GETTING A CLOSER LOOK AT THE DOPING PROBLEM!
MEDIUM LEVEL

SLIDE 2:

The World Anti-Doping Agency (WADA) describes the World Anti-Doping Code as follows:
"One of the most important achievements to date in the fight against doping in sport has been the drafting, acceptance, and implementation of a uniform **set of anti-doping rules**, the World Anti-Doping Code (Code). The Code is the core document that provides the **framework for harmonized anti-doping policies, rules, and regulations** within sport organizations and among public authorities. It works in conjunction with four International Standards aimed at bringing harmonization among anti-doping organizations in various areas: **testing, laboratories, therapeutic use exemptions (TUEs) and the List of Prohibited Substances and Methods**. …".

The complete description and the whole document can be downloaded at http://www.wada-ama.org/en/dynamic.ch2?pageCategory.id=250.

Picture shows: Global structure of the anti-doping policy by the World Anti-Doping Agency according to the World Anti-Doping Code.

- **WADA and the World Anti-Doping Code ("The Code")**
  ➔ international, independent monitoring regulator/watchdog of the global fight against doping in sport and its framework ("The Code").
- **IOC (International Olympic Committee), IPC (International Paralympic Committee), IF (International Sports Federations)**
  ➔ responsible for the testing process and the sanctioning. National Federations often fulfil this role.
- **Governments**
  ➔ financial, political and structural support and much more.
- NOCs (National Olympic Committees), NPCs (National Paralympic Committees), NFs (National Sports Federations)
  ➔ should agree to implement the Code.
- **NADOs (National Anti-Doping Organisation), RADOs (Regional Anti-Doping Organization)**
  ➔ responsible for testing national athletes in- and out-of-competition and adjudicating anti-doping rules violations and anti-doping education.
- **Athletes and Entourage**
  ➔ complying with the Code.

- **LABs (Laboratories)**
  ➔ analyse doping control tests.
- **CAS (Court for Arbitration for Sports)**
  ➔ facilitate the settlement of sport-related disputes.

SLIDE 3:

According to the World Anti-doping Code the following rule violations are defined:

2.1 **The presence of a *Prohibited Substance*** or its *Metabolites* or *Markers* in an *Athlete's* bodily Specimen

2.2 **Use or Attempted Use of a** Prohibited Substance or a Prohibited Method.

2.3 **Refusing, or failing** without compelling justification, to submit **to *Sample* collection** after notification as authorized in applicable anti-doping rules, or otherwise evading *Sample* collection.

2.4 **Violation** of applicable requirements regarding *Athlete* availability for ***Out-of Competition Testing*** including failure to provide required whereabouts information and missed tests which are declared based on reasonable rules.

2.5 *Tampering*, or *Attempting* to tamper, with any part of *Doping Control*.

2.6 Possession of Prohibited Substances and Methods…

2.7 Trafficking in any Prohibited Substance or Prohibited Method.

2.8 **Administration** or *Attempted* administration **of a *Prohibited Substance*** or *Prohibited Method* to any *Athlete*, or assisting, encouraging, aiding abetting, covering up or any other type of complicity involving an anti-doping rule violation or any Attempted violation.

The 2003 World Anti-Doping Code and its originally content is available under: http://www.wada-ama.org/en/dynamic.ch2?pageCategory.id=250.

SLIDE 4:

The "Prohibited List" of the World Anti-Doping Agency is arranged as follows:

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

S1. Anabolic agents

S2. Hormones and related substances

S3. Beta-2 agonists

S4. Hormone antagonists and modulators

S5. Diuretics and other masking agents

Methods prohibited at all times (prohibition in- and out-of-competition)

M1. Enhancement of oxygen transfer

M2. Chemical and physical manipulation

M3. Gene doping

Substances and methods prohibited in-competition

S6. Stimulants

S7. Narcotics

S8. Cannabinoids

S9. Glucocorticosteroids

Substances prohibited in particular sports

P1. Alcohol (e.g. prohibited in archery, automobile sports, motorcycling et al.)

P2. Beta-blockers (e.g. prohibited in bobsleigh, skiing and snowboarding [jumping, freestyle, halfpipe], wrestling)

The list is updated and published annually. The currently available Prohibited List can be downloaded under www.wada-ama.org/en/dynamic.ch2?pageCategory.id=370.

SLIDE 5:

The Anti-Doping rule compliance is controlled by testing procedures encountering all athletes within special testing pools. **International sports federations** should build a **testing pool for their international level athletes**, whereas **national anti-doping organizations** should create a **registered testing pool for national athletes**. The testing procedure is a so called “target testing”, meaning athletes aren’t randomly chosen. Furthermore, there is an **in-competition** testing (for substances and methods prohibited in-competition) and an **out-of-competition** testing (for substances and methods prohibited out-of-competition).

