackled by the international sport authorities, in the form of the International Olympic Committee (IOC), during the 1960s. An official definition of doping first was given by the IOC in 1964 and the first programs of antidoping tests were activated by the IOC and its newborn Medical Commission in 1967 [5–7]. It was in the late 1960s when, in parallel to the official sport competitions, another race began and continues to the present: the race between testers and cheaters.

Classification of performance-enhancing drugs: the "prohibited list"

The first official antidoping tests performed on the occasion of a multisport, international event took place at the Olympic Games of Mexico City in 1968. At that time, the only prohibited substances were those capable of producing a significant effect on sport performance only if administered, in sufficient amounts, right before or during the competition. Although short (compared with its current equivalent), that first list continuously was updated to include any new form of doping substance or method of administration. The periodic upgrades of the list were performed by the IOC Medical Commission until the constitution of the World Anti-Doping Agency (WADA) in 1999. Since then, as mandated by the World Anti-Doping Code [8], the WADA has been responsible for the upgrade and publication of the list. In the framework of the World Anti-Doping Code, the list is an international standard identifying substances and methods, classified by categories, that are prohibited in competition, out of competition, and in particular sports. In the past 40 years, the "prohibited list" has expanded progressively (Box 1): it now reports hundreds of compounds, including so-called "related substances" (ie, substances with similar chemical structure or similar biologic effects to those of a banned prototype) and several prohibited methods, including blood transfusions and gene doping [9].

The chronologic evolution of the "prohibited list" over the past 4 decades leads to identifying three main steps in the parallel expansion of the abuse of drugs in sport:

1. The first period, ranging from the origin of the modern Olympic Games to the early 1970s, coincides with the use of drugs whose efficacy, as discussed previously, is maximal if the administration takes place right before or even during the competition. This is the case with stimulants, narcotics, and some drugs of abuse (eg, cocaine).

Box 1. World Anti-Doping Code: the 2008 "prohibited list"

Substances and methods prohibited at all times (in and out of competition)

Prohibited substances

- S1. Anabolic agents
  1. Anabolic androgenic steroids (AAS)
     a. Exogenous AAS (eg, methyltestosterone, nandrolone, and stanozolol)
     b. Endogenous AAS (eg, testosterone, androsteonedione, DHT, and DHEA)
  2. Other anabolic agents (eg, clenbuterol and selective androgen receptor modulators)
- S2. Hormones and related substances (eg, EPO, human growth hormone, insulin-like growth factors, gonadotropins, insulins)
- S3. β_2-Agonists (eg, salbutamol, salmeterol, terbutaline, and formoterol)
- S4. Hormone antagonists and modulators (eg, antiestrogens and myostatin inhibitors)
- S5. Diuretics and other masking agents (eg, diuretics, epitestosterone, probenecid, α-reductase inhibitors, and plasma expanders)

Prohibited methods

- M1. Enhancement of oxygen transfer (eg, blood transfusions and use of blood derivatives and analogs)
- M2. Chemical and physical manipulation (eg, tampering and intravenous infusions)
- M3. Gene doping

Substances and methods prohibited in competition

- S6. Stimulants (eg, amphetamines, cocaine, strychnine, and ecstasy-like drugs)
- S7. Narcotics (eg, morphine and opioids)
- S8. Cannabinoids (eg, hashish and marijuana)
- S9. Glucocorticosteroids

Substances prohibited in particular sports

- P1. Alcohol
- P2. β-Blockers

Abbreviations: DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; EPO, erythropoietin.

Data From The World Anti-Doping Code. The 2008 prohibited list international standard. World Anti-Doping Agency. Montreal (Canada). 2007. Available at: www.wada.ama.org. Accessed October 31, 2007.

2. In the second period, the PEDs also included those compounds—mainly AAS—requiring repeated administration over a prolonged period of time to be effective. It is with the use of synthetic AAS that doping substances start to be used off label (ie, with the aim of achieving one or more effects that are different from those for which a specific drug originally had been developed and authorized). This period also marks the transition from pinpoint, in-competition doping, to carefully planned, out-of-competition, systematic doping.
3. The third period follows the pharmaceutical industry development of routine techniques in protein chemistry, molecular biology, and genetic engineering, and led to the abuse of peptide hormones (including, but not limited to, erythropoietin, growth hormone, and gonadotropins). The use of PEDs belonging to the class of peptide and glycoproteic hormones led to the development of new analytic strategies for their detection, including the use of "indirect" methods based on the measurements of specific markers.

A fourth period (the recourse to gene doping) is feared by many as the next step in the illicit search for the ultimate PEDs and methods. It is expected that gene doping will develop as soon as gene therapy is available practically.

Regardless of its complexity and length, the prohibited list stands as the fundamental reference document classifying all prohibited PEDs, prohibited methods, and masking agents. The fight against doping in sport has been based—and still continues to be based—on the capability of the antidoping laboratories to develop and apply analytic procedures for the most effective detection of all substances and methods included in the prohibited list.

The role of the World Anti-Doping Agency–accredited antidoping laboratories

There currently are 33 antidoping laboratories accredited by the WADA in the world (Box 2), performing more than 200,000 antidoping tests per year. A comprehensive report of the results of the analyses performed by the WADA laboratories worldwide is released yearly by WADA and made available for consultation through their website (www.wada-ama.org). In spite of the high number of tests, little information can be drawn simply on the basis of results of the antidoping analyses on the real toxic potential and the related mechanism of action of the many PEDs included in the WADA prohibited list. The antidoping analyses are forensic, but not diagnostic, tests. This means that the aim of the analysis is not to verify the "state of health or disease" of athletes but instead "to supply evidence"—based on the principle of strict liability—of the presence in the biologic sample of a substance (drug/metabolite/marker) included in the WADA prohibited list. It follows that the information supplied by the WADA-accredited

Box 2. Geographical distribution of the 33 antidoping laboratories accredited by the World Anti-Doping Agency

Africa: South Africa (Bloemfontein), Tunisia (Tunis)
Americas: Brazil (Rio de Janeiro), Canada (Montreal), Colombia (Bogota), Cuba (La Habana), United States (Los Angeles, Salt Lake City)
Asia: China (Beijing), Korea (Seoul), Japan (Tokyo), Malaysia (Penang), Thailand (Bangkok)
Europe: Austria (Seibersdorf), Belgium (Ghent), Czech Republic (Prague), Finland (Helsinki), France (Paris), Germany (Cologne, Kreischa), Greece (Athens), Italy (Rome), Norway (Oslo), Poland (Warsaw), Portugal (Lisbon), Russian Federation (Moscow), Spain (Barcelona, Madrid), Sweden (Stockholm), Switzerland (Lausanne), Turkey (Ankara), United Kingdom (London)
Oceania: Australia (Sydney)

antidoping laboratories refers to the identification of "markers of exposure," not of "markers of effect," of doping agents and methods.

The data supplied by the WADA-accredited antidoping laboratories also are of little epidemiologic value for the following reasons:

1. Despite the outstanding number of antidoping tests performed worldwide, the total number of positive samples is too limited to support any epidemiologic conclusions.
2. All samples analyzed by the laboratories are anonymous and, therefore, critical information necessary for the correct compilation of a reference database is not available (eg, ethnicity, age, height, weight, body mass index, genetic endowment, training level and regimen, and diet).
3. Samples are not collected as a part of a controlled study, and, therefore, it is impossible to carry out a real toxicity study correctly because of the potential influence of other confounding factors.
4. Finally, the WADA rules state clearly that the biologic samples collected in the framework of official antidoping tests cannot be used for purposes other than the antidoping test itself: this means that the activity of the laboratory has to be limited to the identification of specific compounds (drugs/metabolites/markers) whose presence (or whose concentration above a threshold value) is to be considered a proof of doping. No additional tests (including diagnostic tests) are allowed.

The same points hold true for the research activity performed within the network of the WADA-accredited laboratories via the World Association of Anti-Doping Scientists (WAADS), the international scientific society

promoting the sharing of knowledge among the accredited laboratories and the basic and applied research in development of new analytic methods. Because the result of a positive test constitutes the basis for the possible sanctioning of an athlete, all efforts are not devoted to diagnosing the health risks consequent to the use of PEDs but instead to guaranteeing the maximum of solidity of the experimental results. The International Standard Organization 17025 accreditation has been imposed since 2000 as a further prerequisite of accredited antidoping laboratories, and criteria for reporting positive samples must be in compliance with the WADA rules.

It is self-evident that there is little or no room, at present, for toxicologic evaluations. The potential toxicologic risks for abuse of performance-enhancing substances and methods cannot be evaluated fully by a single measurement of urinary/blood concentration values of drugs, metabolites, or other representative indicators of administration. Therefore, no toxicokinetic information can be estimated.

