Detlef Thieme • Peter Hemmersbach
Editors

Doping in Sports

Springer
Although the definition of doping has been modified over the years, its meaning may be pharmacologically understood as attempts to enhance performance (mainly strength and endurance) in sport by illegal administration of pharmaceuticals or application of prohibited methods (e.g. blood transfusions). Regardless of its individual motivation (e.g. unbounded ambitions, collective chauvinism or excessive financial interest), the doping phenomenon has been increasing in relevance for many years. However, any attempt to describe it from a scientific perspective faces the problem that systematic pharmacological principles are less important than the possible uncovering of its administration in doping control analyses.

Over time, we have seen that some of the early and most potent stimulating agents (e.g. amphetamine) have almost disappeared because relevant dosages are easily detected in doping controls. Instead, alternative and less efficient drugs (e.g. caffeine, modafinil) were used until they appeared on the relevant lists of prohibited substances. In some cases, even untested and unapproved drugs (bromantane, carphedone) were administered to circumvent positive doping controls.

Similarly, the ‘progress’ of doping with anabolic compounds was pharmacologically characterised by a loss of efficacy, which is notably paralleled by performance deterioration in highly ‘doping susceptible’ disciplines (compare world records in shot put). Originally, both injectable and orally administered steroids with high myotrophic potential (stanozolol, nandrolone, metandienone) were abused, resulting in significant gain in muscle mass and performance. Their replacement by lower levels of endogenous steroids could still combine reasonable effects with a moderate risk of discovery. Following further analytical improvements to differentiate endogenous and synthetic steroids (carbon isotope mass spectrometry), the application of mimetics and prohormones became popular. The latter (e.g. androstenedione) were temporarily legally available as ‘nutrition supplements’ and were thus abused in large amounts, although the significance of intended pharmacological effects was not proven. The BALCO affair (Bay Area Laboratory Co-operative), an intentional systematic development of new pharmaceutical analogues of anabolic steroids (tetrahydrogestrinone, THG) for doping
purposes, was certainly intriguing but due to the great effort required and the high risks involved it probably does not represent a general tendency.

Relevant detection time windows differ significantly and have to be seen in relation to the duration of possible performance-enhancing effects. Application of amphetamines, for instance, to stimulate sympathetic and central nervous systems is associated with high therapeutic substance concentrations during the performance and can be easily identified “in-competition”. In contrast, effects of anabolic substances or enhancement of oxygen transport capacity may last longer than the presence of the respective doping agents in the body. Unannounced out-of-competition tests were therefore introduced to specifically search for anabolic substances.

Analytically, the detectability in urine, the main specimen in doping control, and the corresponding detection time windows of relevant compounds are mainly governed by their pharmacokinetics. Detailed knowledge of the biotransformation and excretion kinetics of prohibited compounds is therefore essential in doping control. Quite often, pharmacologically irrelevant terminal metabolites are examined in great detail to enable a long-term detection of steroid abuse.

Recent advances in the development of doping strategies are not restricted to the development of new compounds. Forms of administration are also optimised to avoid the detection of administered substances. Anabolic steroids which were classically administered by intramuscular injection of their esters or taken orally became available as sublingual or buccal tablets and in particular as transdermal gels, enabling an efficient application of low dosages with good bioavailability and moderate detection windows.

Some new developments occurred in the 1990s when cheaper and safer recombinant peptide hormones became available. Erythropoietin (EPO), growth hormone (hGH) and insulin-like growth factor (IGF-1) pose outstanding analytical challenges because of their potentially endogenous nature and their pulsatile biosynthesis. Quantitative analyses are not eligible as proof of administration, and alternative procedures to differentiate the complexity of isoforms (hGH) or glycosylation (EPO) became necessary.

This development from classic – yet highly potent – compounds to new replacement strategies reflects a major challenge in doping control: old compounds and methods are still state-of-the-art and their control needs to be maintained while new analytical procedures must be permanently included. The time lapse between the clinical trials of a new drug with a misuse potential and the introduction of the drug might be used to develop a possible detection strategy. Detection methods for specific androgen receptor modulators (SARMs) have already been developed and the substances are included on the prohibited list even before any preparation is registered.

In addition to potentially performance-enhancing substances, masking agents have been prohibited because compounds influencing their analytical detectability were used. A fascinating facet of the BALCO affair was the documented production of “the cream”, a transdermal testosterone preparation with an in-built fraction of the masking agent epitestosterone to prevent an adverse analytical finding.
Recently, genetic aspects and techniques have gained importance in doping analysis, for instance to understand inter-individual variations (pharmacogenomics of testosterone glucuronidation) or as a diagnostic tool (reporter gene biomarkers). Moreover, the possible abuse of developments in gene therapeutic treatment has revealed a new potential for manipulation (gene doping). The first attempts to detect this are in progress.

The development of doping analysis in human sports has been closely related to the abuse and detection of illegal compounds in animal sports (particularly horse racing), while aspects like the availability of substances, species-related biochemical particularities and specific regulation of the acceptance of medications define their speciality. Similarly, the application of inappropriate dosages of anabolic compounds in bodybuilding and their illegal use in food-producing animals are not fully comparable to situations in sport, but permit useful insights into biotransformation, pathobiocchemistry and the appearance of side effects and attempts to treat them.

Finally, doping cannot be properly understood without some knowledge of its legal implications. The abuse of certain compounds is restricted by a trade-off between potential gain (honour, social, money) and risk (costs, sanctions or legal penalties). The classification of potentially harmful doping agents as scheduled compounds, their control and limitation of their availability are therefore also as important as analytical means.

A comprehensive overview of the health risks of doping practices and their side effects would exceed the scope of this volume. However, we chose to include some aspects which have not yet been covered extensively in the literature: the side effects of anabolic-androgenic steroids from a forensic point of view and the risks of steroid abuse observed from a cardiologist’s standpoint.

As early as 1980, the International Association of Athletics Federations (IAAF) initiated an accreditation programme for doping control laboratories, which was later taken over by the International Olympic Committee (IOC) and the World Anti-Doping Agency (WADA). Major concepts of quality assessment in analytical chemistry (e.g. identification criteria in mass spectrometry) originated in this process. The anchoring of quality control in the concepts of the International Organization for Standardization (ISO) provides the documentation of adequate competence. The fact that analytical results are periodically the subject of public contention reflects the high awareness of doping and strong financial interests rather than scientific insufficiencies.