The testing procedure is divided into two ways. One is the **advance notice test** and the other one is the **no advance notice test** which should be preferred. If a test is announced it should take place within no more than 6 hours after warning. In the case of a no advance notice test less than one hour should pass after approach. Within this hour the tested athletes should be under constant supervision.

The 2003 World Anti-Doping Code and its original content about the testing procedure is available at:
http://www.wada-ama.org/en/dynamic.ch2?pageCategory.id=250.

SLIDE 6:

Doping control samples may be urine samples or blood samples, although the WADA code allows for the collection of other biological samples (hair, saliva, etc) as well. Most samples are still urine samples. However, more and more blood samples (two A- and B-samples of three millilitres of blood) are taken to control the absence of prohibited substances or methods.

Today most blood samples are used for the control of the athlete's health status (e.g. increased haematocrit in cross-country skiing ⇨ higher risk of arterial hypertension and thromboembolic events).

SLIDE 7:

According to the Therapeutic Use Exemption Guidelines of the WADA the definition is as follows: A Therapeutic Use Exemption (TUE) is an **authorization to take a Prohibited Substance under well defined and restricted conditions**. An application for a TUE shall be made in accordance with the International Standard for TUE. A TUE must be obtained for the use of any Substance on the Prohibited List. Depending on the Substance itself and the route of administration …, either a standard TUE or an Abbreviated TUE (ATUE) can be granted. All athletes who need a medical treatment including a Prohibited Substance or Method and are subject to Testing must obtain a TUE from their relevant Anti-Doping Organisation (ADO). In order to obtain an approval for a TUE, athletes must have a well documented medical condition supported by reliable and relevant medical data.

The four criteria that need to be fulfilled to grant a TUE are stated in the International Standard for TUE:

1. The athlete would experience a **significant impairment to health** if the Prohibited Substance or Prohibited Method were to be withheld in the course of treating an acute or chronic medical condition (Article 4.2 International Standard for TUE).
2. The therapeutic use of the Prohibited Substance or Prohibited Method would produce **no additional enhancement of performance** other than that which might be anticipated by a return to a state of normal health following the treatment of a legitimate medical condition. The use of any Prohibited Substance or Prohibited Method to increase "low normal" levels of any endogenous hormone is not considered an acceptable therapeutic intervention (Article 4.3. International Standard for TUE). Under 'enhancement of performance' should be understood: the return by the athlete to the level of performance possessed before the treated medical condition occurred. It means that a certain enhancement of individual performance, due to the efficacy of the

treatment, can occur, but that it cannot go beyond the level of performance of the athlete prior to his/her medical condition.

3. There is **no reasonable therapeutic alternative** to the use of the otherwise Prohibited Substance or Prohibited Method (Article 4.4. International Standard for TUE). Two points for reasonable therapeutic alternatives must be retained:
   - Only valid and referenced medications are considered alternative.
   - The definition of what is valid and referenced can vary in different countries. These differences should be taken into account, e.g. a medicine could be registered in one country and not in another, or still be under testing, etc.
4. The **necessity for the use** of the otherwise Prohibited Substance or Prohibited Method cannot be a consequence, wholly or in part, of prior non-therapeutic use of any substance from the Prohibited List (Article 4.5. International Standard for TUE). A TUE can only be granted if all four criteria are fulfilled.

The complete information on Therapeutic Use Exemptions (TUE) can be downloaded at: www.wada-ama.org/en/dynamic.ch2?pageCategory.id=373.

SLIDE 8:

International level athletes and national level athletes are part of a registered testing pool (according to the WADA code). From this pool athletes are chosen for out-of-competition testing. To make sure that all athletes are available for sudden out-of-competition testing, the athletes have to give their whereabouts to their international or national sports federation.

Athlete's whereabouts describes the duty of the athletes to give information about their current location to secure an adequate out-of-competition testing. Otherwise the athletes risk an anti-doping rule violation.

SLIDE 9:

Most doping substances are originally pharmaceutical drugs. These drugs are used for the medical treatment of a range of medical conditions. According to this aspect, these drugs have on the one hand their desired effects on the illness but on the other hand their undesirable side effects. These biomedical side effects are controlled and tested within several special trials and are proved to be acceptable in reference to the problems arising from the original illness.

The problem of the use of medical drugs as performance-enhancing substances is the fact that healthy athletes take drugs without an adequate necessity. And furthermore most substances abused are taken in so called suprapharmacological

doses or in different combinations ("stacking") without prior medical investigation leading to biomedical side effects which no one can really predict.

Picture shows: The relationship between drugs used for **medical purpose** and drugs abused in sports. The medically used drugs show therapeutic effects within **pharmacological** doses, whereas performance-enhancing drugs could show **hazardous** effects cause of the usage in **suprapharmacological** doses. As a consequence the side effects can be **short-term, reversible, irreversible or result in delayed adverse effects**.