A further step forward will be represented by the final implementation of longitudinal studies, also known as the ''athlete passport'': the goal is to build a database for all athletes in which the main hematologic and hormonal parameters are recorded and monitored. Although these strategies are being developed with the main purpose of detecting, via the evaluation of indirect parameters, some forms of doping otherwise problematic to identify (eg, autologous blood transfusions), they also will contribute to shedding further light on the chronic effects of the abuse of PEDs. The implementation of novel diagnostic approaches, to be performed independently of the forensic antidoping tests, for the overall assessment of the toxicity of PEDs will remain mandatory to fully accomplish the requirements of an effective antidoping strategy [10].

The adverse side effects of performance-enhancing drugs: what is known and unknown

The possible health risks of doping substances and methods have been the subject of several review articles, monographs, and conference proceedings [11–16]. Mostly, these studies have been based on and supported by review of the scientific and medical literature, which have considered the results obtained in controlled, randomized clinical trials and the direct evidence obtained from clinical practice. It is impossible in this context to review, discuss, and outline the biochemical mechanisms of all the adverse effects of the PEDs described so far. To give an approximate idea of the variety of potential side effects of the different classes of substances included in the WADA-prohibited list (with the exception of alcohol, not a drug in the strict sense of the word), Table 1 lists the most common potential direct and indirect effects and the corresponding side effects of PEDs. It is evident that the risks/benefits ratio is always unbalanced toward the risks. Also, it is

virtually impossible for a single drug to produce all or none of the effects listed in Table 1 in one subject.

To correctly assess the real toxicologic potential of PEDs (which easily can include additional effects not considered in Table 1) is not an easy task. Most of the side effects tend to be the same as those reported after the therapeutic use of the same drugs. It is even more difficult to evaluate the actual toxicity for athletes, because information supplied by the WADA-accredited antidoping laboratories is insufficient. Also, administration of a drug for the enhancement of sport performance clearly is different from rules regulating the administration of the same drug when used within correctly planned therapeutic schemes in patients. The range of side effects can be wider than expected and intensity more severe (discussed later).

Use of off-label drugs

With the noteworthy exception of designer steroids (discussed later), all drugs administered for nonphysiologic enhancement of sport performance are well known drugs; but when they are administered within the framework of a doping strategy, they are used off label (ie, out of the range of therapeutic application for their original intent). In most cases, athletes understand that a drug is being used beyond its indicated uses. Under these circumstances, it could be difficult to extrapolate the theoretic side effects and compare with those observed in routine medical practice to obtain a representative picture of the actual risks for athletes.

Overdosing (acute or chronic)

Doping agents generally are used at doses higher than therapeutic doses. Therefore, it is reasonable to think that adverse effects could be more severe as the administered dose increases. Although good pharmacologic practice recommends minimizing administered doses and duration of use, this situation is reversed when the desired effect instead is improvement of sport performance.

Drug-drug interaction

PEDs seldom are administered alone. Many are used in association with other drugs (banned or allowed) and with a wide variety of nutritional supplements. Drugs may be combined to reach different goals, such as maximizing overall efficacy of the doping treatment, reducing risks for undesired side effects, and complicating their detection by accredited laboratories. Because the range of desired effects is broad, it is reasonable to expect that most of the corresponding drug-drug interactions never have been considered. No therapeutic scheme has been considered for the parallel administration (again, to a healthy person) of combined "therapeutic" schemes, which may

Table 1
Most common undesired side effects of the main classes of prohibited substances considered in the World Anti-Doping Agency list

Class of the World Anti-Doping Agency prohibited list	Potential direct/indirect effects enhancing sport performance	Side effects reported most commonly
S1. Anabolic agents AAS (endogenous and exogenous)	Generic anabolic effect, produced with the aim of enhancing muscle growth and weight and increasing strength, power, speed, endurance, and aggressiveness. Recovery times also should be improved.	A broad variety of effects (exhaustively reviewed in Ref. [30]), including, but not limited, to the following: Cardiovascular: hypertension, elevated risk of brain hemorrhages, myocardiac damage Hepatic: abnormal liver functions, cholestasis, development of androgen-dependent adenomas, depletion of high-density lipoprotein production Skeletal: water retention Dermal: seborrhea (steroid acne), oily skin, folliculitis, furunculosis Behavioral: increase of aggressiveness (aggressive psychoses), change in the libido, mood swings (euphoria followed by depression), mental disorders, headaches, dependence, or addiction Specific effects for men: testicular atrophy, altered spermatogenesis, prostate hypertrophy, gynecomastia Specific effects for women: virilization, atrophy of the uterus, effects on the ovary (polycystic ovary syndrome, ovary inflammations), reduction of the breast gland, hirsutism, hypothyroidism, lowering of the voice, alteration of the menstrual cycle, alopecia, effects on the connective tissue (striae distensae)

Other anabolic agents	Same as previously.	For the side effects of clenbuterol, see "S3. β_2-Agonists" Side effects of selective androgen receptor modulators still are under evaluation (these drugs are not yet marketed)
S2. Hormones and related substances		Risk common to all peptide hormones: immunogenicity
Human growth hormone, insulin-like growth factors	Anabolic effect	Data on the effects of prolonged recombinant human growth hormone treatment in adults are limited Acute overdosing could lead to hyperglycemia. Long-term overdosing could result in signs and symptoms of gigantism or acromegaly consistent with the known effects of excess growth hormone Other reported effects are hypertension, cardiomyopathy, respiratory disease, diabetes, abnormal lipid metabolism, and osteoarthritis Increase risk for breast and colorectal cancer
Recombinant erythropoietins	Increased production of red blood cells and hemoglobin, resulting in an augmented efficacy of the transport of oxygen to the muscle	Hypertension, thromboses (thrombophlebitis, microvascular thrombosis, and thrombosis of the retinal artery, and temporal and renal veins), pulmonary embolism, cerebral embolism, seizures Other effects include pyrexia, headache, arthralgias, nausea, edema, fatigue, diarrhea, vomiting, chest pain, skin reaction (on the site of injection), asthenia, dizziness

(*continued on next page*)

Table 1 (*continued*)

Class of the World Anti-Doping Agency prohibited list	Potential direct/indirect effects enhancing sport performance	Side effects reported most commonly
Gonadotropins (human chorionic gonadotropin, luteinizing hormone, and follicle-stimulating hormone)	To stimulate the endogenous production of androgens, and to contrast the negative effects of testosterone doping	Prostate carcinoma or other androgen-dependent neoplasm Sudden ovarian enlargement resulting from ovarian hyperstimulation, ascites with or without pain, or pleural effusion, rupture of ovarian cysts with resultant hemoperitoneum Arterial thromboembolism, headache, irritability, restlessness, depression, fatigue, edema, precocious puberty, gynecomastia, pain at the site of injection
Insulin	To improve glucose transport to muscle	All adverse effects of hypoglycemia (including loss of consciousness, coma, and death) Respiratory adverse effects Chest pain, dry mouth, otitis media
S3. β_2-Agonists	To achieve stimulants and anabolic effects after systemic administration of high doses, significantly higher than those prescribed—by inhalation—for the treatment of asthma	Cardiac arrest and even death may be associated with the abuse of any sympathomimetic medications. Other cardiovascular effect include, but are not limited to, increased pulse rate and blood pressure, ECG changes, seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/minute, arrhythmias. Hypokalemia also may occur Nervousness, headache, insomnia, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and sleeplessness

S4. Hormone antagonists and modulators		
Aromatase inhibitors (eg, anastrozole, letrozole, aminoglutethimide, exemestane, formestane, and testolactone)	To increase the production or decrease the biotransformation of endogenous AAS	At therapeutic doses: nonspecific toxic side effects, including (but not limited to) asthenia, headache, nausea, peripheral edema, fatigue, vomiting, and dyspepsia Long-term endocrinologic side effects can be severe if administered in sequence or in combination with tamoxifen or selective estrogen receptor modulators
Selective estrogen receptor modulators (eg, raloxifene, tamoxifen, and toremifene)	Same as previously	Hot flashes, flu-like syndrome, joint pain, rhinitis Blood clots, including deep vein thrombosis, and pulmonary embolus (rare)
Other antiestrogenic substances (eg, clomiphene, cyclofenil, and fulvestrant)	Same as previously	At high doses, nonspecific toxic side effects, including (but not limited to) nausea, vomiting, vasomotor flushes, visual blurring, spots or flashes, scotomata, ovarian enlargement with pelvic or abdominal pain
Agents modifying myostatin functions	To improve muscle growth by interfering with the action of myostatin.	Unknown: myostatin inhibitors never have been tested in human trials
S5. Diuretics and other masking agents		
Diuretics	1. To obtain a rapid and reversible reduction of the total body mass, an evident potential advantage in sports where weight categories are involved 2. To alter the normal urinary excretion of other PEDs or their metabolites (eg, by increasing the volume of urine and diluting them), making their detection by the antidoping laboratories more problematic	Hypotension Kidney dysfunction, dehydration (risk for central volume depletion), salt and water imbalance, electrolyte dispairement (eg, hyperosmolality, hyponatremia, hypokalemia, hypomagnesemia, hypocalcemia), muscle cramps Dizziness or lightheadedness, gastric effects, rash, impotence, secondary gout