Kreischa, Germany
Detlef Thieme
Olso, Norway
Peter Hemmersbach
Contents

1 History of Doping and Doping Control .......................................................... 1
   Rudhard Klaus Müller

2 Biochemical and Physiological Aspects of Endogenous Androgens ….. 25
   Andrew T. Kicman

3 Phase-II Metabolism of Androgens and Its Relevance
   for Doping Control Analysis ................................................................. 65
   Tiia Kuuranne

4 Detecting the Administration of Endogenous Anabolic
   Androgenic Steroids ............................................................... 77
   Christiane Ayotte

5 Synthetic Anabolic Agents: Steroids and Nonsteroidal Selective
   Androgen Receptor Modulators ....................................................... 99
   Mario Thevis and Wilhelm Schänzer

6 Nandrolone: A Multi-Faceted Doping Agent ................................. 127
   Peter Hemmersbach and Joachim Große

7 Designer Steroids ................................................................. 155
   Ray Kazlauskas

8 Growth Hormone ................................................................. 187
   Martin Bidlingmaier and Christian J. Strasburger

9 Mass Spectrometry-Based Analysis of IGF-1 and hGH .............. 201
   Mario Thevis, Michael Bredehöft, Maxie Kohler, and Wilhelm Schänzer
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Insulin</td>
<td>209</td>
</tr>
<tr>
<td></td>
<td>Mario Thevis, Andreas Thomas, and Wilhelm Schänzer</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>β-Adrenergic Stimulation</td>
<td>227</td>
</tr>
<tr>
<td></td>
<td>Peter Van Eenoo and Frans T. Delbeke</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Erythropoietin and Analogs</td>
<td>251</td>
</tr>
<tr>
<td></td>
<td>Christian Reichel and Günter Gmeiner</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Blood Transfusion in Sports</td>
<td>295</td>
</tr>
<tr>
<td></td>
<td>Sylvain Giraud, Pierre-Edouard Sottas, Neil Robinson, and Martial Saugy</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>The Athlete’s Biological Passport and Indirect Markers of Blood Doping</td>
<td>305</td>
</tr>
<tr>
<td></td>
<td>Pierre-Edouard Sottas, Neil Robinson, and Martial Saugy</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Masking and Manipulation</td>
<td>327</td>
</tr>
<tr>
<td></td>
<td>Rosa Ventura and Jordi Segura</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Hormonal Growth Promoting Agents in Food Producing Animals</td>
<td>355</td>
</tr>
<tr>
<td></td>
<td>Rainer W. Stephany</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Some Aspects of Doping and Medication Control in Equine Sports</td>
<td>369</td>
</tr>
<tr>
<td></td>
<td>Ed Houghton and Steve Maynard</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Androgenic Anabolic Steroid Abuse and the Cardiovascular System</td>
<td>411</td>
</tr>
<tr>
<td></td>
<td>Paul Vanberg and Dan Atar</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Side Effects of Anabolic Androgenic Steroids: Pathological Findings and Structure–Activity Relationships</td>
<td>459</td>
</tr>
<tr>
<td></td>
<td>Andreas Büttner and Detlef Thieme</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Gene Doping</td>
<td>485</td>
</tr>
<tr>
<td></td>
<td>Hassan M. E. Azzazy</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Science and the Rules Governing Anti-Doping Violations</td>
<td>513</td>
</tr>
<tr>
<td></td>
<td>Larry D. Bowers</td>
<td></td>
</tr>
</tbody>
</table>

Index ........................................................................ 533
Contributors

Dan Atar Aker University Hospital, Trondheimsveien 235, N-0514 Oslo, Norway, dan.atar@aus.no

Christiane Ayotte Laboratoire de contrôle du dopage, INRS - Institut Armand-Frappier, 245, boulevard Hymus, Pointe-Claire, Québec H9R 1G6, Canada, christiane.ayotte@iaf.inrs.ca

Hassan M.E. Azzazy Department of Chemistry, The American University In Cairo, 113 Kasr El-Aini Street, Science Bldg Rm # 310, Cairo 11511, Egypt, hazzazy@aucegypt.edu, Azzazy07@gmail.com

Martin Bidlingmaier Medizinische Klinik – Innenstadt, Klinikum der Universität, Ziemssenstr. 1, D-80336 München, Germany, martin.bidlingmaier@med.uni-muenchen.de

Larry Bowers United States Anti-Doping Agency, 1330 Quail Lake Loop, Suite 260, Colorado Springs, CO 80906-4651, USA, lbowers@usantidoping.org

Michael Bredehöft Center for Preventive Doping Research – Institute of Biochemistry, German Sport University Cologne, Am Sportpark Müngersdorf 6, 50933 Cologne, Germany

Andreas Büttner Institute of Legal Medicine, St.-Georg-Str. 108, 18055 Rostock, Germany, buettner.oi@googlemail.com

Frans T. Delbeke DoCoLab Universiteit Gent-UGent, Technologiepark 30, B-9052 Zwijnaarde, frans.delbeke@UGent.be

Sylvain Giraud Swiss Laboratory for Doping Analyses, Chemin des Croisettes 22, 1066 Epalinges, Switzerland, Sylvain.Giraud@chuv.ch
Contributors

Günter Gmeiner Austrian Research Centers GmbH – ARC, Doping Control Laboratory, A-2444 Seibersdorf, Austria, guenter.gmeiner@arcs.ac.at

Joachim Große Institute of Doping Analysis and Sports Biochemistry, Dresden, DE-01731 Kreischa, Germany

Peter Hemmersbach Norwegian Doping Control Laboratory, Oslo University Hospital, Trondheimsvieien 235, N- 0514 Oslo, Norway, peter.hemmersbach@farmasi.uio.no

Edward Houghton Drug Surveillance Group, HFL Ltd, Newmarket Road, Cambridge, CB7 5WW, UK, drehoughton@hotmail.com

Rymantas Kazlauskas Australian Sports Drug Testing Laboratory (ASDTL) – Sydney, National Measurement Institute, 1 Suakin Street, Sydney, NSW 2073, Australia, ray.kazlauskas@measurement.gov.au

Andrew T. Kicman Drug Control Centre, King’s College London, The Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NH, UK, Andrew.kicman@kcl.ac.uk

Maxie Kohler Center for Preventive Doping Research – Institute of Biochemistry, German Sport University Cologne, Am Sportpark Müngersdorf 6, 50933 Cologne, Germany

Tiia Kuuranne Doping Control Laboratory, United Medix Laboratories Ltd., Höyläämötie 14, 00380 Helsinki, Finland, Tiia.Kuuranne@medix.fi

Steve Maynard HFL Sport Science, Newmarket Road, Fordham, Cambridgeshire, UK

Rudhard Klaus Müller Institute of Doping Analysis – Dresden, Dresdner Straße 12, D-01731 Kreischa b. Dresden, Germany, RKMueller.Leipzig@t-online.de, info@idas-kreischa.de

Christian Reichel Austrian Research Centers GmbH – ARC Doping Control Laboratory, A-2444 Seibersdorf, Austria, christian.reichel@arcs.ac.at

Neil Robinson Swiss Laboratory for Doping Analyses, Chemin des Croisettes 22, 1066 Epalinges, Switzerland

Martial Saugy Laboratoire Suisse d’Analyse du Dopage, Institut universitaire de médecine légale, Chemin des Croisettes 22, CH-1066 Epalinges, Switzerland, LAD.Central@chuv.ch, Martial.Saugy@chuv.ch
**Wilhelm Schänzer** Laboratory for Doping Analysis, German Sports University Cologne, Carl-Diem-Weg 6, D-50933 Köln, Germany, schaenzer@biochem.dshs-koeln.de