SLIDE 10:

Anabolic steroids or **anabolic-androgenic steroids (AAS) are hormones**. Like most hormones they travel in the blood to **regulate specific body functions.** AAS for example may enhance the metabolism of proteins leading to an increased muscle mass.

Anabolic means "**to build up**"

Andro + **genic** means "**male**" + "**to produce**"

Steroids are a kind of **lipid molecules**

For example, **testosterone** is an anabolic steroid, in particular a male sex hormone which is endogenously produced in the testis, ovary, and adrenal cortex and in the liver. An example of the medical use of an application of anabolic steroids is muscle dystrophy (muscle diseases that cause progressive muscle weakness).

Picture shows: The hormone is produced by specific cells in the respective organs and afterwards secreted into the blood (**vascular system**). In the vascular system the hormone can be transported to any place within the body. Target cells have specific receptors which recognize the steroid hormone and respond accordingly.

SLIDE 11:

Anabolic androgenic steroids (AAS) are used for **medical** purposes like:

- A **lack of androgens** ➔ hypogonadism is a reduced capacity of the testis or ovary to produce androgens ➔ AAS use as a replacement therapy
- A **male gigantism** ➔ enormous height
- An **endometriosis** ➔ Proliferation of the uterus mucosa (growth beyond or outside the uterus)

- An **anaemia** ➔ lack of blood cells ➔ AAS use to stimulate erythropoeisis
- **Muscle dystrophy** ➔ muscle diseases that cause progressive muscle weakness
- **Impotency or erectile dysfunction** ➔ consistent inability to achieve or maintain an erection

SLIDE 12:

The desired effects of an AAS-abuse in sports derive from the anabolic part of the substance (cell growth). Athletes sometimes want to **"build up"** muscles by misusing steroids, which enhance the protein synthesis leading to an increased muscle tissue growth. Because of the increased protein synthesis, steroid abuse may also help to regenerate faster. AAS can have an effect on the musculature in particular when training is carried out under the influence of these agents.

Nevertheless, the athletes have to stay active, because anabolic **steroids do not lead to a muscle growth for itself**. Furthermore, muscles (in fact the whole human body) are **physiologically not prepared for such an extreme and fast growth**, so that damages on the muscles can appear resulting from the abuse of anabolic steroids during training.

Picture shows: AAS may be taken in the form of tablets, or else given as an intramuscular injection, leading to additional indirect health risks, like infections (e.g. hi-virus or hepatitis caused by sharing neddles).

SLIDE 13:

The slide shows a case report about multiple tendon ruptures by an athlete (football) abusing anabolics.

Original Abstract of Isenberg et al. (2008): Unfallchirurg, 46-49:

Successive ruptures of patellar and Achilles tendons. Anabolic steroids in competitive sports

Derivatives of testosterone or of 19-nor-testosterone are used as anabolics for the purpose of improving performance although the effect of anabolics is known still to be under discussion. The use of anabolic steroids continues among competitive athletes despite increased controls and increasingly frequent dramatic incidents connected with them. Whereas metabolic dysfunction during anabolic use is well documented, ruptures of the large tendons are rarely reported. Within 18 months, a 29-year-old professional footballer needed surgery for rupture of the patellar tendon and of both Achilles tendons. Carefully directed questioning elicited confirmation that he had taken different anabolic steroids regularly for 3 years with the intention of improving

his strength. After each operation anabolic steroids were taken again at a high dosage during early convalescence and training. Minimally invasive surgery and open suturing techniques led to complete union of the Achilles tendons in good time. Training and anabolic use started early after suturing of the patellar tendon including bone tunnels culminated in histological confirmed rerupture after 8 weeks. After a ligament reconstruction with a semitendinosus tendon graft with subsequent infection, the tendon and reserve traction apparatus were lost. Repeated warnings of impaired healing if anabolic use was continued had been given without success. In view of the high number of unrecorded cases in competitive and athletic sports, we can assume that the use of anabolic steroids is also of quantitative relevance in the operative treatment of tendon ruptures.

Upper picture shows: The patella (yellow arrows) and their lost connection to the tibia (rupture of the patellar tendon).

Below picture shows: The place of rupture in an anatomically picture (red arrow marks the patellar tendon).

SLIDE 14:

The misuse of AAS results in an enhancement of the motivation to train and along with this an increased risk of over-training, with all the detrimental effects that this has on the motor apparatus.

There is a widely held view, too, that the misuse of AAS in great quantity will produce considerable effects, while the organic side-effects will often be rendered harmless or denied. In actual fact, however, side-effects that appear harmless make an appearance at an early stage, and these are the precursors of the much more dangerous side-effects to the internal organs.

The health hazards of anabolic-androgenic steroids are largely based on the androgenic part. **Male abusers** could show an enlargement of breast growth, the so-called gynaecomastia (**getting more female**) and in contrast **female abusers** show an increased development of male sexual characteristics (**getting more male**).