(*continued on next page*)

Table 1 (*continued*)

Class of the World Anti-Doping Agency prohibited list	Potential direct/indirect effects enhancing sport performance	Side effects reported most commonly
Probenecid	To interfere with the normal excretion of other PEDs, especially AAS	Metabolic effects: precipitation of acute gouty arthritis Central nervous system: headache, dizziness Gastrointestinal: hepatic necrosis, nausea, anorexia, sore gums, vomiting Genitourinary: nephritic syndrome, uric acid stones with or without hematuria, renal colic, costovertebral pain, urinary frequency Hematologic: aplastic anemia, leucopenia, hemolytic anemia Integumental: dermatitis, alopecia, flushing (Rarely) severe allergic reactions and anaphylaxis
Epitestosterone	To adjust the value of the ratio of testosterone to epitestosterone	Unknown (epitestosterone is not a registered drug), even if likely overlapping to many of the side effects of the AAS
α-Reductase inhibitors (eg, finasteride and dutasteride)	Alteration of the endogenous steroid profile, interfering with the quantitation of some AAS and with the correct evaluation of longitudinal data	Alteration of the sexual function (impotence, decreased libido, decreased volume of ejaculate and other ejaculation disorders, breast enlargement, breast tenderness)
Plasma volume expanders (eg, dextran, hydroxyethylstarch and other modified polysaccharides)	To mask the effects of blood doping by blood dilution	Febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation, hypervolemia
S6. Stimulants Including, but not limited to Central nervous system stimulants	Increased alertness Improvement in coordination Increased strength and endurance, as a consequence of a decreased perception of pain and fatigue	Increased alertness Insomnia, anxiety Inhibited judgment

Respiratory stimulants Cardiovascular stimulants Appetite suppressants	Glycogen sparing effect in muscle	Increased competitiveness, aggressiveness, and hostility Reduced fatigue (risks for muscle and cardiac overload) Tremor Effect on the cardiovascular systems (increased heart rate and blood pressure) Increased risk for stroke, heart attack, or sudden death Effects on the skeletal muscle (rhabdomyolysis).
S7. Narcotics	Increased tolerance to pain and fatigue Transient reduction of tremor in precision events	Addiction (also as gateway to other drugs), tolerance, physical and psychologic dependence Increased pain threshold Euphoria Excitement, psychologic stimulation Incorrect perception of danger Loss of coordination/equilibrium Reduced capacity of concentration Nausea, vomiting, constipation Depression Reduced breath capacity Reduced cardiac frequency/output Overdosing can lead to respiratory depression and death Effects on the skeletal muscle (rhabdomyolysis)
S8. Cannabinoids	To relieve precompetition tension Social drugs: motivation for their use or abuse may be different from the illicit enhancement of sport performance	Drug dependence Psychomotor changes Antimotivational syndrome (loss of ambition)

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Table 1 (*continued*)

Class of the World Anti-Doping Agency prohibited list	Potential direct/indirect effects enhancing sport performance	Side effects reported most commonly
S9. Glucocorticosteroids	Effect on glucose metabolism (stimulation of de novo synthesis of glucose, conversion of amino acids into glucose, release of glucose from glycogen storage, and activation of the lipolysis in fat cells) Anti-inflammatory and analgesic properties, accompanied by euphoria Effects on the immune system	Acute: Hyperglycemia Fluid retention Mood alteration Chronic: Immunosuppression Suppression of the hypothalamic-pituitary-adrenal axis Musculoskeletal problems, also due to alteration of calcium metabolism and bone homeostasis Nonspecific effects (cataracts, diabetes mellitus, hypertension, peptic ulcer disease, weight gain, skin thinning, ecchymoses, striae, acne, hirsutism, fat redistribution, and various psychiatric disorders)
P2. β-Blockers	To reduce tremor, which gives a competitive advantage in specific sports/disciplines (eg, shooting, archery, curling, gymnastics)	Cardiovascular effects: bradycardia, cold extremities, postural hypotension, leg pain Central nervous system/neuromuscular effects: reversible mental depression progressing to catatonia, emotional lability, dizziness, vertigo, tiredness, fatigue, lethargy, drowsiness, depression, insomnia Hematologic effects: agranulocytosis Allergic: fever, sore throat, laryngospasm, respiratory distress Gastrointestinal: mesenteric arterial thrombosis, ischemic colitis, diarrhea, nausea Respiratory effects: wheeziness, dyspnea Other effects: impotency, hypoglycemia

include (1) erythropoietin, (2) anticoagulant agents, (3) anabolic steroids, (4) branched-chain amino acids, (5) glucocorticosteroids, and (6) diuretics [17]. It is evident that in such conditions the range of undesired side effects cannot be foreseen adequately.

Physical activity

The overall evaluation of PED side effects has to consider that active principles are administered during intense physical exercise in competition or out of competition (ie, during the training sessions). It is not unlikely to expect the range of undesired effects are more broad than those that listed in Table 1 or their intensity much more pronounced, given their use at the time of concurrent intense training.

The risks of the unknown: the dark side of designer steroids

Although used off label, many PEDs officially are approved drugs and have undergone a full toxicologic premarketing evaluation. A series of antidoping investigations performed recently have revealed that that new families of drugs, previously unknown to more mainstream pharmacology methodologies, have been developed to be used by athletes seeking enhancement of sport performance. Most of these drugs have been designed to obtain completely new substances, with only some minor modifications in their molecular structure from known synthetic AAS—these are called ''designer steroids.'' These previously unknown compounds have been synthesized illicitly by clandestine laboratories, operating out of the channel of the pharmaceutical industry. These steroids were supposed to be undetectable, because the practice of the antidoping laboratories is based on the availability of certified reference materials for all target substances: the final proof of the presence of a target within a biologic sample requires the comparison of the analytic signal with that obtained on a certified positive reference sample. There is no reference material available for detection of many of the designer steroids. Furthermore, no pharmacokinetic data are available regarding the metabolism and the excretion profile of the designer steroids. Therefore, it has been nearly impossible for laboratory-mediated selection of suitable urinary markers to detect designer steroids. Consequently, designer steroids have been referred to as the perfect anabolic agents: effective and invisible.

The discovery of the first designer steroid was in 2002, when a previously unknown synthetic AAS, norbolethone, was identified by the WADA-accredited antidoping laboratory of Los Angeles [18]. The discovery of norbolethone was followed by detection of other designer AAS, including tetrahydrogestrinone and desoxy-methyl testosterone (or madol) [19–21]. The antidoping laboratories reacted immediately to face this new analytic

challenge by making available suitable reference materials (most of them through the WAADS network) and developing a new series of analytic procedures for the detection of designer steroids and related substances. This task has been made possible by the development of a new generation of scientific instruments that provides additional tools for the early detection of designer steroids. A particularly promising approach couples a liquid chromatographer to a time-of-flight mass spectrometer [22]. The unique feature of time-of-flight mass spectrometer is its ability to record a broad amount of information from a single assay, giving the ability to return to a previously stored electronic data file and reassess for the possible presence of substances unknown at the time of initial analysis. Other analytic strategies, based on the use of simpler instrumentation, are those based on the use of triple quadrupole liquid chromatography coupled to mass spectrometry with sequential fragmentations (LC/MS-MS) operating in precursor ion scan acquisition mode, a technique that allows identification of compounds derived from a prototype molecular structure based on class-specific fragmentation patterns. This process can be applied to the screening not only of AAS but also other classes of structurally related compounds [23,24]. Although designer steroids no longer may be invisible to antidoping laboratories, their toxicologic profiles remain unknown. Designer steroids add a further item to the list of substances sought after, but because they are not ''known'' drugs, there have not been any official toxicologic studies performed on them [25].

The process by which the effectiveness and toxicity of a newly developed drug are determined with human volunteers can be structured into three stages (phases) after a drug is designed, synthesized, and preliminarily tested in vitro and in animal models.

1. In phase I clinical trials, a new drug or treatment is tested for the first time in a small group of people (20–80) to evaluate its activity, determine a safe dosage range, and identify the most evident side effects.
2. In phase II clinical trials, a study drug or treatment is administered to a larger group of people (100–300) to verify efficacy and further evaluate safety.
3. In phase III studies, a study drug or treatment is given to large groups of people (1000–3000) to confirm evidence obtained in phases I and II, to monitor the potential side effects further, to compare features to those of reference drugs and treatments, and to collect as much clinical information as possible to a the drug or treatment to be used safely in routine medical practice.