**Jordi Segura** Institut Municipal d’Investigacio Medica, Unitat de Farmacologia, c/ Doctor Aiguader, 88, S-08003 Barcelona, Spain, jsegura@imim.es

**Pierre-Edouard Sottas** Swiss Laboratory for Doping Analyses, Chemin des Croisettes 22, 1066 Epalinges, Switzerland

**Rainer W. Stephany** Verhulstlaan 12, NL-3723 JR Bilthoven, the Netherlands, rainer_stephany@yahoo.com

**Christian J. Strasburger** Division of Clinical Endocrinology, Charité Campus Mitte, Charitéplatz 1, 10117 Berlin, Germany, christian.strasburger@charite.de

**Mario Thevis** Center for Preventive Doping Research – Institute of Biochemistry, German Sport University Cologne, Am Sportpark Müngersdorf 6, 50933 Cologne, Germany, thevis@dshs-koeln.de

**Detlef Thieme** Institute of Doping Analysis and Sports Biochemistry – Dresden, Dresdner Straße 12, D-01731 Kreischa b. Dresden, Germany, det.thieme@web.de

**Andreas Thomas** Center for Preventive Doping Research – Institute of Biochemistry, German Sport University 4 Cologne, Carl-Diem Weg 6, 50933 Cologne, Germany

**Paul Vanberg** Chief Physician/Senior Cardiologist, Oslo University Hospital – Aker, Trondheimsveien 235, 0514-Oslo University Hospital, Norway, paul.vanberg@medisin.uio.no

**Peter Van Eenoo** DoCoLab, Department of Clinical Chemistry, Immunology and Microbiology, UGent, Technologiepark 30b, B-9052 Zwijnaarde, Belgium, Peter.VanEenoo@Ugent.be

**Rosa Ventura** Institut Municipal d’Investigacio Medica, Unitat de Farmacologia, c/ Doctor Aiguader, 88, S-08003 Barcelona, Spain
History of Doping and Doping Control

Rudhard Klaus Müller

Contents

1 The Expression “Doping” ................................................................. 1
2 Early Attempts of Doping .............................................................. 2
3 Doping and its Emerging Prohibition .............................................. 2
   3.1 Stimulants ............................................................................ 5
   3.2 Anabolic Agents ...................................................................... 5
   3.3 Fatalities with Presumptive Correlation to Doping .................. 7
4 Development of General Anti-Doping Regulations ....................... 7
5 Doping Analysis and Accreditation of Anti-Doping Laboratories ... 9
6 Doping and the Cold War .............................................................. 11
7 Developments from the 1990s Onward ........................................ 12
Appendix 1 Historical Definitions of Doping ....................................... 15
References .................................................................................. 18

Keywords History of doping • Definition of doping • Anti-doping regulations • Doping control

1 The Expression “Doping”

Although attempts to enhance athletic performance are probably much older, the word “doping” was first mentioned in 1889 in an English dictionary. It described originally a mixed remedy containing opium, which was used to “dope” horses.
“Dope” was a spirit prepared from the residues of grapes, which Zulu warriors used as a “stimulant” at fights and religious procedures and which also reportedly was called “doop” in Afrikaans or Dutch.

Later, the meaning of “dope” was extended in a broader sense to other beverages with stimulating properties. The expression was introduced into English Turf Sport about 1900 for illegal drugging of racehorses.

2 Early Attempts of Doping

According to reports of Philostratos and Galen, various remedies were used to enhance athletic performance as early as the end of the third century BC (Burstin 1963). Chinese physicians recommended the use of Ma Huang (an extract from the plant Ephedra) to increase performance over 5,000 years ago, when this drug was usually used to suppress coughing and to stimulate circulation (Abourashed et al. 2003).

The Indian physician Sutruta recommended the eating of testicles to enforce virility around 300 B.C., and the Huns consumed testicles before battles – obviously with the same aim (Chinery 1983). Hallucinogenic mushrooms were taken in the third century BC to enhance performance during Olympic competitions, which were held between 776 BC and 393 AD (Burstin 1963; Prokop 1970, 1972; Hanley 1983).

Critically considered, the materials available at that time may probably be categorized between nutrients or nutritional supplements (like eggs, meat, blood) and real “drug-like” substances with objectively expected activity (like bull testicles, or alcoholic beverages with their nevertheless two-edged effect on performance).

This antique “doping” was strictly prohibited by the rules of the classic Olympic Games, just as today. The sanctions were however much more severe in the old Greek Olympics as well as in horse doping: Prokop (2002) mentions that even death penalties were given. When Emperor Theodosius abolished the ancient Games in the year 395 AD, the reasons he gave were that they had become “a hotbed of cheating, affronts to human dignity and doping” (Dirix and Sturbois 1998).

3 Doping and its Emerging Prohibition

While there are some reports about doping – including related attempts and their prohibition – we do not yet have any knowledge about their role in a large gap of time from the Greek Olympics through the Middle Ages to our modern times.

The use of the strong stimulant cocaine (coca leaves) in parallel to caffeine (coffee, guarana, cola nuts and mate tea) is reported from Latin America. Incas
were reportedly able to run the distance from Cuzco to Quito (1750 km) in 5 days under the influence of those stimulants – almost incredible even with cocaine (Wadler and Hainline 1989).

Later, strychnine, caffeine, cocaine and alcohol were often used by cyclists and other endurance athletes in single as well as combined administrations. Among the preparations promising to provide power was “Mariani wine”, first produced and patented 1863 by Angelo Mariani, and made from Bordeaux wine and coca extracts. Among high-ranking consumers (e.g. Thomas Edison, Henrik Ibsen, Jules Verne), Pope Leo XIII conferred a gold medal on Vin Mariani. This beverage became later forbidden under the “Opium” (or Narcotics) Law in Germany in 1920 (Eckart 2003).

Increasing use of mineral drugs/poisons such as arsenic, and developing knowledge about vegetable drugs, might have led to their use for this “paramedical” purpose also. The purification, definition and structural elucidation of alkaloids and other active ingredients of plants, overlapping with the first synthetic organic pharmaceuticals, were the final preconditions for the beginning of the “modern era” of doping in the nineteenth century.

Numerous individual doping cases were reported between the late nineteenth and the second half of the twentieth century, when official testing of human athletes was initiated. In parallel, the first definitions and regulations against doping in sport appeared. The International Athletic Federation (IAAF) was the first to ban the use of stimulating substances in sport, but this remained inefficient until testing possibilities were available.

Although certainly less important, the opposite of normal doping has also played some role in history: “doping to lose” or “negative doping” – attempts to impede the performance of athletes, as well as horses (initially called “antidoping”) or other competing animals, by clandestine administration of sedatives etc.

Contemporary allegations to explain adverse analytical findings in urine samples as consequences of the introduction of doping agents by others can be considered as an extrapolation of these early attempts at sabotage.

A series of cases are reported by Ludwig Prokop (Prokop 1957, 1970, 1972, 2002), although in general briefly and not always with original sources. Following his documentation, the first doping case was detected at a British Channel swimming event in 1865 (Pini 1964). The death of the cyclist Linton in the Paris–Bordeaux race was correlated to an overdose of caffeine. (This might have possibly been a simplification with regard to the very low toxicity of caffeine.)

