

Performance Enhancers UPDATE 2013

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A PROGRAM OF
**Rady
Children's**
Hospital
San Diego

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. 12th grade HS students and 8th 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



Finish World Champion:
Where were they at Salt
Lake 2002?

I. Prohibited classes of substances

Stimulants, Narcotics

Anabolic agents

Anabolic steroids (testosterone and derivatives)

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

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



CJ Hunter in Oslo, Norway

July 20, 2000

+ nandrolone x1,000

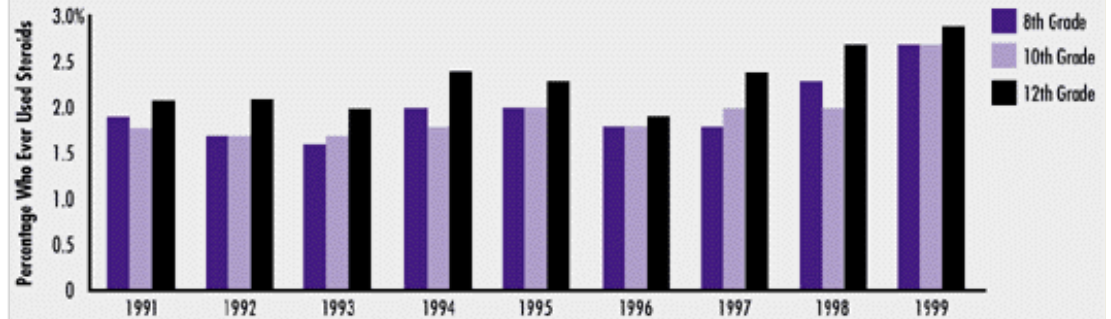
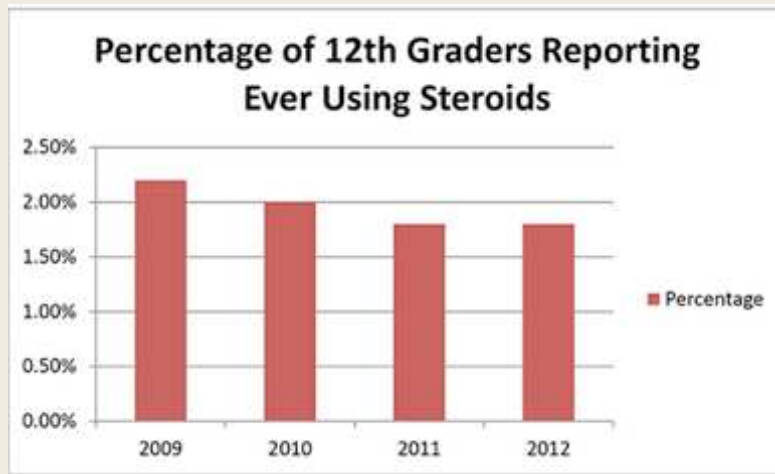
Poll 198 US Olympians

- 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*...

04/05/2009

Scope of the problem-AAS

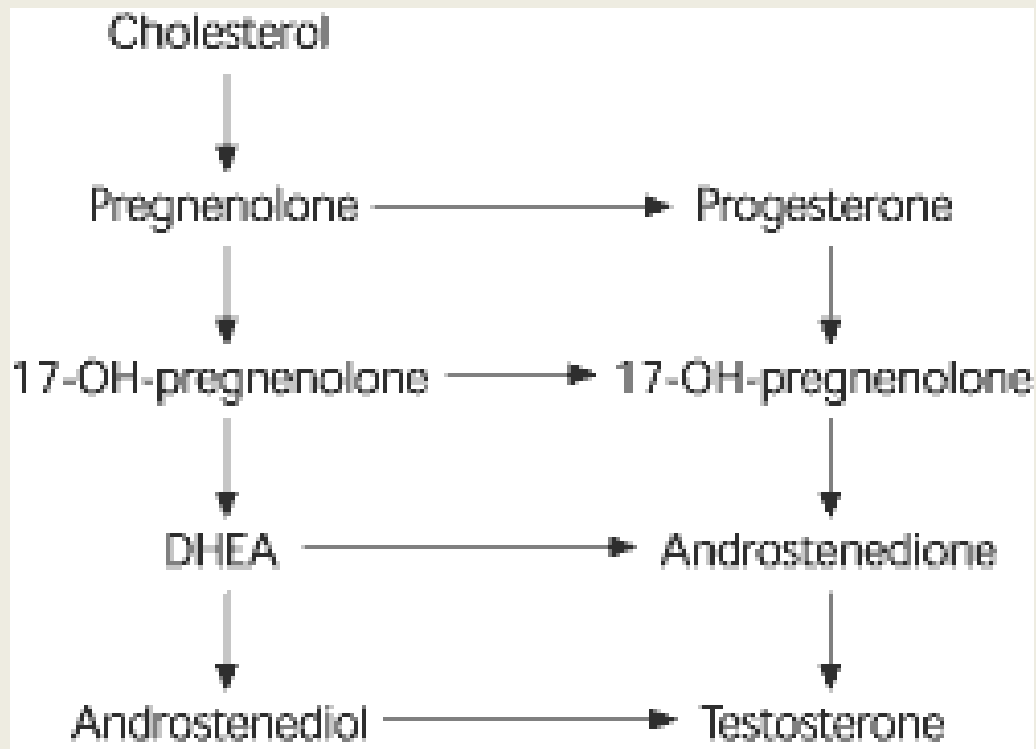
- >1 million Americans, >250,000 adolescents¹