None of these steps ever has been performed or considered for designer steroids. For this reason, designer steroids represent perhaps the most dangerous threat to the health of athletes, and the administration of these drugs or any illicitly produced drug should be discouraged.

The hidden risks of nutritional supplements and the parallel market

A final aspect that has to be considered is the massive use by athletes of nonpharmaceutical products, especially nutritional supplements. These products (originally containing only amino acids, vitamins, and mineral salts) readily are available, actively marketed, and massively used by athletes. Because nutritional supplements are not drugs and generally seen as ''performance-allowing'' rather than ''performance-enhancing'' substances (and, as such, not included in the WADA-prohibited list), they are not actively included in many studies. If used correctly, nutritional supplements generally are believed safe, with the only known health risks consequent to intolerance or overdosing [26,27]. There are some cases in which the situation is not that simple: for instance, when a product contains one or more substances (or their precursors) included in the WADA list, especially when an athlete is not aware of their presence [28]. This is the case for (1) herbal products, in which the active principles may be indicated with different names (eg, ma huang instead of ephedrine); (2) prohormones, in which the active principles, correctly indicated in the label, are metabolic precursors of endogenous steroid hormones (such as androstenedione and norandrostenedione, precursors of testosterone and nandrolone, respectively); and (3) contaminated or mislabeled products, in which an athlete may be unaware of the presence of a forbidden substance. In the last case, presence of the illicit substance can be the result of accidental contamination or fraud. This problem was identified first by WADA-accredited laboratories. The Cologne Laboratory performed a thorough investigation of the products available on the international market (including those marketed via the Internet), identifying a high percentage of contaminated products [29]. Even in those products in which the concentration of nonlabeled ingredients is low (less than 0.01%), the risks for accumulation cannot be neglected, as many athletes regularly ingest considerable doses of nutritional supplements for long durations of time.

These observations also apply to the broad variety of pseudopharmaceutical products that increasingly are available via the Internet: in these cases, the lack of any pharmaceutical-grade quality control during their productive process could add further risks to those described for ''pure'' substances. The basic recommendation (as stated by the IOC Medical Commission in 2001) is to limit the use of nutritional supplements to certified products. Any other product should be evaluated carefully and possibly tested by specialized laboratories before being used.

Some conclusions and perspectives: toward a comprehensive toxicology of performance-enhancing drugs

The study of the adverse side effects of PEDs is far from complete. Stimulation of the development of novel investigative tools could complement

(1) the toxicologic studies performed as a part of the development of any new drug; (2) the statistic data supplied by the WADA-accredited antidoping laboratories (also considering the forthcoming activation of specific protocols for the longitudinal follow-up of athletes); (3) the indirect evidence obtained by studies performed on animal models; and (4) the anecdotic information circulated within athletes' environments. A complete assessment of the overall toxicologic profile of the many different PEDs likely will result from such thorough investigations.

The authors also believe that a decisive contribution could originate from the results of ad hoc in vitro studies, which could simulate conditions in which PEDs are used. It is ethically unacceptable to design toxicity studies on humans to reproduce the effects of a real doping protocol; at the same time, the simple extrapolation of results obtained from animal models likely are overly simplistic. The toxic effects of a drug likely are different in patients or healthy volunteers versus intensively training athletes, who are exposed to acidosis, hypoxemia, and tachycardia; toxicodynamic and toxicokinetics can be altered in those conditions. A further result of such an integrated approach would be to shift the interest in use of PEDs from a forensic to a clinical context, allowing not only the identification of markers of exposure to but also of markers of effects of doping substances and methods.

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An Open Letter to Those Promoting the Medical Supervision of Doping

By Dr. Alain Garnier, Medical Director, World Anti-Doping Agency

Following recent declarations of certain doctors who consider that doping is necessary and even healthy for athletes, it is time to reaffirm, once again and without equivocation, some very basic principles in medical practice and deontology.

If one is considering, in one's role as a sports physician, that elite sport is not healthy, then it means that this kind of practice is not well adapted to human physiology. If this is true, then it is difficult to justify the support and involvement of physicians in sports. After all, medical doctors have the obligation to protect the health of the athletes.

If a particular situation in sports is not compatible with human physiology and may be detrimental to the health of the athlete, one has in fact only two options: to change the sport or the rules that govern that sport to make it more compatible with the human condition, or to adapt athletes to the sport. The former is the action supported by the scientific literature in physiology, public health, and occupational medicine. The latter, regrettably chosen by certain doctors, leads one to justify doping as "indispensable."

To change sport or to change humans? That is the question. Given the imminence of gene therapy, we must not delay in addressing this question once and for all.

Always and without exception, a medical doctor should follow the principles of medical practice and defend the health of the athlete, independent of the level of competition or the potential economic consequences. In turn, sport organizations should always ensure this right to physicians, guaranteeing physicians independence in their medical decisions and protecting them from conflicts of interest. When faced with a situation that poses a threat to the athlete's health, a physician should neither accept the situation, nor act to render it bearable. Not following these basic principles of medical ethics leads to very serious consequences. Should a physician confronted with torture propose medical support in order to make it less detrimental to the individual? Certainly not, but those who propose medical supervision for doping are following exactly the same distorted logic.

In addition to the ethical reasons presented above, many other medical arguments oppose the acceptance of medically supervised doping.

Regardless of whether drugs or methods used for doping purposes can effectively enhance performance, there exists no scientific evidence that such practices are healthy, particularly in the mid- and long-term. Depending on the nature of the substance used for doping, the athlete may be able to compete for a longer time, perform faster, tolerate higher workloads, or better withstand pain—but these are certainly far from beneficial to health. To illustrate this point, one should consider a question frequently asked of physicians: in case of injury or fever, what should the legitimate medical attitude be? In general medical practice, the answer is always clear. Why should it be any different in sport? Can one imagine a doctor prescribing amphetamines to a truck driver because he or she is too tired to continue driving?

The use of even the most common drugs is associated with risks and potential side effects. Given this basic fact of pharmacology, any physician must understand the risk/benefit ratio before writing any prescription. Promoting doping for all athletes contradicts this basic principle of medicine. To argue that medically supervised doping is safer because a doctor is in charge misses the point entirely. There exists no credible data indicating that a drug is less dangerous when prescribed by a doctor. Everyday, in hospitals and clinics worldwide, patients experience the side effects of drugs despite strict monitoring by highly experienced doctors.

In medical practice the use of drugs is very strictly codified with indications and contra-indications. There is no evidence that competing in sports or exhausting exercise is an indication

Contrary to what the physicians defending doping pretend, accepting the idea of medical supervision of doping would immediately and irremediably lead to a generalization of doping and an exclusion from sport of all clean athletes who are opposed to using unnecessary drugs and want to defend the spirit of sport.

Use of doping agents, particularly anabolic steroids, in sports and society

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Lancet 2008; 371: 1872–82

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The use of doping agents, particularly anabolic androgenic steroids (AAS), has changed from being a problem restricted to sports to one of public-health concern. We review the prevalence of misuse, the evidence that some drugs improve performance in sport, their side-effects, and the long-term consequences of AAS misuse for society at large. There is substantial under-reporting of the side-effects of AAS to health authorities. We describe neuropsychiatric side-effects of AAS and their possible neurobiological correlates, with particular emphasis on violent behaviour. Analytical methods and laboratories accredited by the World Anti-Doping Agency can detect the misuse of all doping agents; although the analysis of testosterone requires special techniques, and recently discovered interethnic differences in testosterone excretion should be taken into account. The prevention of misuse of doping agents should include random doping analyses, medical follow-ups, pedagogic interventions, tougher legislation against possession of AAS, and longer disqualifications of athletes who use AAS.

Prevalence of doping in sport and society

The use of pharmacologically active substances to improve performance in work or sports goes back centuries but has increased in the past 40 years since the introduction of anabolic androgenic steroids (AAS; table 1).[1–7] In an article entitled "The toxic torch of the modern Olympic Games", Prendergast and coauthors state that the quest for greatness has driven many athletes and coaches to push for unfair advantages by the use of performance-enhancing (ergogenic) drugs, commonly referred to as "doping".[6] After the reunification of Germany, the horrifying features of the doping of Olympian competitors in the former East Germany were revealed.[7]

The use of doping agents is no longer restricted to competing athletes; young sportspeople in schools and non-competing amateurs also use them. Misuse of AAS is increasing among gym customers for whom bodily appearance is a priority. Estimates of misuse have to be interpreted with great caution due to the difficulties of reliable studies of illicit drug use. In the USA, between 1 million and 3 million people are thought to have misused AAS;[8,9] the estimate for Sweden is 50 000–100 000, among a population of 9 million. These estimates roughly equate to 1% of the respective populations.