Further side effects are:

- Steroid-related **acne** is less dangerous but an aesthetically unpleasant side-effect *(Picture a)*
- Inflammations of the liver; fatty degeneration of the tissue and the formation of **liver cysts** are examples of the direct damage to tissue that may occur *(Picture b)*
- **Shrinking of the testis** *(Picture c)*

- **Gynaecomastia** *(Enlargement of breast in males; Picture d)*
- **Degeneration on skeletal system**
- **Cardiovascular disturbances** appear on the heart as an inadequate supply with oxygen because of the heart muscles growth without adaptation of the blood vessels, further disturbances are seen on the circulatory system with a reduction of High Density Lipids (HDL), which protect the walls of the blood vessels and an increase of Low Density Lipids (LDL), which damage the walls of the blood vessels
- **Deepening of the voice** *(women)*
- **Beard growth** *(women)* **/ go bald** *(men)*
- **Increased aggressiveness** *(roid-rage)*

SLIDE 15:

Summary and keywords to know!

SLIDE 16:

Hormones and related substances are **endogenous or exogenous messenger molecules** released by endocrine glands or taken as drugs. They travel in the blood to **regulate specific body functions** such as:

- **Erythropoietin** is a hormonal substance that is formed especially in the kidney and stimulates red blood cell formation (will be explained in detail on the next slides).
- **Human growth hormone** is the naturally occurring growth hormone of humans or a recombinant version stimulating growth.
- **Insulin like growth factor** is a peptide structurally similar to insulin that is secreted either during fetal development or during childhood and that mediates growth hormone activity.
- **Mechano growth factor** is a subcategory of the insulin like growth factor.
- **Human chorionic gonadotrophin** is a glycoprotein hormone that is found in the urine and blood serum of pregnant women, is commonly tested for as an indicator of pregnancy, is used medically to induce ovulation and to treat male hypogonadism and cryptorchidism, and is produced in certain cancers (as of the testes).
- **Insulin** is a protein hormone that is synthesized in the pancreas that is essential for the metabolism of carbohydrates, lipids, and proteins that regulates blood sugar levels by facilitating the uptake of glucose into tissues, by promoting its conversion

into glycogen, fatty acids, and triglycerides, and by reducing the release of glucose from the liver. A failure to produce sufficient insulin is the cause of diabetes mellitus.

- **Corticotrophin** is a preparation of ACTH (adrenocorticotropic hormone / a protein hormone of the anterior lobe of the pituitary gland. It stimulates the adrenal cortex that is used especially in the treatment of rheumatoid arthritis and rheumatic fever.

SLIDE 17:

The abbreviation EPO stands for the **hormone erythropoietin** which is a growth factor formed especially in the kidney and **stimulates synthesis of the red blood cells**. **Red blood cells** or erythrocytes **carry oxygen to the tissues**.

The cycle of the formation of red blood corpuscles is controlled by the oxygen content in the blood, which is "measured" by receptors on an ongoing basis as a control variable. If the oxygen content is reduced and the body reaches a state of hypoxia, the production of EPO will be triggered, and following from this red blood corpuscles will be formed in the bone marrow. The important organ in connection with this cycle is the kidney, the tissue of which EPO is very probably formed.

It is possible to intervene in this control loop by introducing EPO externally, bringing about an increase in the red blood corpuscle count even without training.

Erythropoietin is used for **medical treatment** of anaemia.

Picture shows: **Erythropoietin** is produced by the **renal cells** and secreted into the blood (**vascular system**). It stimulates the red blood cell production in the bone marrow.

SLIDE 18:

Erythropoietin stimulates the production of **red blood cells** or erythrocytes in the bone marrow, which are responsible for the carriage of oxygen. This oxygen is essential for the physiological functions of the human body. In addition to the brain, the muscles need most of the oxygen to **secure endurance performance**. As a consequence, some cyclists, long-distance runners or cross-country skiers are tempted to abuse EPO to **increase their tissue oxygenation**.

A **legal and much more secure option** to increase endurance performance or more precisely oxygen binding capacity is **high altitude training**. The reduced availability of oxygen in the mountain air leads to a stimulation of the synthesis of red blood cells: this is a perfectly legal way to increase the number of red blood cells.

Picture shows: The Finnish Nordic skier Eero Mäntyranta has a mutation in the gene of his erythropoietin receptor. This led to an increased capacity to transport oxygen in the blood, giving him a legal advantage and leading him to several Olympic gold medals.

SLIDE 19:

Erythropoietin is used for medical treatments of **anaemias** (a condition in which the blood is deficient in red blood cells, in haemoglobin, or in total volume) **associated with chronic kidney disease**, **cancer treatment**, **AIDS** or **critically ill people**.

Graphic shows: A tissue develops a hypoxia, which is a lack of available and necessary oxygen. As a consequence the human body induces the production of erythropoietin leading to an increased synthesis of erythrocytes - with a delay of several days.