National Institute on Drug Abuse
Research Report Series

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Basic Chemistry & Physiology of AAS



Estrogen

- Males

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

- Women

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

Mechanism of action of AAS

- ↑ skeletal muscle via
 - ↑ RNA → protein
- Anticatabolic
 - ↓ effect of glucocorticoids
 - ↑ 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)



MEXICAN ANABOLIC STEROIDS



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.**
-



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Patterns of AAS abuse

- Stacking

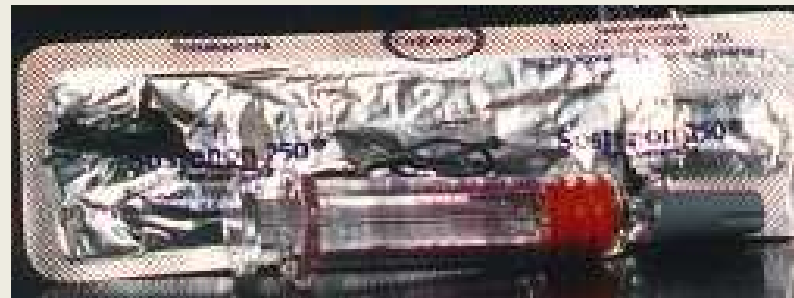
- Ave = ~5 AAS (oral & injectable)

- Cycling:

- 6 to 12 weeks → then stops for 10 to 12 weeks

- Pyramiding

- ↑ dose over 6-12 w



Sustanon 250 pre-stack blend of four testosterone

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Side effects of AAS

(Traditionally overstated?)



Breasts, Balding, Acne
Shrunken Testicles
Stunted Height
Hostility & Aggression
Body Image Disorder
Prostate, Liver & Kidney Cancer
Heart Disease, Risk of HIV

STERIODS
ANABOLIC - ANDROGENIC

An advertisement for anabolic-androgenic steroids (AAS). It features a muscular man in a green tank top lifting a large black weight. The text lists various side effects, with "Prostate, Liver & Kidney Cancer" and "Heart Disease, Risk of HIV" circled in orange. The word "STERIODS" is written in large red letters, and "ANABOLIC - ANDROGENIC" is in smaller black letters below it.

HEART DISEASE
KIDNEY CANCER
LIVER CANCER
DEPRESSION
HOSTILITY & AGGRESSION
EATING DISORDERS
STUNTED HEIGHT
BEARD
ACNE
RISK OF HIV

ANABOLIC - ANDROGENIC
STEROIDS

An advertisement for anabolic-androgenic steroids (AAS) targeting women. It features a muscular woman in a pink tank top. The text lists various side effects, with "KIDNEY CANCER" and "LIVER CANCER" circled in orange. The word "STEROIDS" is written in large white letters, with a female symbol (♀) integrated into the letter 'O'. "ANABOLIC - ANDROGENIC" is written in smaller white letters above it.

Azospemia → duration?