Interviews of high-school students in several European countries and the USA reveal that 1–5% have used AAS, but this measure is of doubtful relevance for the population at risk of serious side-effects, which develop during long-term use.[10] An investigation of 6000 Swedish people age 16–17 years with an anonymous multiple-choice questionnaire revealed that 3·2% of males had used AAS, but none of the females had.[11,12] There was an association between the misuse of AAS and the use of substances such as alcohol, growth hormone, and narcotic drugs. In males, visible results of physical training were thought important for self-confidence, respect from girls, and security in nightlife and beach culture.[13] An informational intervention programme led to a decrease of almost 50% in misuse in males.[14]

Much higher estimates of misuse of AAS have been obtained in groups such as bodybuilders, weight-lifters, and prison populations.[10] A German study assessed the use of AAS among visitors to fitness centres by use of anonymous questionnaires. Although only 34·5% of these were returned, 13·5% in this selected group reported that they had used AAS at some point.[15] In this study, only 3·9% of women had used AAS, and studies in Great Britain and the USA have found similar levels of use among women.[16]

The best estimates of stimulant drug misuse are available for ephedrine. Ephedra alkaloids are popular components of many nutritional supplements and are also used as stimulants on their own. As many as 2·8 million US recreational athletes might have used ephedrine in 2001.[16]

Since 1993, the Swedish government has sponsored the antidoping hotline—a telephone service answering questions about doping from anonymous callers involved in or exposed to doping.[17] Between 1993 and 2006 the organisation received about 40 000 calls. Callers connected with gyms were the largest group (30%). Most calls were about AAS such as testosterone, nandrolone decanoate, methandienone, and stanozolol (table 2).

Substances prohibited in sports

The World Anti-Doping Agency (WADA) publishes a yearly list (panel 1) of substances and practices prohibited at all time in and out of competition. When prescribing listed drugs, physicians must be prepared to verify that the drug is medically justified and can be given a therapeutic-use exemption,[18] a decision that requires assessment by the relevant sports organisation. As an example, a therapeutic-use exemption is needed if a β2-adrenoceptor-agonist or corticosteroid inhalation is prescribed for bronchoconstriction.[19]

There are different rationales for including a drug on the WADA list. The original idea was to list drugs known or suspected to improve performance in sports. After

For the **World Anti-Doping Agency** see www.wada-ama.org

confrontation with the realities of doping, other reasons were accepted, such as the safety of the athletes, social unacceptability, and attempts to make doping analyses insensitive. Anti-oestrogens are on the list because they are sometimes used to antagonise the oestrogenic side-effects of AAS and other drugs.

There is also a list of substances prohibited in competition (panel 2). Alcohol is prohibited only in certain sports (eg, racing with automobiles and motorcycles). β blockers are prohibited in sports in which absence of a high pulse rate and tremor is advantageous (eg, shooting).

Prohibited practices in sports include enhancement of oxygen transfer (eg, blood doping), chemical and physical manipulation of samples collected during doping controls, and gene doping to administer erythropoietin or other genes that might affect athletic performance, which is a possible future development. Blood doping is any method or substance used for non-medical purposes that improves aerobic performance by increasing oxygen flow to peripheral tissues in athletes, and it includes blood transfusion and the use of recombinant erythropoietin.[20]

Do doping agents improve sporting ability?

Experimental studies

There is plenty of empirical evidence that doping agents improve performance in sport but very few experimental studies of the kind that are needed for a drug to be approved for marketing. An exception are Smith and Beecher's classic studies,[21,22] results of which showed that amphetamine in therapeutic doses (14 mg per 70 kg) improved performance in short-distance swimming and sprinting. The difference between the effects of placebo and amphetamine was small but enough to make the difference between competitive renown and obscurity.[23] In a double-blind, randomised, crossover study, a 180 mg dose of pseudoephedrine (three-times the therapeutic dose) decreased the time to complete a 1500 m run by 2·1% with no reported side-effects.[24] The use of ephedrine itself is thought unsafe because of its cardiovascular side-effects,[25] and its ergogenic effects are equivocal.[26,27] The same is true for several other central stimulants such as phenylpropanolamine, cocaine, and methylphenidate.[9] Despite this risk, ephedra and other central stimulants are commonly used, for example, by college athletes before a hockey game.[28] A combination of ephedrine and caffeine is popular for doping purposes, and evidence suggests that the combination is more effective than either drug alone.[27]

There is no conclusive evidence that growth hormone improves athletic performance.[29,30] This drug is usually taken in doses that are ten to 20 times the therapeutic level and commonly in combination with AAS in cycles of 4–6 weeks.[30] Up to 5% of US high-school students have tried growth hormone as an anabolic agent.[30]

	Use of doping agents
Centuries ago	Incas chewed coca (*Erythroxylon* spp) leaves to sustain strenuous work; Berserkers, Norse warriors, ate mushrooms containing muscarine before battle
Ancient Olympians	Bread soaked in opium, mushrooms, strychnine
Early 1900	Canal swimmers and cyclists taking central stimulants
World War II	Amphetamine to counter fatigue among soldiers and pilots
1950	Anabolic androgenic steroids introduced in doping; dianazol synthesis inspired by people in sports
1959	Classical controlled studies show that amphetamine improves performance in short distance swimming and running
1960 Olympics	First documented doping fatality—amphetamine induced heatstroke
1964	The International Olympic Committee (IOC) bans doping for Olympic athletes
1966–72	East Germany introduces a secret national system for hormone doping of both men and women with methandrostenolone and state manufactured oral-turinabal
1967	Doping death during Tour de France, IOC adopts a drug-testing policy
1970	Diuretics used to reach the "right" weight and to dilute urine before drug testing
1973	Olympic champion Connolly testifies on the common use of anabolic steroids among athletes to US Senate committee
1974	Anabolic androgenic steroids (AAS) put on the doping list
Up to 1980	Amphetamine, cocaine, caffeine, and strychnine dominate doping incidents
1980	AAS spread to many sports
1980	β-blockers used to improve shooting; misuse of growth hormone appears
1988	First Olympian gold medal in track and field stripped due to doping with AAS
2000	Tetrahydrogestrinone (THG or "the clear"), an AAS designed to escape detection in doping analyses, is developed
2007	Marion Jones admits having taken "the clear", a performance-enhancing drug listed to the Bay Area Laboratory

Table 1: **Historical overview of doping in society and sports**[1-7]

Early experimental studies of the ergogenic effects of AAS in sports were inconclusive. Many of these studies lacked adequate controls and had other weaknesses in design,[31,32] such as small groups of volunteers (10–24) and doses far below those used in sports.

Athletes commonly take megadoses of steroids—doses 50–100 times the amount needed to replace physiological steroid concentrations. Steroids are taken out of the competition season in cycles lasting 4–12 weeks. Many athletes take multiple steroids at once, known as stacking, and "pyramid" the dosing schedule, taking the highest total doses in the middle of the cycle. Breaks, known as drug holidays, of varying duration are common between the cycles.[5]

The opinions about the efficacy of AAS have gradually shifted from scepticism[31,33,34] to a consensus that these drugs might have some positive effects on strength when combined with muscular training, such as bench presses and lifts.[35,36] Athletes taking anabolic steroids can expect increases in muscular strength but not in aerobic gains.[37] In a randomised controlled study, healthy men received 600 mg of testosterone enanthate or placebo weekly for 10 weeks, the highest dose reported in volunteers.[38] When combined with strength training, testosterone increased fat-free mass, muscle size, and strength.[38] AAS might cause hypertrophy in human skeletal muscle even in the absence of strength training.[39,40]

	Substance being misused (%)		Substance being discussed (%)	
	1996–2000	2001–06	1996–2000	2001–06
AAS	(n=5505)	(n=3876)	(n=3372)	(n=1426)
Testosterone	27%	26%	26%	19%
Methandienone ("Russian")	26%	16%	19%	14%
Nandrolone	16%	24%	18%	22%
Stanozolol	9%	12%	13%	11%
Others	23%	21%	21%	34%
Other hormones and related agents	(n=421)	(n=679)	(n=509)	(n=186)
hCG/tamoxifen	58%	58%	37%	53%
GH/IGF1/insulin	42%	42%	63%	47%
Other substances	(n=1733)	(n=1594)	(n=4161)	(n=687)
Ephedrine	23%	24%	21%	27%
Clenbuterol	12%	10%	12%	10%
GHB	6%	2%	7%	2%
Narcotics unspecified	16%	17%	4%	21%
Alcohol	1%	2%	0·3%	8%
Creatine	11%	10%	8%	3%
Dietary supplement	16%	19%	14%	14%
Prescription drugs not specified here	15%	17%	33%	14%

AAS=anabolic androgenic steroids. hCG=human chorionic gonadotropin. Grt=growth hormone. IGF1=insulin-like growth factor 1. GHB=γ-hydroxybutyric acid.