SLIDE 20:

Erythropoietin (EPO), whether in the form natural to the body (human [h] EPO) or that produced by gene technology (recombinant human [rh] EPO), has minor side-effects based on its structure like allergic (seldom) or immunological reactions. All its effects that are hazardous to health are linked to the formation of red blood corpuscles leading to an **increased blood viscosity**. Accordingly, EPO-abuse **increases the risk of arterial hypertension** (high blood pressure) **or of thromboembolic events** (blood clots) in the lung, brain or heart, that can result in an infarct or stroke.

EPO-abuse can be strongly life-threatening!

Picture shows: On the left side of the picture you see the right heart ventricle; and on the right side you see the left heart ventricle of a pathologically enlarged heart, and the infarction is marked with the blue circle.

SLIDE 21:

Summary and keywords to know!

SLIDE 22:

Beta-receptors are a group of receptors that are present on cell surfaces of some organs and tissues **innervated by the sympathetic nervous system mediating certain physiological responses** like vasodilatation, relaxation of bronchi and increased heart rate when bound by specific adrenergic agents.

Beta-receptor-blockers are a group of drugs **blocking the activity of beta-receptors** to decrease the heart rate and force of contractions and consequently lowering high blood pressure. Therefore, they are frequently taken by heart injury.

A receptor is usually a membrane protein where specific molecules can bind to signal a certain response.

Picture shows: Beta-receptor-blockers are taken orally, absorbed by the gastrointestinal tract into the blood and passed by the liver to the heart. There they are blocking the beta-receptors.

SLIDE 23:

Beta-blockers have no direct performance enhancing effect. They are prohibited in several sports needing less excitement like archery or automobile sports. **A slowing of the heart rate and the circulation** is observed. Furthermore, beta-blockers **reduce excitement, stage fright and hand tremor**, leading to an **increased tranquillisation.**

Picture shows: A normal body responds to extreme stress by activating the "fight-or-flight" response mechanism, i.e. pumping adrenaline into your system, raising your heart rate, and giving you a sudden burst of energy and power.

- During a stressful situation the sympathetic nervous system stimulates the adrenal glands to produce adrenaline.
- The adrenaline flows through the blood vessels to the heart.
- Adrenaline activates the receptors on the heart.
- Heart rate goes up, producing fight-or-flight reactions.
- After oral intake of beta-blockers they enter the bloodstream through the gastrointestinal tract and prevent adrenaline from attaching to the receptors on the heart cells.
- Heart rate stays normal and the fight-or-flight reactions do not occur.

SLIDE 24:

Biomedical side effects of beta-blockers are:

- **Bradycardia** is a decreased heart rate.
- During **blood pressure reduction** an unexpected blood pressure reduction occurs.
- **Acoasma or hallucination** are a perception of something with no external cause usually arising from a disorder of the nervous system or in response to drugs.
- **Sleep disturbances** are observed.
- **Bronchial spasm** is the contraction of muscles of the airway system, leading to a difficulty in breathing.
- **Depression** is a psychotic disorder marked especially by sadness, lethargy, difficulty with thinking and concentration, a significant increase or decrease in appetite and time spent sleeping, feelings of dejection and hopelessness, and sometimes leading to suicide.
- Weariness or exhaustion from labour, exertion, or stress is called **Fatigue**.

SLIDE 25:

Summary and keywords to know!

SLIDE 26:

Beta-2 agonists (also called beta-sympathomimetics) **simulate the sympathetic nervous action on beta-receptors** and therefore primarily work via relaxation of smooth muscle tissue of the airways. Biochemically, beta-2-agonists affect beta-2-receptors which are found in the lung. The **medical use** of beta-2 agonists is in the treatment of **asthma**.

Athletes have to pay attention to the possibility of a **TUE (therapeutic use exception)** in the case of asthma.

Picture shows: The mode of action of beta-2 agonists on bronchial muscle! A contracted bronchial muscle, like it happens in case of an asthmatic attack, could be relaxed by the donation of beta-2 agonists.

SLIDE 27:

Athletes abusing beta-2 agonists believe that they can increase their endurance **performance by an increased lung function** or influence their strength by an

increased protein synthesis. But nevertheless there is at present **no clear scientific verification**.

One of the best known stories of a beta-2 agonist being abused is the story of Katrin Krabbe (German sprinter) and her clenbuterol abuse. Clenbuterol was first developed as a growth promoter in animal production to increase lean muscle mass and reduce fat, and was only later abused for doping purposes in sports.

SLIDE 28:

Known side effects of beta-2 agonists are:

- **Increase of heart beat and an increased blood pressure.**
- **Fine tremor of the hands, restlessness and headache**
- **Flushing and palpitations**
- **Behaviour disturbances in children**
- **Muscle cramps and allergic reactions**
- **Irritation of throat and the upper airways**

SLIDE 29:

Summary and keywords to know!