Increased premature Mortality of Competitive Powerlifters suspected to have used anabolic steroids

- Subjects
 - 62 powerlifters who placed 1st-5th in the Finnish championships during 1977-1982
 - 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:

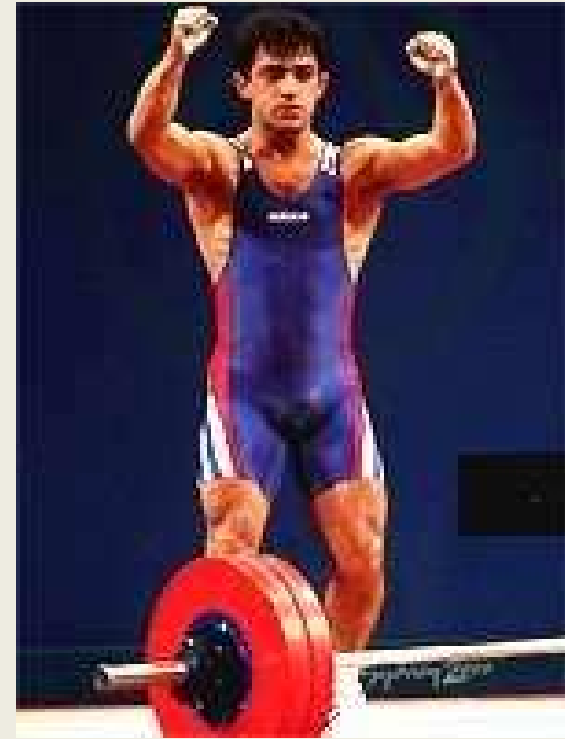
Taylor Edward Hooton

6/10/1986 – 7/15/2003

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

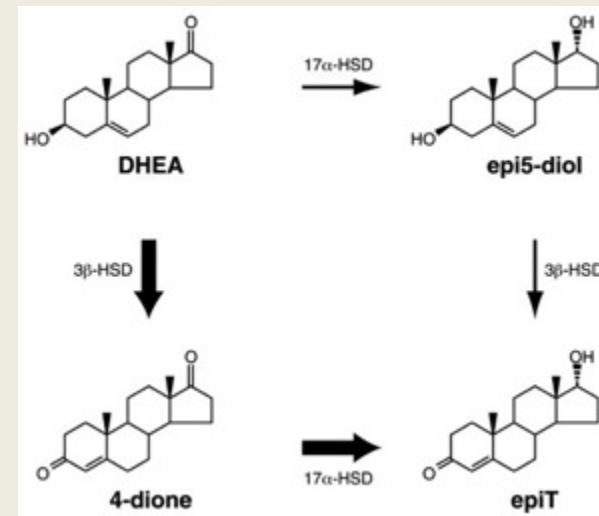
08/12/07



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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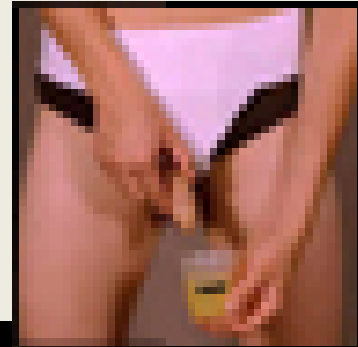
Detection of banned anabolic steroids

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.)



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ORIGINAL
THE
WHIZZINATOR



Purity?

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



NEW 100% Pure
HGH "liquid under the
tongue" formula.
Only \$89.50

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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