Six-day cycling races (established in 1879) and professional boxing as well as horse and dog racing obviously fostered the increase of doping attempts with alcohol, cocaine, caffeine, heroin, nitroglycerol and strychnine. The marathon winner at the St. Louis Olympics in 1904, Thomas Hicks, received – besides the consumption of raw eggs and brandy – injections of strychnine during the run.
Various mixtures were tried to increase the stimulation of these substances. Such as:

– Alcohol, caffeine and nitroglycerol,
– Cocaine and heroin,
– Alcohol and cocaine

(Dorando Pietri, London 1908).

In 1908 Belgian football teams tried to enhance performance by breathing pure oxygen, but they obviously abandoned this attempt soon.

It is hard to envisage how these first cases might have been discovered – by direct observation, by confession or otherwise.

The first application of chemical analysis in connection with a series of unexpected results in horse racing occurred in Austria at the beginning of the twentieth century. Ludwig Prokop reports that the Austrian Jockey Club – following suspicious events during horse races – invited the Russian chemist Bukowski to come from St. Petersburg to Vienna. He was able to detect alkaloids in the horse saliva. While Bukowski kept his method secret, Professor Siegmund Frenkel elaborated his own method at Vienna University. In 1910/1911, 218 analyses were performed, leading to several sanctions being imposed on the coaches after positive findings in the horse saliva samples.

While restrictions for the use of pharmaceuticals in sports have reportedly been introduced since 1920, and the IAAF prohibited doping (use of stimulating agents) in 1928, official testing of humans was not yet performed. Therefore, the restrictions remained ineffective due to the lack of testing possibilities.

In 1966 the international federations UCI (cycling) and FIFA (football) introduced doping tests in their World Championships. The International Olympic Committee (IOC) instituted its own Medical Commission and set up its first List of Prohibited Substances in 1967. It introduced the first tests at the Summer Olympic Games in 1968 in Mexico.

The tests performed during competitions proved to be ineffective in controlling long-acting agents such as anabolic agents due to the possibility of withdrawing them prior to competitions, while the performance enhancement lasted long enough after the excretion of the agent itself. This led to the conclusion that sample collections were also necessary outside the competition. Despite some resistance they were introduced and now form the backbone of doping control.

The spectacular stanozolol misuse of the runner Ben Johnson at the 1988 Summer Olympic Games in Seoul caused a shock among the sports community and led to an increased readiness to support effective doping control measures. In parallel, the number of potential doping agents began to increase continuously with the development of synthetic organic drugs, which still continues.

Nevertheless – and notwithstanding the overwhelming number of pharmaceuticals on the worldwide market – the development of new pharmacological agents has been slowed down considerably by the very strict requirements of toxicological testing prior to registration. Because the agents under development are known about much earlier than their final registration and introduction to the market, this contradicts the
popular assumption in the media that doping control and analysis would always remain far behind the progress of doping strategies.

3.1 Stimulants

Early doping agents were mainly stimulants (cocaine, caffeine, strychnine, etc.). The introduction of synthetic phenylethylamine derivatives (mainly amphetamine [Benzedrine] and methamphetamine [Pervitin]) as strong-acting stimulants led to their increased use in sports (as well as in the military for improved vigilance). Amphetamines and analeptics (central, respiratory, and psychotonic) as well as several alkaloids (e.g. ephedrine, strychnine), narcotics and some hormones therefore became prohibited as the first classes of doping agents.

Following L. Prokop (2002), cases of misuse of amphetamines occurred first between 1950 and 1970. Amphetamine was first synthesised in 1887 (Edeleanu 1887) simultaneously with the isolation of ephedrine. Gordon Alles synthesised it again in 1927 in Los Angeles while searching for derivatives of ephedrine, and coined the term amphetamine. Since 1932, Smith, Kline and French sold inhalation remedies containing amphetamine, called “Benzedrine”, and after 1936 also Benzedrine tablets. Amphetamines were reportedly used for the treatment of child hyperactivity and as stimulants during the Second World War.

In a cycling competition in 1955, five samples out of 25 tested positive for amphetamine (Venerando 1963). In 1956, a cyclist needed psychiatric treatment after amphetamine misuse. During several high-level cycling competitions (e.g. World Amateur Championship, Professional Cycling World Championship Zürich, Austria Tour) numerous cyclists (e.g. from Austria, The Netherlands, and Poland) tested positive and had to be sanctioned. It was reported that several athletes carried amphetamines in their clothing.

As a psychological aspect of doping and its motivation, placebo doping effects were objectively shown by Ludwig Prokop as early as 1957: he included more than 100 athletes and control persons in a study and showed significant psychological and physiological effects after the administration of placebo remedies.

3.2 Anabolic Agents

Anabolic steroids came into use in sports first as agents supporting recovery after massive stress and exhaustion. They were developed after the isolation and structural elucidation of the mother compound testosterone, the principal male sexual hormone, in the 1930s. Testosterone was first isolated as a crystallised pure substance by E. Lacqueur and coworkers in 1935 (Freeman et al. 2001). A. Butenandt elucidated the structure. His chemical synthesis, published almost simultaneously with that of L. Ruzicka and A. Weltstein, was honoured by the
Nobel Prize in 1939. Soon after, numerous synthetic derivatives were synthesised and used as pharmaceuticals in parallel to the natural hormone.

The activity of a hormone governing (male) sexual functions had been revealed much earlier, when A.A. Berthold linked testicular action to circulating blood constituents. Interestingly, an experiment of C.-E. Brown-Sequard in Paris, attempting to prove the activity of a testicle extract (dog, guinea pig) in 1889 was considered ridiculous by his colleagues after his statement of a marked restoration of his feeling of wellbeing and vigour. This led to him and his successors abandoning research for several decades, until it was initiated anew in 1927 in Chicago by the group of F.C. Koch.

Among the various actions and side effects of anabolic steroids, their potential for enhancing aggressive behaviour (still under discussion due to the difficulty of gaining objective proof of causality; Müller and Müller-Platz 2001) has gained importance less in sport than in forensic aspects – having been claimed as an explanation and excuse of violent behaviour and violent crimes. Testosterone was given to soldiers during World War II to increase their aggression, and Adolf Hitler used testosterone just after it had been synthesised (Spitzer 2005b).

The structural elucidation of testosterone was followed by the synthesis of numerous derivatives as well as by the revelation of the complete “family” of steroid hormones (precursors, metabolites and also antipodes of the main androgenic hormone testosterone).

Soon after the 1950s, the class of anabolic androgenic steroid hormones became the leading group in the statistics of doping cases and later also the leading group in adverse analytical findings, after the methodology enabled laboratories to detect them (see also Duchaine 1989; Fahey and Fritz 1991; US FDA 2008; Wright and Cowart 1990; Yates and Wolff 1993; Fainaru and Williams 2003). Special problems such as the need to distinguish exogenous intake of the endogenous compounds from their normal, physiological presence in the body and in urine led to the concept of the testosterone/epitestosterone ratio (T/E) of Manfred Donike (Donike et al. 1983).

