Performance Enhancers
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What does Canseco say?

• Days of William Osler
  – huckster selling long-life elixir at a rural county fair?

• Quotes
  – "Steroids, used correctly
    • “will not only make you stronger and sexier, they will also make you healthier,"
    • “can cure certain diseases.”
    • “better quality of life and also drastically slow down the aging process."

  – Then he helpfully adds, "I’m forty years old, but I look much younger."
Which of the following is false

1. >250K adolescents use Anabolic steroids in the US
2. >1 million adults abuse AAS
3. 12\textsuperscript{th} grade HS students and 8\textsuperscript{th} junior HS students use AAS nearly at the same level
4. Twice as many girls abuse AAS as boys
IOC list of prohibited substances & methods

I. Prohibited classes of substances

Stimulants, Narcotics
Anabolic agents
  Anabolic steroids (testosterone and derivates)
  Beta-2-agonists (e.g., clenbuterol)
Diuretics
Peptide hormones, mimetics and analogues (hGH, IGF-I, EPO, hCG, insulin)

II. Prohibited methods

Blood doping
Administering artificial oxygen carriers or plasma expanders
Pharmacological, chemical and physical manipulation
Gene doping

III. Classes of prohibited substances in certain circumstances

Alcohol, Tobacco, Cannabinoids, Local anesthetics
Glucocorticosteroids, Beta-blockers,
Beta agonists low dose
  Salmeterol, formoterol, salbutamol in accordance to manufacturers recs

Finish World Champion: Where we they at Salt Lake 2002?
History of “Doping”

• 1935 Testosterone
• 1950’s -Eastern block Olympians pump more than iron
• Testing
  – IOC banned AAS use in 1975 and began urine testing in 1976
  – The NCAA started testing in 1986
Poll 198 US Olympians

• Athletes were asked whether they would take a banned performance-enhancing substance if they were guaranteed to win and not get caught…??

• Would they take the same undetectable substance if it would contribute to winning every competition for 5 years, then result in death?…
Scope of the problem-AAS

- >1 million Americans, >250,000 adolescents\(^1\)
Basic Chemistry & Physiology of AAS

- **Males**
  - 4-10mg of testosterone/day
  - 1-2 mg of androstenedione/day

- **Women**
  - 0.04-0.12mg testosterone/day
  - 2-4mg of androstenedione/day

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Mechanism of action of AAS

- \( \uparrow \) skeletal muscle via
  - \( \uparrow \) RNA -> protein

- Anticatabolic
  - \( \downarrow \) effect of glucocorticoids
  - \( \uparrow \) Nitrogen balance

- **Steroid rush!**
Natural effects of testosterone analogues

• Anabolic: non reproductive effects
  – ↑ muscle mass
  – ↑ bone growth before epiphyseal closure
  – ↑ heart, liver & kidney size
  – ↑ erythropoiesis
  – ↓ body fat

• Androgenic effects
  – ↓ Spermatogenesis
  – ↓ testes
  – ↑ Axillary, facial & pubic hair

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“Designer Steroids”

• Can we improve the androgenic/anabolic ratio?
Common Drugs

• **Oral**
  – Oxymetholone (Anadrol)
  – Oxandrolone (Anavar)
  – Methandrostenolone (Dianabol)

• **Intramuscular**
  – Nandrolone decanoate (Deca-durabolin)
  – Nandrolone phenpropionate (Durabolin)
  – Testosterone cypionate (Depo-Testosterone)
  – tetrahydrogestrinone (THG)
The Balco Investigation: The Clear and the Cream!

FDA Statement on THG: October 28, 2003

- THG tetrahydrogestrinone:"
  - synthetic "designer" steroid derived by simple chemical modification, from two other synthetic anabolic steroids, gestrinone and trenbolone.