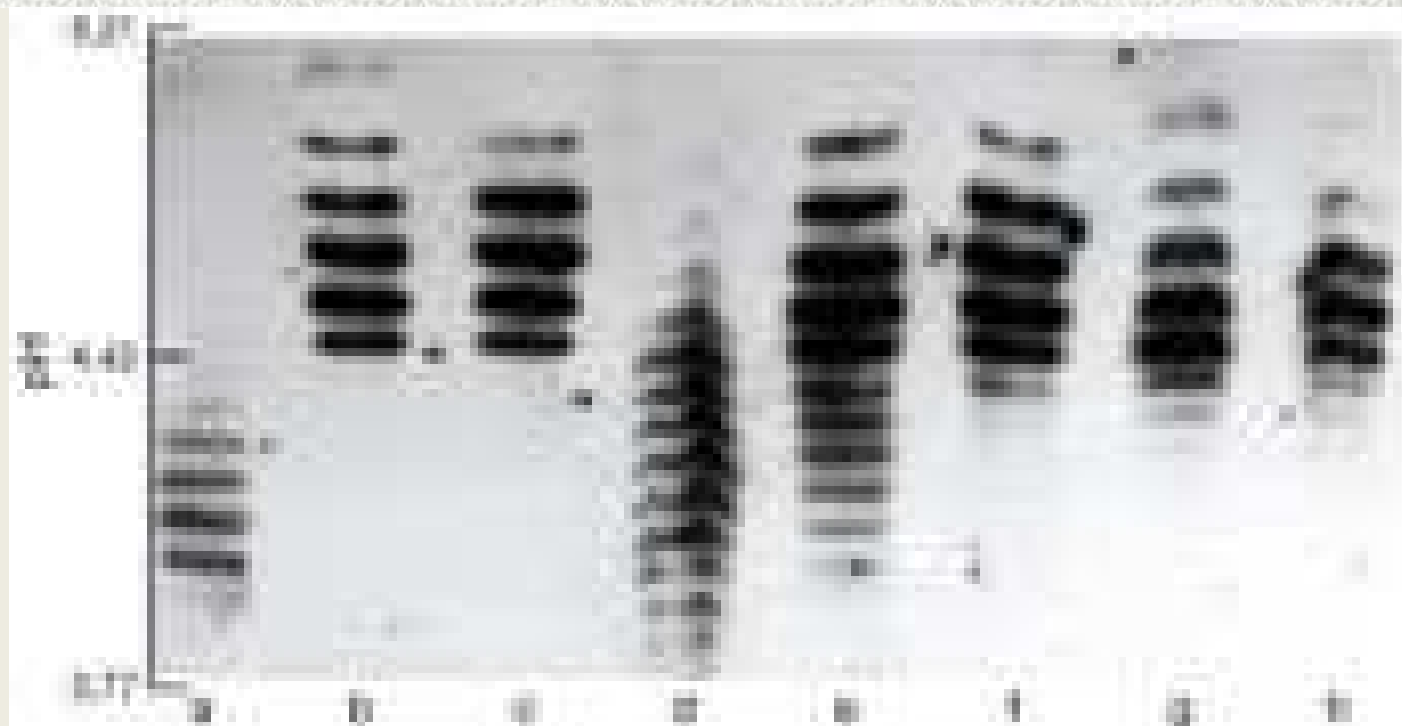


ANGUISHED CYCLIST: A member of the Banesto team tries to hide from the press after his group withdrew from the 1998 Tour de France amid a sprawling scandal linked to the drug erythropoietin.

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

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 & pulmonary edema: **Age 34?**



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Spinning in Their Graves

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

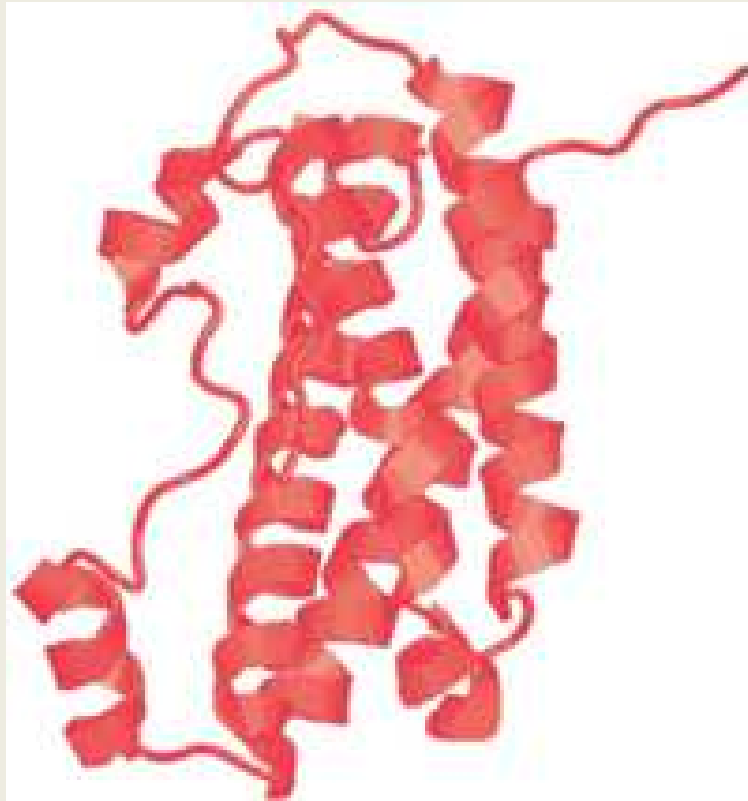


- ON FEBRUARY 13 2004, an amateur Belgian cyclist named Johan Sermon slipped into bed early, hoping to rest up for an eight-hour training ride the next morning.
- A 21-year-old with strong prospects for a professional career, Sermon had undergone a complete cardiac evaluation a few days earlier, and 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”