Clinical tests (e.g. ketoconazol administration, the “steroid profile”) and later the application of isotope ratio mass spectrometry, IRMS (Ayotte 2009) have been included as additional means to suspect, to detect or to prove the misuse of testosterone and other – mainly endogenous – anabolic steroids.

When pursuing directed hints led to the detection of clenbuterol in 1992 (Beckett 1992; Maltin et al., 1987a, b), and to the suspicion of its obvious misuse as a replacement for anabolic steroids, a definition problem became apparent. While the examples for the agents belonging to the respective prohibited classes was followed by the expression “... and related substances”, an argument arose over the meaning of the term “related”. Clenbuterol – already known for its misuse in animal nutrition for enhanced muscle growth – was undoubtedly an anabolic, but certainly no steroid. Hence some experts suggested that clenbuterol – due to its side effect – had to be considered as a prohibited agent, whereas others claimed that it was not related due to its nonsteroidal chemical constitution.
3.3 Fatalities with Presumptive Correlation to Doping

Lethal cases contributed to the growing public awareness of this problem, such as the death of the Danish cyclist Knut Enemark Jensen in the Summer Olympic Games in 1960 in Rome and of the British cyclist Tommy Simpson in 1967 at Mont Ventoux (Houlihan 1999) during the Tour de France (Blickensdörfer 1972). Fatal cases in other sports at that time were also related to doping, e.g. the weightlifter Billi Bello in 1963 (with heroin) and Dick Howard, a 400-m hurdler in 1960.

But it has to be emphasised that such a correlation of sudden death in sport to doping at that time was very probably a suspicion rather than a justified diagnosis according to forensic standards. Even the detection of doping in an actual case or beforehand cannot really prove that doping was the cause of death, and this can be relevant even vice versa (Bux et al. 2008). An example of erroneous suspicion of earlier doping occurred in the early 1990s after the sudden death of the American athlete Florence Griffith-Joyner. The autopsy revealed a natural cause of death (intracranial bleeding by rupture of an obviously connatal brain stem cavernoma). Primarily, the media assumed her death was the lethal consequence of doping during her active career. On the other hand, a natural cause of death does not necessarily exclude any earlier use of doping agents. Only nowadays are such rare fatal cases of death in active periods of high performance sport thoroughly investigated (Bux et al. 2008; Goldmann 1984; Kohler et al. 2008; Lüderwald et al. 2008; Raschka 2008).

When single urine analyses immediately pre or also post mortem provide no unequivocal conclusions, hair analyses have provided very helpful additional information about possible long-term doping (Sachs and Möller 1989; Sachs and Kintz 2000; Lüderwald et al. 2008).

4 Development of General Anti-Doping Regulations

In 1928 the International Amateur Athletic Federation became the first International Sport Federation to ban the use of stimulating substances (WADA 2009a). The IOC claims to have contemplated doping problems at the Olympic Games since its IOC Sessions in 1937/1938 in Warsaw and Cairo (Dirix and Sturbois 1998). It stated in 1938: “The practise of doping is to be condemned utterly, and any person accepting or offering to supply dope should not be allowed to enter amateur meetings or the Olympic Games.” Alerts were given by Drs. Ludwig Prokop and Albert Dirix in 1952 and 1956, “regarding obvious signs of the reckless use of medicinal substances, while some athletes exhibited symptoms which were worrying to say the least”.

At the IOC Session in Athens in 1961, a Medical Commission was created, and at the Session in Madrid in 1965 Prince Alexandre de Merode (Belgium) presented a report on doping problems in the light of the Tokyo Games in 1964 (Dirix 1986). This report can be considered as the starting point for the anti-doping efforts of the
IOC and its Medical Commission. Beginning with the first anti-doping legislation in France in 1963 and several international congresses, anti-doping laws and regulations were issued in a series of countries and by International Federations (IFs) in sport. Since then, UCI and FIFA introduced doping tests in 1966, and several other international federations followed in subsequent years.

The first doping tests at the Olympics were taken during the Winter Games in Grenoble and the Summer Games in Mexico in 1968, when the first disqualifications occurred. In parallel to the first regulations, anti-doping commissions were established, e.g. France 1959; Austria 1962; Council of Europe and Italy 1963; IOC (Medical Commission) 1961/1967.

The approach of the Mexico City Games brought the problem of doping into particularly sharp focus and prompted further debate at top level within the IOC. At the 66th Session of the IOC in Teheran from 6 to 9 May 1967, the problems associated with drug testing, the list of products and the methods used for doping and gender testing for the 1968 Games were expounded by the retiring chair of the IOC Medical Commission, Sir Arthur Porritt. Prince Alexandre de Merode (Belgium) was appointed Chairman of the IOC Medical Commission on May 9, 1967, and held the chairmanship until his death in 2003.

The Medical Commission of the IOC also elaborated scientifically based requirements for doping analyses and for the qualification and equipment of anti-doping laboratories, which only after IOC accreditation are exclusively entitled to perform analyses for international competitions including the Olympic Games.

On 3rd September 1968, from the Château de Vidy in Lausanne, IOC President Avery Brundage issued in a press release a circular letter to all IFs, NOCs and IOC Members on the IOC initiative towards an anti-doping campaign (Dirix and Sturbois 1998). This document contained the following general statements about the standpoint of the IOC towards doping:

“... The use of dope has always been prohibited by Olympic Rules and by those of most amateur sport organisations. ...

... It was never intended that the IOC itself should take responsibility for testing seven or eight thousand competitors ...

... The International Olympic Committee has its rules, it has defined dope, and it should see that provisions are made by the Organising Committee for testing. But the actual testing is left in the hands of others. This is a responsibility that the IOC is not prepared to take. The responsibility of the IOC is to have intelligent regulations to see that the adequate facilities are provided, and that correct methods are used.”

Under the supervision of the IOC Medical Commission, doping tests were first carried out during the Winter Olympic Games in Grenoble and during the Summer Games in Mexico City in 1968. Most IFs introduced doping tests in the 1970s. In 1986, the IOC inaugurated the International Olympic Charter against Doping in Sport, and in 1989 the Anti-Doping Convention of the Council of Europe was finalised. The Appendix summarises the historical period of changing doping definitions and regulations up to that time (Council of Europe 1989; Dirix 1984, 1992, 1986; Todd and Todd 2001).
5 Doping Analysis and Accreditation of Anti-Doping Laboratories

Although the first attempts at detecting doping practices reach back for about a century, the analytical possibilities with regard to sensitivity and certainty of results remained rather restricted until the 1970s. While the first attempts had probably started with test-tube chemistry, the recommendations for analyses during the 1972 Olympic Games in Munich comprised thin-layer chromatography and gas chromatography (Beckett et al. 1967; Beckett and Cowan 1979; Clasing et al. 1974; IOC 1972; Donike and Kaiser 1971; Donike et al. 1974; Merode 1999; Hemmersbach 2008; Kim et al. 1999). Immunoassays had been used in some laboratories for pre-testing (screening), but positive results were considered as preliminary and had to be confirmed by chromatography (Brooks et al. 1975, 1979).