SLIDE 30:

Blood doping belongs to the illegal methods of manipulation and is a **direct form of enhancing the oxygen transfer** with an immediate effect by enhancing the amount of red blood cells. In contrast, EPO only induces an increased synthesis of red blood cells.

There are two different methods athletes could manipulate:

- **collecting their own blood and reinject later**
- **taking the blood of a donor and reinject if required**

The physiological effects are the same as for EPO-abuse:

- increased red blood cells

- increased capacity of oxygen delivery

Blood bottles are **used in medicine to treat enormous blood losses**.

SLIDE 31:

More red blood cells, more oxygen carrying, **more endurance-performance!** The effects are the same as those of EPO-abuse, but with an immediate consequence.

Graphic shows: The impressive effect of blood transfusion on physical performance is expressed in the following trial, showing the effect on **time to run a 10 km race with reinfusion or with placebo**. Group 1: No effects can be seen after infusion of the placebo solution, but a significant effect results after blood reinfusion ⇨ the time to run decreases.

Group 2: The time to run 10 km decreases immediately after blood reinfusion. This improvement of time was sustained for 13 days after reinfusion of red blood cells and therefore was still present at the time of placebo infusion.

Original abstract of Brien & Simon (1987): JAMA 257 (20), 2761-2765:

The effects of red blood cell infusion on 10-km race time

The purpose of this study was to investigate the effect of infusion of 400 ml of red blood cells (RBCs) on 10-km track race time, submaximal heart rate, hematocrit, 2,3-diphosphoglycerate, and partial pressure of oxygen at 50% hemoglobin saturation. Six highly trained, male, distance runners twice donated a unit of RBCs, which was frozen for subsequent reinfusion. Eleven weeks after the second donation, they undertook a series of three competitive 10-km races on a standard 400-m track: before infusion, after 100 ml of saline solution, and after 400 ml of autologous, previously frozen deglycerolized RBCs. All subjects took all trials in this double-blind, placebo, crossover, experimental design. Running time was recorded at each 400-m split, and blood was collected prior to each trial. The data were analyzed by analysis of variance. Results following the RBC infusion showed a significantly higher hematocrit concentration, a significantly faster 10-km run, a nonsignificant decrease in submaximal heart rate, a nonsignificant decrease in submaximal heart rate (10 beats per minute), and no significant changes in either 2,3-diphosphoglycerate or partial pressure of oxygen at 50% hemoglobin saturation. Erythrocythemia induced by the infusion of 400 ml of autologous packed RBCs effectively increased performance capacity in a 10-km track race, probably due to an increase in oxygen delivery to the working muscles.

SLIDE 32:

Most of the biomedical side effects are similar to those of EPO-abuse.

Blood doping places an increased stress on the cardiovascular system leading to a **high blood pressure and an increased risk of thrombosis**. Furthermore, blood transfusions hold the **risk of a transfusion accident by allergies or**

incompatibilities (ABO-system) and the **risk of severe infections like hepatitis or HIV**.

SLIDE 33:

Summary and keywords to know!

SLIDE 34:

Plasma volume expanders belong to the group of diuretics and other masking agents of the Prohibited List. Plasma expanders **increase the fluid part of the plasma leading to a decreased haematocrit**, which is used for emergency medical aid in case of **enormous blood losses or extensive burns**.

Definition of haematocrit: The proportion of blood volume that is occupied by red blood cells, usually expressed as a percentage of the total blood volume.

Picture shows: The human blood can be separated into the plasma (yellow) and into the blood cells (red). The **yellow** fluid portion consists of **water** and its dissolved constituents including **proteins** (as albumin, fibrinogen, and globulins), **electrolytes** (as sodium and chloride), sugars (as glucose), lipids (as cholesterol and triglycerides), metabolic waste products (as urea), amino acids, hormones, and vitamins. The **red** portion consists of the cellular structures of the blood, e.g. **erythrocytes, leukocytes** etc.

SLIDE 35:

Plasma expanders are abused by athletes to compensate for a high **haematocrit** level by **reducing the blood viscosity**. A high haematocrit is normally found after EPO-abuse and plasma expanders could be misused in order to cover this doping violation. Another aspect is the **balancing of fluid loses by endurance performances** which are leading to decreased blood volumes. Plasma expanders can **increase the blood volume** by compensating for this fluid loss.

Picture shows: The effect of abuse of a plasma volume expander is demonstrated in this picture.

- Left column: Blood composition before an abuse of the plasma volume expander and with an increased haematocrit.

- Right column: Blood composition after an abuse of the plasma volume expander and with an decreased haematocrit.

The amount of the cellular part of the blood (red column) stays the same (compare left to right column). Only the amount of the plasma (yellow column) is increased so that the percental distribution of solid to fluid parts of the blood (haematocrit) is decreased through the abuse of the expander.