Table 2: **Substances reported to the Swedish Anti-Doping Hot-Line during 1996–2000[17] and 2001–06 (unpublished data)**

Although there was academic controversy about published results, the secret doping programme using megadoses of AAS in East Germany confirmed the ergogenic effects of this class of drugs. Franke and Berendok[7] reported how hundreds of physicians and scientists became involved in unethical doping to promote the sporting success of East Germany from 1966 until the reunification of Germany in 1990.

Recent studies of muscular biopsies from athletes involved in doping[41–43] showed that AAS further increased the muscle-fibre hypertrophy induced by strength training. The number of nuclei per muscle fibre was higher in powerlifters using AAS than in controls. Unexpectedly, the number of myonuclei remained high in people who had stopped taking AAS several years previously.

Blood transfusion has been used for doping purposes as an effective way to increase the oxygen-carrying capacity of the blood.[20] Recombinant human erythropoietin, the ergogenic effects of which were documented in professional skiers in 1991,[44] has replaced this practice. Erythropoietin provides significant benefits due to substantial increases in haemoglobin, haematocrit, maximum oxygen uptake, and exercise endurance time.[45]

Empirical evidence

Many case reports suggest that doping with AAS is effective. Notable examples include Ben Johnson's gold medal for the 100 m at the Seoul Olympics in 1988, and hundreds of other winning elite athletes who have been caught in doping tests. Furthermore, world records in power sports seem to have reached a steady state since the introduction of sensitive doping tests.

Adverse reactions to doping agents

Central stimulants

Central stimulants still dominate doping in sports, but their dose-dependent adverse reactions preclude the use of megadoses. The most prominent side-effects include adrenergic effects in the CNS and the cardiovascular system. Amphetamine causes euphoria, relieves fatigue, and promotes self-confidence. Somatic effects include increased pulse-rate, hypertension, arrhythmias, and hyperthermia. High doses may produce aggressive behaviour and psychosis.[21,26]

Ephedrine has a particularly bad reputation for its many side-effects. In 2001, ephedra accounted for 0·8% of herbal product sales in the USA but for 64% of adverse herbal reactions.[46] These include cardiovascular symptoms (hypertension, arhythmias), central nervous symptoms (anxiety, tremor, paranoid psychoses), potentially life-threatening events (myocardial infarction), and even death.[47,48]

Furthermore, exposure to amphetamine and cocaine in sport can lead to misuse later in life.

Anabolic androgenic steroids (AAS)

Endocrine effects and side-effects

All AAS bind to the one type of androgen receptor, albeit with different affinities. Since these receptors are saturated in unmedicated men, supraphysiological doses of AAS may exert secondary effects, for example, by displacing cortisol from its receptors thereby inhibiting its catabolic effects.[49]

The structure, distribution, and regulation of the androgen receptors are well characterised[50,51]—they are located not only in the male reproductive and accessory sex tissues but also in other tissues, such as skeletal muscle, skin, and parts of the brain.[50] The steroids bind to androgen receptors in the cytoplasm. In the nucleus, the binding of receptors to target genes triggers DNA transcription and the synthesis of specific proteins that mediate hormonal function.[50,51] All androgenic hormones exert both masculinising and anabolic effects. The endocrine effects are dominated by testicular atrophy, sterility, disfiguring gynaecomastia in males, and virilisation in females—including hirsutism, amenorrhoea, clitoral hypertrophy, and a hoarse voice.[49,52–54] Androgenisation of sportswomen in the former East Germany has had severe adverse results, such as hirsutism with gynaecological disorders, such as long-term amenorrhoea and ovarian cysts.[6]

Somatic side-effects

The unfavourable changes in blood lipid profiles caused by AAS[10] include an increase in the concentration of

Panel 1: Substances and methods prohibited in sports at all times according to WADA, 2008

Anabolic agents
- AAS
- Exogenous AAS (eg, danazol, nandrolone, stanozolol)
- Endogenous AAS (eg, testosterone)
- Other anabolic agents (eg, desbuterol, androgen-receptor modulators)

Hormones and related substances*
- Erythropoietin
- Growth hormone, insulin-like growth factors (eg, IGF1), mechano growth factors (MGFs)
- Gonadotropins (eg, LH, human chorionic gonadotropin; prohibited in males only)
- Insulins
- Corticotropins

β-2-agonists
- All β-2-agonists including their D and L isomers
- Inhalation of β-2-agonists requires a therapeutic-use exemption

Hormone antagonists and modulators
- Aromatase inhibitors (eg, anastrozole, letrozole)
- Selective oestrogen-receptor modulators (eg, tamoxifen)
- Other antioestrogenic substances (eg, clomiphene)
- Agents modifying myostatin functions (eg, myostatin inhibitors)

Diuretics and other masking agents
- Diuretics
- Epitestosterone
- Probenecid
- α-reductase inhibitors (eg, finasteride, plasma expanders)

*Unless the athlete can prove that the concentration is due to a physiological or pathological disorder.

Panel 2: Substances prohibited in competition according to WADA, 2008

- Stimulants, both optical isomers (eg, amphetamine, cocaine, ephedrine*, methylephedrine, fenfluramine, D-methamphetamine, methylphenidate, modafinil, pemoline, selegiline, sibutramine, strychnine)
- Narcotics (eg, all opiates)
- Cannabinoids (eg, hashish, marijuana)
- Glucocorticosteroids, all are prohibited and their use requires a therapeutic-use exemption

*Threshold value of 10 μg/mL.

LDL, a decrease in the concentration of HDL by 30–50%, and a reduction in the concentration of apoprotein A1.[55–58] These metabolic changes explain the many reports of cardiovascular disease and hypertension in people who misuse AAS.

In 1993, Kennedy and Lawrence[59] reported the deaths of two young footballers who had misused oxymesterone;[59] both sustained fatal cardiac arrests during training and hypertrophic cardiomyopathy, irritability, and sudden rages had been noted soon before death. The authors also described six published cases of myocardial infarction, of which three were fatal, associated with the use of anabolic steroids.

Madea and Grellner[60] described several serious somatic side-effects in a 25-year-old man on multiple steroids. The patient had practised body-building with steroids from the age of 15 years and developed severe disturbances of lipid metabolism, had hormonal changes in his blood profile, and died with extreme hypertrophy of the heart. He had hypertension, obesity, mood disorders, ruptures of various muscles, and secondary hypogonadism. A recent case report also showed the serious cardiac side-effects of AAS.[61] Echocardiographic examinations indicate an association between AAS abuse and left-ventricular hypertrophy.[62–64]

62 Finnish powerlifters who were strongly suspected of having used megadoses of AAS over several years were followed up for 12 years.[65] Mortality in this group was 12·9% (mean age at death was 43 years) compared with 3·1% in the control group of 1094 people participating in the WHO MONICA study (mean age at death not reported). Suicide and acute myocardial infarction accounted for six of the eight deaths.

Rare cases of hepatic complications have also been reported, such as cholestasis, peliosis, adenomas,[66–68] and raised concentrations of liver transaminases.[56] Premature closure of the epiphyseal growth plates is a concern among adolescents taking AAS.[69] Up to 2·7% of middle-school students (age 9–13 years) have used steroids.[70] Physical signs of high doses of AAS are summarised in panel 3.[71]

Neuropsychiatric side-effects

In 1974, Wilson and colleagues observed that small doses of methyltestosterone added to imipramine provoke paranoid delusions in patients with depression.[72] And 20 years ago, Pope and Katz[73] reported psychosis in sportsmen misusing steroids. In a controlled but retrospective study, 20 male weight-lifters using AAS were compared with 20 male weight-lifters who had never used steroids.[74] The steroid users had more psychiatric side-effects than the control group; these included anxiety, depression, hostility, and paranoia. In a controlled study of 156 athletes, 88 using steroids, 20 (23%) of the users reported major mood changes, such as mania, hypomania, and major depression—symptoms that were not seen in non-users.[75]

The first placebo-controlled trial of an AAS (methyltestosterone in doses of 40 mg/day and 240 mg/day) in 20 healthy male volunteers was published

Panel 3: **Physical signs in patients using megadoses of AAS[71]**

Vital signs
Increased blood pressure (relatively uncommon)

Skin
Acne, male pattern baldness, striae, jaundice with liver disease, hirsutism in women

Head and neck
Jaundiced eyes with liver disease, deepening of the voice in women

Chest
Gynaecomastia with tenderness in men

Abdominal
Right-upper-quadrant tenderness and hepatomegaly with liver disease

Genitourinary
Testicular atrophy and prostatic hypertrophy in men
Clitoral hypertrophy in women

Musculoskeletal
Generalised muscle hypertrophy with disproportionately large upper-body mass (especially neck, shoulders, arms and chest)

Extremities
Oedema due to water retention for which diuretics may be used

in 1993.[76] This trial had a 2-week, double-blind, fixed-order, placebo-controlled, crossover design. The healthy volunteers were medication-free, somatically and psychiatrically healthy, not involved in athletic training, and had no history of AAS use. There were small but statistically significant increases in symptom scores at the 240 mg dose both in positive (euphoria, energy, and sexual arousal) and negative mood (irritability, mood swings, violent feelings, and hostility) and in cognitive impairment (distractibility, forgetfulness, and confusion). One of the participants developed an acute manic episode and one became hypomanic, thus indicating pronounced interindividual differences in the effects on CNS functions.