Quickly following the technical development of new analytical principles, mass spectrometry (MS) and its combination with gas chromatography became the standard instrumentation for the detection and quantitation of the majority of doping agents. This principle and similar “hyphenated techniques” combine the high separation power of a chromatographic technique with the very high information capacity and sensitivity of the mass spectrometer (Catlin 1987, 1999; Donike et al. 1974, 1976, 1983, in his booklet “Dopingkontrollen” 1978–1996; Hemmersbach and de la Torre 1996; Maurer 2006; Müller et al. 2003; Pfleger et al. 2000; Westwood et al. 1999).

GC–MS (the combination of gas chromatography with unit mass resolution mass spectrometry) has been extended in its possibilities by the introduction of high resolution mass spectrometry (HRMS), tandem mass spectrometry (MS–MS) and isotope ratio mass spectrometry (IRMS) as well as by the combination of MS with liquid chromatography (LC) instead of GC during the 1990s (Aguilera et al. 1996; Ayotte 2006; Becchi et al. 1994; Horning and Donike 1994; Horning et al. 1996; Mareck et al. 2008; Pozo et al. 2008; Shackleton et al. 1997; Thevis and Schänzer 2005, 2007; Thevis et al. 2005; WADA 2008a, b, c, d.

The increasing complexity of the analyses and the growing importance of the analytical results with regard to the consequences (sanctions) of doping offences in the course of the establishment of strict regulations led to the adoption by the IAAF at first of restrictive rules for analytical procedures and quality testing for laboratories performing drug tests. The IAAF Council accepted the rules for accreditation (as part of a continuous accreditation programme) in Dakar in April 1979. In 1981, a joint communiqué of the IAAF Medical Commission and the IOC’s Sub-Commission for Doping and Biochemistry in Sport combined the intention and initiative and accredited the first anti-doping laboratories worldwide: Cologne (Germany), Kreischa (Germany/GDR), Leningrad (USSR), London (GB), Magglingen (Switzerland) and Montreal (Canada). Up to 2008, the number of accredited anti-doping laboratories (WADA 2008c), now accredited by WADA according to the International Standard for Laboratories (WADA 2008b), and based in addition on the International Standard ISO 17025, increased to 34.
The challenges to the laboratories for the analysis of prohibited doping agents and methods grew considerably during the 1990s due to the misuse of new substances and methods, mainly peptide hormones like erythropoietin (EPO), human growth hormone (hGH) and others. Most newer doping agents of lower molecular size (below 1000 Da) can be included into the normal scheme of GC–MS or LC–MS procedures without great difficulty, and have sometimes been detected even if completely unused and more or less unknown, and have afterwards been explicitly included in the Prohibited List, e.g. clenbuterol 1992 (Maltin et al. 1987a, b); bromantane 1994 (Badyshtov et al. 1995; Bumat et al. 1997; Grekhova et al. 1995; Kudrin et al. 1995); carphedone or phenylpiracetam 1996 (Müller et al. 1999; Kim et al. 1999); RSR13 (Breidbach and Catlin 2001); hydroxyethyl starch (HES) (Thevis et al. 2000; Deventer et al. 2006); tetrahydrogestrinone (THG) 2004 (Catlin et al. 2004; Fainaru and Williams 2003; Jasuja et al. 2005).

For the peptide and glycoprotein hormones (with much larger molecules between $10^3$ and $10^5$ Da and with many different chemical properties), immunoassays – partly combined with electrochemical separation – as well as an “indirect approach” have been introduced. The direct approach identifies the hormone itself (and has to distinguish the exogenous product from the physiological one), while the indirect principle quantifies and evaluates parameters which are physiologically correlated with the hormone (such as erythropoietin haemoglobin or hematocrit, ferritin, soluble transferrin receptor, reticulocytes) (Catlin et al. 2002; Gore et al. 2003; Lasne 2001; Lasne and de Ceaurriz 2000; Lasne et al. 2002; Parisotto et al. 2000, 2001).

The question of whether blood sampling would either be desirable or would become necessary for the detection of doping agents (and methods) in general or in particular for peptide hormones was intensively discussed in the 1990s due to the legal impact: blood sampling was partly considered legally unacceptable, while a sample category whose sampling could be refused would remain ineffective in doping control (Donike et al. 1996). At present, blood sampling is becoming more and more usual in connection with the storage of health tests and individual “blood profiles” of athletes, and can be used if necessary in addition to the traditional urine sample if the nature of agents (or methods) so requires. This will very probably be necessary in connection with approaches to detect autologous blood doping, and perhaps also for other factors enhancing oxygen transport capacities.

Hair as a potential sample material for doping detection has also caused discussion: many doping agents are incorporated into growing hair and remain stable for long periods, so that a longer individual history of the incorporation of agents can be gained by hair analysis. The very sensitive hyphenated MS-techniques permit detection even in a few milligrams of available hair material. On the other hand, a single administration of low dose is hardly detectable (and with some delay, due to the slow growth of the hair out of the follicle), so that a negative hair analysis cannot exclude a unique doping offence, whereas it can elucidate retrospectively a repeated consumption (Müller and Thieme 2000; Sachs and Kintz 2000).
The inclusion of gene doping in the Prohibited List (since 2003) created a new challenge for doping control and analysis (Müller 2001). While methods for the detection of genetic constitution and changes as well as methods for genetic manipulation are already very far developed experimentally, their transfer into medical treatment – and therefore also the possibility to misuse potentially performance-enhancing manipulations in sport – is not yet practicable. In spite of this, research projects on the elaboration of detection methods – whether directed to the detection of genetic changes themselves or of the indirect markers related to them – are under way. The results will decide whether the necessary completely new techniques can be introduced in the laboratories accredited for doping control, or how far cooperation with specialised (e.g. forensic DNA) laboratories will be indicated.

6 Doping and the Cold War

Between about 1970 and 1990, sport in general and doping in sport undoubtedly played their roles not only for the personal ambition of athletes, coaches, officials and even some physicians, but also were misused for nationalism, for competition among ideologies and political systems and as a welcome tool to balance other national inferiorities. While in democratic states doping was applied individually or organised by single teams, sport associations or institutions (partly made easier due to the still weak or differing rules and insufficient control), in a series of mainly Eastern European states doping was organised systematically by governments and parties in their struggle for acknowledgement or recognition against the background of their rather inferior economic and scientific performances. Although this was characteristic for all satellite states of the Soviet Union, the German Democratic Republic (East Germany) led this strategy based on its intention to obtain international recognition as a second German state following the division of Germany by the Allies at the end of the Second World War. As a matter of fact, the astonishing results in high performance sports by this comparatively small country at this time (certainly not only, but in considerable part, as a result of the secret systematic doping strategy by “supporting agents” – “Unterstützende Mittel, UM”) were very much acknowledged throughout the world, creating an image which disregarded the political suppression by and the growing economical inferiority of this regime (Berendonk 1992; Franke 1997; Spitzer 1989; Spitzer et al. 1999; Teichler 2003; Spitzer 2005a).