SLIDE 36:

The biomedical side effects of plasma volume expanders can be

- **allergic reactions like itching,**
- **dizziness/vertigo,**
- **asthmatic symptoms or**
- **a circulatory collapse**.

SLIDE 37:

Summary and keywords to know!

SLIDE 38:

Diuretics are products that **help to eliminate fluid from the body**. They influence the function of the kidney leading to an increased excretion, water losses and weight reduction. They cause a **loss of water by partially paralyzing water reabsorption**, i.e. the **rate of urination is elevated**. These effects can be achieved within a few hours. Powerful diuretics can increase the flow of urine to about 6 litres per day.

The medical indication of diuretics is **high blood pressure, heart failure or liver cirrhosis.**

SLIDE 39:

A direct performance enhancement would not be expected to result from the use of diuretics. They are abused for a **fast weight reduction** leading to the possibility to start in a lower weight class. Or they are abused to **dilute a urine sample** by an increased part of water in it **for masking the abuse of other doping substances.**

Diuretics are also very common in the **bodybuilder scene**. The aim is after all to **improve the muscle appearance** by loss of water and to show as much muscle as possible and as much definition and striation within that muscle.

The case report shows the rapid weight loss strategy of a rower and its fatal consequences. Besides his efforts to loose weight by extreme activity an abuse of diuretics could be diagnosed.

Abstract of Dunker et al. (2001): Anaesthesist, 500-505:

Exertional heatstroke. Lethal multiorgan failure due to hyperthermia in a 23-year-old sportsman

We report the case of a 23-year-old rower who suffered from an exertional heatstroke while trying to lose 2 kg in weight by jogging before a competition. The development of this illness was favoured by clothes that were inappropriate for the environmental conditions and which the sportsman wore intentionally to enhance sweating. The maximum core temperature was over 43°C. As a consequence the comatose patient developed a fulminant multi-organ failure with the liver ceasing its function, renal failure, massive rhabdomyolysis, and disseminated intravascular coagulation. In addition, he suffered from pericardial effusion and acute pulmonary failure (ARDS). In spite of maximum intensive care with an extensive substitution of blood products, continuous hemodiafiltration, and inhalative administration of nitrous oxide the young sportsman died 48 h after his admission to the intensive care unit. This tragic course demonstrates the danger of the widespread habit of losing weight by vigorously exercising with inappropriate clothes. In this article, potential risk factors, symptomatology, therapy, and methods of preventing an exertional heatstroke are shown and discussed.

SLIDE 40:

Health hazards are the **disruption of the water- and salt-balance** leading to **dehydration and electrolyte imbalances**. Further side effects are:

- **loss of minerals**
- **increased muscle cramps and renal disease**
- **among males: impotence**
- **among females: disturbances of the menstrual cycle**

Explanation side effects of case report please see abstract above!

SLIDE 41:

Summary and keywords to know!

SLIDE 42:

Stimulants, like amphetamine, ephedrine or caffeine were the first group of effective agents which were placed on the doping list that was drawn up in 1967. However, caffeine is no longer considered as a doping agent and thus not on the "Prohibited List". This group of substances includes very different agents, both natural agents and their derivatives and those that are artificially produced. Stimulants are exogenous substances (like ephedrines) **affecting the central nervous system** by stimulating the release of several transmitters (e.g. Acetycholine). These substances **increase the heart rate, breathing rate and brain function** and may lead to euphoria.

Their counterparts in the human body are adrenaline or noradrenaline. These endogenous substances increase the energy metabolism, too.

Stimulants or amphetamines are used for medical purpose mainly for local administration like **relaxing bronchi** or to decongest the nasopharynx mucosa (**cold medicine**). Furthermore, stimulants are also widely abused as drugs, e.g. XTC.

Picture shows: A neurone – the functional cell of the brain – with its input structures (dendrites) and its output structure (axon) communicating with other cells by synapses. The synapse is a cell junction for the communication between cells - stimulants affect here! Stimulants lead to an increased release of transmitters.

SLIDE 43:

Stimulants increase the excitation of the brain and the body. The abuse by the athletes is based on the attaining of **increased alertness**, **reduced tiredness** and an **increased competitiveness and aggression with less sensitivity to pain**. **Stimulants do not directly increase physical performance**.

The most commonly used stimulants in sport are amphetamines, cocaine, ephedrine and caffeine.

Graphic shows: The state of “total exhaustion” is under normal circumstances (e.g. in sports) not achievable. It is something like an autonomously protected resource and can only be activated under specific circumstances. But with stimulants it is possible to take the last resources of the body!

SLIDE 44:

Stimulants lead to the suppression of fear or exhaustion. Their effect is so powerful that an athlete will not realise how exhausted he is, and there have been cases of

overexertion leading to death, especially in top-level competitive sports. Associated with these effects, dehydration may also occur as a result of prolonged effort, and generally hyperthermia as well.