Several articles have confirmed the psychological and behavioural side-effects of endogenous testosterone and AAS and documented increased aggressive behaviour in volunteers.[77–79] The range of psychiatric side-effects induced by AAS and their severity increase with the intensity of misuse.[80]

The first case report of violent criminal acts induced by an anabolic steroid (oxymethalone) was published 20 years ago.[81] Aggression and violence toward women who are partners of strength athletes illicitly using AAS was later described.[82] In our experience, many female callers to our antidoping hotline worry about aggression and violence from partners using AAS.

In 1997, Thiblin and colleagues[83] pointed out that alcohol and AAS seem to be strongly synergistic in producing impulsive violent behaviour. The authors retrospectively analysed information from forensic psychiatric assessment, police reports, and court records of 14 users of AAS. This series comprised five cases of murder, five cases of assault, and four of robbery, one resulting in homicide. In eleven of these cases the perpetrators were intoxicated with alcohol while committing the crime. In agreement with anecdotal reports, there is greatly increased mortality in young people who misuse AAS.[84]

Early attempts to relate violent crime to misuse of AAS have been made in studies of Swedish prisoners; although no associations were found, the studies were hampered because a high percentage of the prisoners refused to give urine samples.[85] Petersson and co-workers recently used a new approach to the study of morbidity and mortality in users of AAS.[86] Patients referred from inpatient and outpatient clinics and who had tested positive for AAS (n=248) while receiving medical care were compared with patients who tested negative (n=1215). The proportion of patients who had received institutional care for substance use or psychiatric disorders was significantly higher in the AAS-positive group, as was the standardised mortality rate.[86]

The same research group[87] also reported the manner of death in 52 autopsied users of AAS (confirmed by drug analysis); the control group comprised 68 dead users of amphetamine, heroin, or both who tested negative for AAS. The AAS positive individuals died at a mean of 24·5 years, compared with 34 years for users of heroin and amphetamine and 40 years in amphetamine users; suicide or homicide were also more common among the users of AAS. The AAS users additionally used other illicit drugs to a great extent, particularly opiates. These data strongly suggest that AAS users are more likely to become involved in incidents leading to violent death than are other users of illegal drugs. In another study, weapons offence and fraud were more common in individuals testing positive for AAS than among control individuals.[88]

Further epidemiological studies are needed to assess whether the AAS precipitates antisocial behaviour or whether people prone to such behaviour are particularly inclined to use these drugs.

Research into mechanisms involved in the behavioural effects of AAS has focused on the serotoninergic system. Chronic administration of testosterone to rats induces a decrease in brain concentrations of serotonin and its main metabolite, 5-hydroxyindolacetic acid (5-HIAA), which is associated with increased aggression.[89,90] AAS also decreases the number of serotonin receptors in the limbic system.[91] However, there are many other neurobiological changes caused by AAS in animals,[92]

such as increases in the concentrations of nerve growth factor in the hippocampus and decreases in the hypothalamus.[93] Extrapolation to human beings is difficult because of species differences in drug metabolism. Furthermore, plasma and brain concentrations of AAS have not been measured in animals to permit such a comparison.

In human volunteers who received methyltestosterone at a dose of 40 mg per day for 3 days and 240 mg per day for a further 3 days,[94] there were increases in 5-HIAA concentrations in cerebrospinal fluid, which were related to the hypomanic behaviour.[94] Mood and behavioural effects of AAS may, in part, reflect secondary hormonal changes,[95] but the 5-HIAA findings are particularly interesting because low cerebrospinal-fluid concentrations of this serotonin metabolite are linked to depression and suicidal behaviour.[96–98]

People who use AAS are more likely than non-users to misuse other drugs and alcohol.[12,99] Rats treated with AAS have higher voluntary alcohol consumption than control rats.[100] A much debated question is whether the misuse of AAS is a gateway to substance abuse in general.[101] In a case-control study, many users of AAS misused several other substances—either recreational or prescription drugs.[102,103]

According to Brower,[71] no misuse has occurred after therapeutic doses of AAS. By contrast up to 2002, there have been 165 reported instances of AAS dependence among body-builders and weight-lifters taking supraphysiological doses, commonly in combination with misuse of other drugs.

Erythropoietin

The risks with erythropoietin doping are serious and include myocardial infarction, cerebrovascular disease, and serious thromboembolic events,[20] such as cerebral sinus thrombosis.[104] Predictable complications include polycythaemic disorders and hypertension.[20]

Under-reporting of side-effects

As most of these substances are illegal and cannot be obtained by prescription, physicians rarely report their side-effects to national centres of pharmacovigilance. During 1996–2000, 4335 people reported about 10 800 side-effects to the Swedish antidoping hotline.[17] In the same period, prescribers reported only 27 cases involving doping agents to the Swedish adverse-drug-reactions committee. Side-effects of doping agents, particularly AAS, are a much bigger problem in society than hitherto recognised.

Detection of misuse

Analytical methods accredited by WADA

Athletics drug testing has been described in several reviews.[4,105] Not until the 1976 Olympic Games did suitable tests for AAS become available to enable an enforceable ban.[105,106] Abuse of doping agents in sports can be verified by the 30 laboratories accredited by WADA for doping control in national and international events, including the Olympic Games. Some laboratories are also involved in random unannounced doping controls between games. The analytical methods have a much better precision and sensitivity than the usual routine methods used in clinical chemistry. Urine or blood samples are first screened and suspicious results ultimately confirmed with advanced methods based on mass spectrometry.

Attempts to mask the presence of doping agents in urine (eg, by use of diuretics and probenecid) have generally failed. New anabolic steroids have been designed to avoid detection in doping controls, but laboratories have developed tests to detect these substances as well.

Special problems with analysis of testosterone—pharmacogenetic aspects

The large differences in urinary kinetics of various AAS are a poorly explored problem and present a challenge

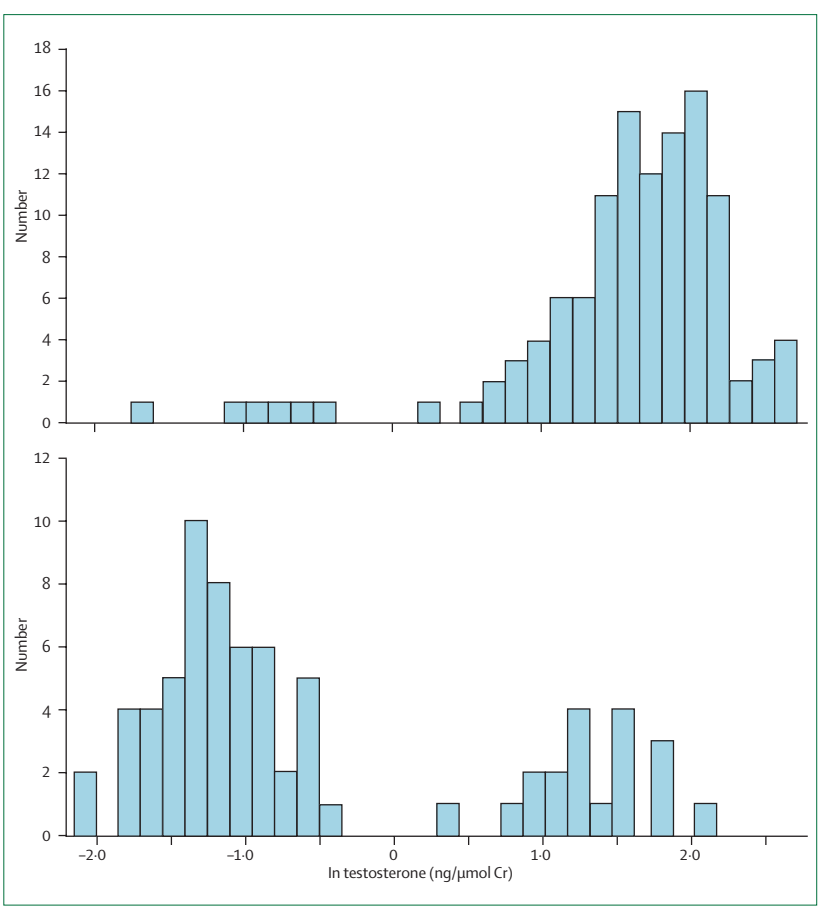

Figure 1: **Urinary excretion of testosterone**
Frequency distribution of natural logarithms of urinary unconjugated + glucuronide conjugated testosterone (ng/μmol Cr) in Swedish (n=122; top) and Korean (n=74; bottom) populations of healthy men. Both groups show a bimodal distribution of testosterone excretion rate. Fast excretors dominate in the Swedish sample but are rare in the Korean sample.[123]