This was a very complex problem ranging from scientifically based practices to secret research, irresponsible applications disregarding acute and long-term side effects, from obvious coercion or deception of athletes to the readiness of others to reach higher performances even with the risk to health, to misuse of laboratory results for the avoidance of adverse findings at international competitions, etc.

Anabolic androgenic steroids – registered pharmaceuticals (testosterone itself, its various esters and derivatives including the legendary dehydrochloromethyltestosterone named Oral-Turinabol\(^{[1]}\)) as well as synthetic substances developed in
secret research projects—were certainly the most important doping substances during these decades. The risks were increased when the synthetic agents were applied without the rigorous toxicological testing that is compulsory for the official registration of new pharmacological agents.

More effective test methods have led to a remarkable drop in the level of top results in some sports, which obviously could not be attained in a natural way. Some track and field results of this time—obviously obtained under the action of those agents—are still waiting to be equalled again, very probably for this reason.

The consequences of the widespread use of doping in sports in the GDR were a series of court trials against former sport officials responsible, and claims after the German reunification in 1990 of numerous athletes alleging late health problems. Attempts to elucidate and solve as far as possible the malpractices encountered considerable difficulties of proof due to the time interval and the secrecy of the whole strategy in the 1970s and 1980s. Notwithstanding the undisputable fact of state-supported doping in countries behind the “Iron Curtain” and of the associated doping-related sports results, doping has undoubtedly been applied also in many other countries, although more as an individual misbehaviour than as a strategic practice. Nevertheless, the general standpoint both of officials and of the public has slowly developed from acceptance through a negative image to total prohibition; this is still continuing.

7 Developments from the 1990s Onward

The Anti-Doping Convention of the Council of Europe (1989) was the first step on the side of states towards international harmonisation in the fight against doping, including obligations of governments and their dialogue with international and national federations and associations in sport. A Monitoring Group was established as the forum of the member states, seconded by the Sport Division under the Directorate General in the Council of Europe. This Convention was open for the membership of states inside and outside Europe from the beginning, and the actual membership has grown to 47 in 2008.

For the various aspects of the common activities, Advisory Groups of experts have been established for legal issues, education, science and for the common database. The Monitoring Group as a kind of “parliament” or General Assembly for this Anti-Doping Convention convenes usually twice a year in Strasbourg, whereas the Advisory Groups meet according to actual necessities.

Starting in the 1980s, rumours came up alleging the misuse of peptide hormones—mainly erythropoietin (EPO) and human growth hormone (hGH)—in sports. The lack of detection methods for proving the external origin of those hormones (whose clinical detection and quantitation has been possible for a long time) hampered confirmation of the suspicions for about a decade.
After the elucidation of the effects of blood transfusions and of the correlation between oxygen partial pressure and haemoglobin formation, Paul Carrot (1869–1957) and Catherine Deflandre assumed in 1906 that erythropoiesis would be governed by a humoral factor. After contradictions and final confirmation, Allan Jacob Erslev was able to show the existence of this factor, erythropoietin, in 1953. Eugene Goldwasser and Leon Orris Jacobson detected its production by the kidney in 1957 and first isolated the hormone in 1977 from human urine. The identification of the human EPO gene by Fu-Kuen Lin followed at Amgen in 1983. The first cloning and expression of recombinant human EPO gene was obtained in 1984 by Sylvia Lec-Huang in New York, followed soon after by the manipulation of mammalian cells (Fisher 2003).

Following the spectacular events at the Tour de France in the second half of the 1990s, in 1998 the IOC proposed the idea of an international Anti-doping Agency. First discussed at a World Conference in Lausanne in February 1999, the International Olympic Committee, the Council of Europe and the Monitoring Group to its Anti-Doping Convention, as well as several representatives of Governments, played an active role in supporting the foundation of the World Anti-Doping Agency, WADA, in December 1999. After having first established an office in Lausanne, WADA moved to Montreal as a political decision with the intention of emphasising the independence of this new institution from the IOC and from the international federations. This independence is guaranteed by a foundation based on Swiss Law, and mainly by the constitution of the governing bodies by equal numbers of representatives from sport (Olympic Movement, i.e. IOC and International Federations) and governments (delegates of states and international bodies such as the Council of Europe). The financial support of WADA is also shared between those two partners, sport (Olympic Movement) and Governments. Europe pays almost half (47.5%) of the governmental contribution, while the remaining 52.5% is contributed by the other four continents.

In the following years, the foundation and establishment of WADA created an entirely new situation. The first big success was the elaboration of the World Anti-Doping Code (WADC) in a huge project and with extraordinarily broad discussion until 2003, when this document was adopted at the World Conference in Copenhagen. It replaced the Medical Code of the IOC and the Olympic Movement Anti-Doping Code of 1999 and became the first anti-doping regulation with worldwide acceptance – after resentment and intensive discussion by all international federations.

Associated with the WADC are the International Standards (level 2 document) for the Prohibited List (WADA 2008a), for the Laboratories, for Testing and for Therapeutic Use Exemptions (TUEs). A third level of documents comprises Recommendations or Guidelines for related activities like education/prevention, result management, etc.

The need to harmonise the consequences of doping offences internationally and among the various federations and associations led to an international court of arbitration, CAS (Court of Arbitration in Sport, Lausanne), which is now considered the supreme authority in disputed cases (McLaren 2001).
The responsibility for the Prohibited List was taken over by WADA in 2003. The annual review is opened for discussion inside WADA and with its stakeholders. The WADA List Committee usually issues a draft with the suggested changes, and after extensive discussions with stakeholders the final version is accepted by the WADA Executive Committee at the end of September and becomes effective on 1 January the following year.

The inclusion of gene doping as a prohibited method was the most significant change since then, notwithstanding the inclusion of new substances, withdrawal of single compounds (most importantly caffeine), the establishment of a paralleling Monitoring Programme for permitted agents with some potential for doping, changes in the structure of the list and in the status of different classes and substances, and clarification of the processing of adverse findings.

A problem of definition – the widening of the lists of examples of prohibited classes by adding the expression “... and other substances with similar chemical structure or similar biological activity” could not be eliminated despite intensive discussions (Müller et al. 2000). The difficulty of obtaining complete lists of relevant agents and the possibility of misuse of “gaps” by synthesising designer compounds (such as was attempted with THG, tetrahydrogestrinone: Catlin et al. 2004; Fainaru and Williams 2003) are impeding “closed” lists so far.

When it remained a legal problem for governments formally to join a body based on a national law like WADA (a foundation under Swiss Law) and to agree about obligations derived from such an international document like the World Anti-Doping Code, after some discussions an idea originating from the Anti-Doping Convention of the Council of Europe (COE) and its Monitoring. Group led to the elaboration of the global UNESCO Anti-Doping Convention (UNESCO 2005). While the theoretical possibility to extend the (open) Convention of the COE to all other states has not found support, this UNESCO Convention was elaborated in several conferences and adopted in 2006. After ratification by the adopted minimum of 30 states, it came into effect in 2007. A General Assembly will be the future governing body, besides a permanent bureau at the UNESCO Headquarter in Paris.