- FDA is working with other Federal law enforcement agencies to aggressively engage, enforce, and prosecute those firms or individuals who manufacture, distribute, or market THG.
Patterns of AAS abuse

• **Stacking**
  – Ave = ~5 AAS (oral & injectable)

• **Cycling:**
  – 6 to 12 weeks then stops for 10 to 12 weeks

• **Pyramiding**
  – ↑ dose over 6-12 w

Sostenon 250 pre-stack blend of four testosterone

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Side effects of AAS
(Traditionally overstated?)
Increased premature Mortality of Competitive Powerlifters suspected to have used anabolic steroids

• Subjects
  – Control group

• 12 year follow up

• Results
  – Death rate
  – 12.9% for powerlifters vs 3.1% for controls

• Causes of premature death (8/62)
  – Suicide (3), MI (3), hepatic coma (1),
  – Lymphoma (1)

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Taylor Hooton
16 y/o Plano Texas

In Loving Memory of:

Taylor Edward Hooton

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Ancillary drugs

• hGH-
• HCG/Clomid (BB)
• Insulin
• Stimulants
• Diuretics
• Anti-estrogens
  – The SERM tamoxifen: prevents binding to the estrogen receptor in the breast, reducing the risk of gynecomastia.[
• Anti acne medications

08/12/07

Ivan Oiva-weight lifter
Bulgaria (+) diuretics
2000 Summer Olympics
Detection of Steroids!

- Testosterone level?
  - variable

- Epitestosterone?
  - chemically similar natural steroid produced in the liver
  - Not performance enhancing
  - Reasons for > T/E
    - low epitestosterone excretion: ethol?
    - androgen producing tumour
T/E ratio: What is the nl ratio?

- The natural ratio of T/E in humans is usually between 1:1 and 2:1
  - WADA rules > 4:1 is +
  - 2004 Tour de France = 6:1.

- Does ethnicity affect it? -- ↓ Asians

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Detection of banned anabolic steroids

A urine specimen is split into two samples, usually labeled ‘A’ and ‘B’, so that a confirmation test can be run if the initial test result shows the presence of a drug. (Photo by Daniel Käsermann.)
Purity?

- DEA: >50% of hGH and AAS products are phony!
- Are nutrition companies adding AAS to supplements?
Recombinant Human Erythropoietin

The Chemical Games

Biotechnical advances and administrative loopholes enable devious athletes to take performance-enhancing drugs without much risk of being caught or sanctioned.

ANGUISHED CYCLIST: A member of the Banesto team tries to hide from the press after his group withdrew from the 1998 Tour de France amid a sprawling scandal linked to the drug erythropoietin.

- Boosts delivery of O2
- Banned by IOC in 1990
- Detection was a problem until 1998
- Olympic survey results

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Recombinant erythropoietin in urine
Lasne F. Ceaurriz J. Nature 405, 635 June 2000

- Autoradiograph of isoelectric patterns of exogenous and endogenous erythropoietin

a) Human natural epo  b) & c) recombinant epo
d) control  e) & f) pts treated with epo for anemia
g) & h) two cyclists from Tour de France
“The Pirate” Patini
1970-2004

• 1995: Takes on Miguel Indurain in the Alps
• 1998: Won Giro d'Italia and Tour de France
• 1999: Thrown out of Giro for failing blood test
• 2001: Syringe of insulin found in Pantani’s room during Giro
• 2003: Admitted to hospital for detox and depression
• 14/Feb/2004: Dies of Cerebral & and pulmonary edema: **Age 34?**

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Spinning in Their Graves

The Tour's new scandal: Elite cyclists are mysteriously dropping dead

- ON FEBRUARY 13 2004, an amateur Belgian cyclist named Johan Sermon slipped into bed early, hoping to rest up for an eight-hour training ride the next morning.
- A 21-year-old with strong prospects for a professional career, Sermon had undergone a complete cardiac evaluation a few days earlier, and doctors for his team, Daikin, had deemed him to be in excellent health.
- But shortly after dawn, Sermon's mother found him lifeless in his bed. An autopsy listed the cause as heart failure—an astonishing exit for a young athlete in peak condition.