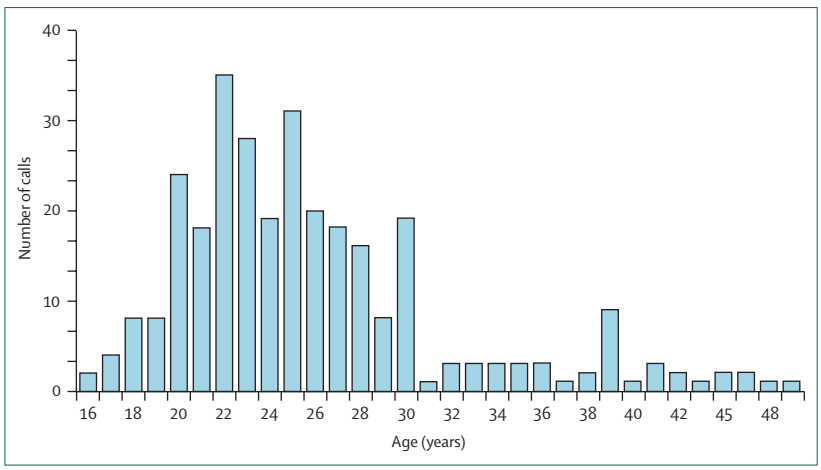

Figure 2: **Age profile of people who contacted the Swedish antidoping hotline in 2006**
People contacted the hotline in person or via a relative for information. Data were similar for years before 2006.

for future research. Although water soluble compounds (such as oxandrolone) yield positive doping tests for only a few days after oral administration, an intramuscular injection of nandrolone decanoate results in metabolites that can be detected several months later.[4]

The challenge has been to differentiate between exogenous and endogenous testosterone.[106] Manfred Donike suggested, in 1983, that the urinary ratio of testosterone and the naturally occurring isomer epitestosterone (T/E ratio) might indicate the use of exogenous testosterone[107] as the concentration of epitestosterone is not affected by intake of testosterone. Statistical reasons suggested that a T/E ratio greater than 6 was highly suggestive of testosterone doping. Subsequent observations from limited studies indicated, however, that urinary T/E ratios vary a lot between individuals,[108–111] suggesting an influence of genetic factors.

The adrenal glands are a major source of precursors of sex steroids. Prohormones such as dihydroepiandrosterone and androstenedione, also used in doping, are secreted into the blood and then bioactivated in the gonads and the prostate into testosterone and dihydrotestosterone. The gonadal function is partly governed by pituitary LH and FSH, which are kept in balance with the circulating hormones by virtue of an endocrine feedback system. Although most circulating testosterone is generated in the testes, the prostate also contributes substantially through bioactivation of dihydroepiandrosterone and androstenedione,[112] which are sometimes used in doping to increase testosterone production.[112]

The major drug metabolising enzymes in the cytochrome P450 (CYP) family are inherited in a polymorphic way which may confer 100–1000-fold differences in metabolic capacity among individuals.[113] Because the same or related enzymes, such as CYP3A:s and CYP17, metabolise many androgens and drugs,[114–117] there is probably genetic variability in the metabolism of AAS.[118,119] This variation may affect not only renal excretion patterns but also intracrine concentrations of androgens and, hence, their organ effects.

Testosterone is excreted mainly as conjugates after glucuronidation by uridine diphospho-glucuronosyl transferases (UGT). These enzymes have a key role in the homoeostasis of several endogenous molecules, including steroid hormones, facilitating their excretion in urine.[120,121] There are seven members of the UGT2B subfamily,[122–124] of which UGT2B17 and UGT2B7 are particularly active in the glucuronidation of testosterone and epitestosterone.

We compared the excretion of testosterone, epitestosterone, and many other androgens in a large sample of Swedish and Korean people. Swedish people had 16-times higher excretion of unconjugated and glucuronidated testosterone (hereafter called testosterone) than did Koreans.[123] These findings predict different effects of testosterone intake on the T/E ratio in the two ethnic groups. The difference is a confounder in programmes of antidoping testing. There is a bimodal distribution of the natural logarithm of urinary testosterone concentrations in both Europeans and Asians, suggesting monogenic inheritance.[123] The recent report of a deletion polymorphism in the UGT2B17 gene[124] inspired investigation of this polymorphism and the testosterone excretion pattern. All individuals lacking UGT2B17 had no or negligible testosterone excretion (figure 1). Interestingly, and consistent with the pattern of testosterone excretion, the deletion genotype was seven times more common in Koreans (67·0%) than in Swedish people (9·3%).[123]

Although provisional results indicate genetic variation, we found no relation between the excretion of epitestosterone in urine and the UGT2B17 genotype.[123] Our findings indicate that consideration of genetic variation in androgen metabolising enzymes will help refine the detection of testosterone doping.

Erythropoietin

Methods for diagnosing the abuse of erythropoietin have been difficult to develop. A combination of indirect and direct methods seems most suitable, but there is still room for improvements, particularly of sensitivity. The indirect methods are based on multiple markers of increased erythropoiesis, while the direct method for urine analysis of erythropoietin is based on isoelectric focusing, which differentiates between the recombinant and endogenous types.[20,125]

Clinical diagnosis

The diagnosis of misuse is most difficult for anabolic steroids. The mostly likely users are young men who do weight training or sports that require strength and power.[71] The investigation should include a compre-

hensive drug history as well as physical and mental examinations (panel 3). Clinical assessment should be complemented with laboratory tests, such as LH and FSH, and urinary screening for AAS.

Prevention

Doping analyses

The introduction of doping analyses has held back doping in elite sports. In Sweden, the proportion of positive doping tests among athletes has declined from 2% to below 0·5% during the past 5 years. Between 1981 and 2005, hormones (62%) were the most commonly detected, stimulants accounted for 7% and narcotics for 5%. 23% of athletes refused to participate and were disqualified. The proportion of positive doping tests is much higher among risk groups in society than among athletes (unpublished).

Education

Information and education are the most important tasks for our antidoping hotline established in 1993 (www.dopingjouren.nu). Professional advice is given by trained nurses with physicians trained in clinical pharmacology as back-up. As most misusers are age 17–27 years (figure 2), it is particularly important to improve information about AAS and other doping agents in high schools. Similar antidoping hotlines are now available in Norway, Denmark, and Holland.

Pedagogic intervention programmes to prevent the use of AAS should be encouraged.[13] Physicians and other health personnel must be better educated in AAS misuse, which is an underappreciated part of prevention of narcotic misuse. In a recent Danish study, a third of 571 practising physicians had encountered patients with side-effects of AAS, usually males age less than 40 years.[126] Unfortunately, users of AAS commonly mistrust physicians and prefer to consult friends, internet sites, or even the people who sold them the steroids.[127] This credibility gap is believed to be related to the fact that members of the medical community have claimed for a long time that AAS are ineffective for gaining muscular strength.[127]

The educational programmes against doping should also emphasise the ethical and moral issues involved. The scientist and powerlifter Anders Eriksson elegantly expressed it as follows in his thesis: "Three times in my career I have received medals several months after the competition because lifters finishing ahead of me were caught in a drug test. This means that three of the greatest moments in my sport career were reduced to a letter with a medal."[43]

Legislation

Many countries are on the way to strengthening the laws against possession and use of AAS and now consider these drugs as equivalent to narcotics. In a recent news story in the *BMJ*,[128] MPs in the UK were reported to be calling for tougher methods to tackle doping in sports. An important concern is the ease with which banned substances can be obtained by athletes and the public.

The results of studies by Eriksson[41–43] show the effect of AAS on muscle fibres lasts much longer than believed, which suggests that athletes using anabolic agents should be disqualified for longer than 2 years. His histological observations may be the cellular correlate to an old observation in East Germany that "androgenic initiation" has long-lasting effects, particularly in women.

Conclusion

Our review summarises the increasing medical concerns about the widespread misuse of doping agents, particularly anabolic androgenic steroids (AAS), that started in athletes and now affects the general population. Compared with the attempts to prevent the misuse of narcotic drugs, the illegal use of AAS has not elicited sufficient interest from health authorities to hold back the problem, and the many side-effects of AAS remain largely unrecognised. As with narcotics, AAS have neuropsychiatric side-effects, including aggressive and even violent behaviour. Preventive measures include increased awareness among physicians, proper doping analyses, pedagogic interventions, and updated legislation. Doping in sport must be combated with much longer disqualifications of athletes using AAS, a proposal that has scientific support.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

Some of our own research described in this article was supported partly by the World Anti-Doping Agency (WADA) and partly by the Swedish Science Council and the Swedish Cancer Society.

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