The World Anti-Doping Code was revised by a third Anti-Doping World Conference in Madrid in November 2007; the new version came to effect on January 1, 2009 (WADA 2009b).

Similarly, and subsequent to the formation of those international bodies, National Anti-Doping Organisations (NADOs) as well as Regional Anti-Doping Organisations (RADOs) have been established in a series of states and regions, mostly combining the efforts of sport organisations with governmental and public participation in the fight against doping. This again has led to an international group ANADO (Association of National Anti-Doping Organisations), which aims to the worldwide harmonisation of doping control measures.

For the Anti-Doping Laboratories, the World Association of Anti-Doping Scientists (WAADS) provides the forum for exchange of knowledge and problems as well as the possibility to communicate with one voice to the other bodies bearing responsibility in this common activity.
Appendix 1 Historical Definitions of Doping

1933 Beckmanns Sport Lexikon

Doping, the use of stimulating (performance enhancing) agents, which shall push the athlete beyond his/her normal limits of performance.

Used for this purpose are:
Adrenalin, extracts of testes, caffeine, digitalis, strychnine, camphor, nicotine, cocaine, colanine, heroin, morphine, arsenic, phosphorous, calcium, alcohol etc.

The application of doping agents is rejected for reasons of sports ethics and health and is sanctioned in many sport disciplines by dismissal and sanctions.

1952 Association of German Sport Physicians (Deutscher Sportärztebund)

The intake of any pharmaceutical – regardless its activity – with the intention to enhance performance during a competition is considered as doping.

1952 Keysers Sportlexikon

Doping: Administration of stimulating agents for the enhancement of performance in sport. Application before or during the competition causes disqualification.

1956 Lexikon des Sportes (Dictionary of Sport)

Doping: Attempts by artificial stimulants of any kind, to enhance the performance of the body beyond the natural limits.

1963 Council of Europe (Madrid)

If a necessary medical treatment carried out by any means, which by its nature is capable to enhance physical performance beyond the normal level, this is considered as doping and excludes the capability to compete.

1963 Council of Europe, Committee of General (Out-of-school) Education

Doping is the administration or the use of xenobiotic substances in each form and on each way or of physiological substances in abnormal form or by abnormal ways to healthy persons with the only aim of artificial and unfair enhancement of performance for competition. In addition, various psychological measures for performance enhancement of the athlete have to be considered as doping.

1965 Belgian Law

It is the intention of this Law that doping is considered as the use of substances or the application of methods for the artificial enhancement of performance of an athlete, who participates in a competition or prepares for a competition, if the use can be harmful for his physical or mental integrity.

The Anti-Doping Committee recommends that the Legislative should prepare such a list of substances and methods, including an adequate declaration of the prohibited doses of these substances.
1970 German Sports League (Deutscher Sportbund)
Doping is the attempt to obtain an increase of performance of athletes for competition by nonphysiological substances. Doping substances as defined by these Guidelines are phenylethylamine derivatives (strong central stimulants or “Weckamines”, ephedrines, adrenaline derivatives), narcotics, analeptics (camphor- and strychnine derivatives), sedatives, psychopharmaceuticals and alcohol.

1971 Medical Commission of the International Olympic Committee:
All substances, also if applied for therapeutic purposes, which influence performance by their composition or dosage, are doping agents, including in particular

1. Sympathomimetic amines (e.g. amphetamines, ephedrines, etc.)
2. Central stimulants (e.g. strychnine, analeptics, etc.)
3. Narcotic analgesics (e.g. morphine, methadone, etc.)

1971 German Track and Field Association (Deutscher Leichtathletik-Verband, DLV)
“Each athlete is prohibited to take part in a competition, if he/she is under the influence of pharmaceuticals on the prohibited list. The proof of doping is obtained by qualitative detection. Time, dosage and potential of the agent are irrelevant.”

1976 International Olympic Committee
A definition of doping is not introduced.
Doping comprises the application of the substances on the following list. This list contains 76 different agents.

2. Narcotics and analgesics: morphine and derivatives
3. Vasodilatators: nitrites
4. Anabolic steroids

1977 German Association of Sport Physicians (Deutscher Sportärztebund)
1. Doping is the attempt at unphysiological enhancement of performance of an athlete by application (intake, injection or administration) of a doping substance by the athlete or an assisting person (e.g. team leader, coach, physician, nurse or physiotherapist) prior to a competition and, for the anabolic hormones, also during training.
2. Doping substances according to these guidelines are in particular: Phenylethylamine derivatives (“Weckamines”), ephedrines, adrenaline derivatives, narcotics, analeptics (camphor and strychnine derivatives) and anabolic hormones. In specific sports, additional substances can be prohibited as doping agents (e.g. alcohol, sedatives, psychopharmaceuticals).
1978 German Association of Sport Physicians
Doping is the use of substances from the prohibited classes of agents:

(a) Psychomotoric stimulants
(b) Sympathomimetic amines
(c) Various stimulants of the Central Nervous System
(d) Narcotics and analgesics
(e) Anabolic steroids

1986 German Association of Sport Physicians
Doping is the use of substances belonging to the prohibited classes of agents, and the application of non-permitted measures like blood doping.

Five classes of substances are defined as doping agents:

1. Psychomotoric substances (stimulants)
2. Narcotics
3. Anabolic steroids
4. Beta-receptor blockers
5. Diuretics

1988 International Olympic Committee
Doping is the use of substances from the prohibited classes of agents and the use of prohibited methods.

List of prohibited classes of substances and methods

I. Prohibited classes of substances
   A. Stimulants
   B. Narcotics
   C. Anabolic steroids
   D. Beta-receptor blockers
   E. Diuretics

II. Prohibited methods
   A. Blood doping
   B. Pharmacological, chemical and physical manipulation

III. Substances, permitted with certain restrictions
   A. Alcohol
   B. Local anaesthetics
   C. Corticosteroids

1989 Anti-Doping Convention of the Council of Europe
According to this Convention are defined

“Doping in sport” the administration to or the use of pharmacological doping agents or of doping methods by athletes.

(a) Pharmacological doping agents or doping methods according to paragraph 2 are those doping agents or doping methods which have been prohibited by the respective international sport organisations and are included in
lists, which according to article II.1b. are confirmed by the Monitoring Group,
(b) “Athletes” are those persons who participate regularly in organised sporting activities.

Until the date when a list with the prohibited doping agents and methods has been confirmed by the Monitoring Group according to Article II.1.b., the list of agents and methods attached to this Convention is valid as List of Agents and Methods.

Doping in this sense means each attempt to enhance performance by means, which normally are not administrated to the organism, whereby the intention of stimulation is essential and the manner of administration is irrelevant.

References

Beckett AH, Tucker GT, Moffat AC (1967) Routine detection and identification in urine of stimulants and other drugs, some of which may be used to modify performance in sport. J Pharm Pharmacol 19:273
Blickensdörfer H (1972) Der Tag, an dem Tom Simpson starb (The day when Tom Simpson died). In: Acker H (ed) Rekorde aus der Retorte (Records from the retort). Deutsche Verlagsanstalt, Stuttgart, p 104