Biomedical side effects of stimulants are on the one hand the development of **psychological disturbances like an addiction or depression or on the other hand physiological effects** like:

- **dysregulation of the body temperature**
- **loss of appetite and sleep**
- **hallucinations**
- **body trembling, restlessness, agitation, tension**
- **cardiac arrhythmia**

Due to their euphoric effect, stimulants are abused in the field of sports and out of sports!

SLIDE 45:

Summary and keywords to know!

SLIDE 46:

Nutritional supplements are **substances that** are normally present in the body and are consumed in addition to normal daily nutrition, like **glucose, minerals, vitamins or trace elements.** Some of these substances are **essential for the growth and development** of a multicellular organism, like the human body, but others have no effect or may even be harmful. The nutritional supplements contain the respective substances in a concentrated form and mostly consist of several substances. The **medical purpose** for the use of nutritional supplements **is a deficiency in the body** due to malnutrition or illnesses.

The main reason for the public to use nutritional supplements is the belief that they promote health, reduce risk of getting sick and at least control body weight. Most of the supplements are not prohibited within the “List”.

SLIDE 47:

Nevertheless, a well-balanced nutrition is much better than any nutritional supplementation and of course intake levels have to be taken into account to avoid the effect of an ‘overdosage’.

Nutritional supplements might help **some competitive athletes to perform the intensity and duration of their sports. They have an extremely high calorie usage level that cannot be covered by normal daily nutrition** (like Tour de France etc.).

Critical substances are some vitamins of the B group in vegetarian athletes.

SLIDE 48:

Nutritional supplements themselves are not prohibited, unless they contain a prohibited substance, albeit this is mentioned or not mentioned on the label.

One of the main risk factors of nutritional supplements can be positive doping testing by contaminated supplements. These **unlabelled** ingredients can lead in the extreme case even to positive doping testing. As a consequence the **biomedical side effects depend on the kind of the "unlabelled" substance**. **Most detected substances are various anabolic-androgenic steroids or stimulants**.

It is a matter of fact that a lot of sportsmen are using supplements without the knowledge of side effects and recommended intake levels. In the face of the great market of nutritional supplements (about 12 billion US$ in the USA in the year 2001) and the tremendous selling worldwide, the edge between a recommended use and misuse is floating.

Furthermore, the assumption that the use of nutritional supplements can be used to prevent possible nutritional deficiencies may lead to less attention concerning a healthy, well-balanced diet.

Table shows: An International Olympic Committee analysis of 600 over-the-counter nutritional supplements found that one-quarter of the investigated supplements contained banned substances such as anabolic steroids.

SLIDE 49:

Summary and keywords to know!

SLIDE 50:

Genes are single sections of the DNA including the hereditary information. These **genes contain the information** for the composition of the body and therefore **for the single proteins**, too, e.g. muscle proteins. One aspect of **gene therapy is the attempt to change the information on the selective genes**.

The 2008 Prohibited List defines gene doping as *"the non-therapeutic use of cells, genes, genetic elements, or of the modulation of gene expression, having the capacity to enhance athletic performance".*

Picture shows: The idea of gene therapy is to implement the modified genes into the cell by the help of specific transporters. After the implementation the corrected/new functional proteins can be synthesized by the cell and the disease can be healed or at least lowered.

The medical purpose of gene therapy is to correct defective genes that are responsible for the disease development, like hereditary diseases. But the problem is the abuse of the therapeutic idea for sport purposes.

SLIDE 51:

If the correction of defective genes is possible, it wouldn't be far to the modification of muscle genes. Possible aims of abuse could be:

- an **increased erythropoietin production** (remember Eero Mäntyranta, the Nordic skier), to **enhance the endurance performance**
- the **stimulation of specific** muscle growth factors **to enhance power and speed**

Left picture shows: A male child at the ages of seven months. He appeared extraordinarily muscular, with protruding muscles in his thighs and upper arms. At 4.5 years of age the male baby showed increased muscle mass and strength due to a genetic myostatin mutation leading to an increased muscle mass. He could hold two 3-kg dumb-bells in horizontal suspension with extended arms.

(The original data could be found by Schuelke et al. (2004) N Engl J Med. 350: 2682-2688)

Right picture shows: A so-called "Belgian Blue" cow with a mutation in the myostatin gene. The increased muscle mass is a distinctive visual sign.

Nevertheless, an **abuse** of gene therapy or the idea of the known gene mutations **in sports is currently not known**.

SLIDE 52:

The lack of control of the artificial gene is the major concern in gene therapy. Neither desired effects nor unwanted side effects can be predicted according to the widespread mechanisms of gene regulation.

Results from clinical trials for gene therapy methods reported that the following problems can appear:

- **cancer,**
- **multiple organ failure and**
- **other strongly life-threatening events**

Further risks are totally unknown, due to the sparse studies and publications and thus the biomedical side effects of gene therapy are uncontrollable!

SLIDE 53:

Summary and keywords to know!