- Phil Liggett, the veteran cycling broadcaster, “100 international racers have died prematurely during the past decade, most from heart attacks. The likely cause, EPO”
Human growth hormone (HGH), also known as somatotropin

- Peptide hormone of 191 amino acids arranged in a bundle of four α-helices.
- It is synthesized and secreted by cells of the anterior pituitary.

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Claims for GH as an anti-aging treatment date back to 1990 NEJM study where GH was used to treat 12 men over 60.
- + statistically significant increases in lean body mass, equivalent to 10 to 20 year aging period.
- No claim that GH had reversed the aging process.
- Results were mis-interpreted as indicating GH was an effective anti-aging agent.

Between 20,000 and 30,000 people in the United States used growth hormone as an anti-aging therapy in 2004, a tenfold increase since the mid-1990s.

- **Side Effects**
  - Preadolescence, -> gigantism
  - Adults -> Acromegaly
  - DM, Htn, CAD, cardiomegaly , CHF, peripheral neuropathy, impotence amenorrhea, osteoporosis

- Creutzfeld-Jacob?
- 5% (50%AAS)
Detection of doping with recombinant hGH

- 1/2 life of HGH = 15 min.
- Two techniques
  - Indirect Method:
    - Detect HGH-dependent variables
      - IGF-1
      - IGF binding protein 3
      - Bone turnover proteins
        » PIIIP, Osteocalcin
      - Advantage detect up 84 days after injection
  - Direct Method: Isoform detection
    - Disadvantage 1-2 days only
- No urine test!
Terry Newton (7 November 1978 – c. 26 September 2010)

- English international Rugby Hooker
  - Leeds Rhinos, Wigan Warriors, Bradford Bulls and Wakefield Trinity Wildcat

- In February 2010, two-year ban tested positive for human growth hormone. (targeted testing)

- He was found hanged in his home seven months later.
Gene Doping
Will athletes go for the ultimate high?
Jeffrey Leiden 1997
University of Chicago
*(Human Gene Therapy, vol 8, p 1797)*

- **Adenovirus:** deliver the *epo* gene to mice & monkeys
  - virus injected into animals' muscles spurring the cells to pump out the protein.

- **HCT**
  - boosted from 49 per cent to 81 *(Human Gene Therapy, vol 8, p 1797)*.
  - A single injection elevated hematocrits
    - over a year in the mice and
    - 12 weeks in the monkeys.
Brave New World

Gene Doping

- HEAVY WORKOUT. This rat, injected with a muscle-enhancing gene, boosts its strength by lugging weights up a ladder.
Current events & Gene Doping

  - Discouragement on the use of genetic testing for performance.

- The first product to be associated with genetic doping emerged at Torino 2006 Olympic Games, with Repoxygen.
Repoxygen™ 1st type of gene therapy preclinical development

- Induces controlled release of (EPO) in response to low oxygen concentration in mice.

- Viral gene delivery vector
  - carrying the human EPO gene under the control of a so-called "hypoxia control element" ("HRE").
  - HRE: sense low oxygen concentrations & to switch a gene on in response?

- Repoxygen
  - delivered by injection into muscle
  - induce syntheses of EPO in the muscle tissue. (Normally, EPO is synthesized in the kidneys)
Testing

Gene Doping?

• Gene doping may be undetectable?
Therapeutic use exemption

• Form from WADA
• Requirements
  – Athlete would experience a significant health problem if he did not take the prohibited medication
  – The medication would not produce significant enhancement of performance, and there is no reasonable therapeutic alternative.
  – Example is an athlete who takes testosterone because he has had bilateral orchiectomy for testicular cancer.

04/05/2009
Sir William Osler

• “One of the first duties of the physician is to educate the masses not to take medicine”

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Questions?

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• Want to help with research?