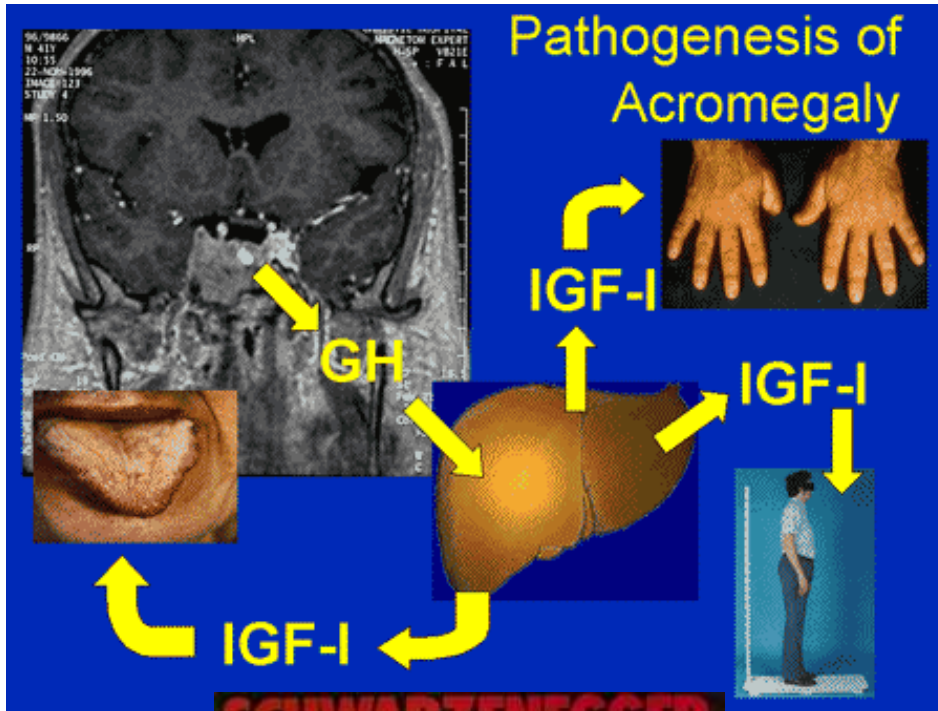


Human growth hormone (HGH), also known as somatotropin



- 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.

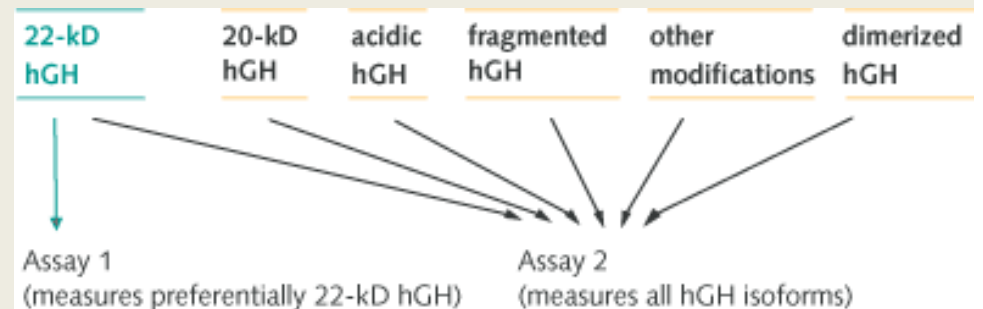
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- 1990
 - Claims for GH as an anti-aging treatment date back to 1990 NEJM study where GH was used to treat 12 men over 60.
 - + statistically significant increases in lean body mass, equivalent to 10 to 20 year aging period.
 - No claim that GH had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

- 1/2life of HGH = 15 min.
- Two techniques
 - Indirect Method:
 - Detect HGH-dependent variables
 - IGF-1
 - IGF binding protein 3
 - Bone turnover proteinds
 - » PIIP, Osteocalcin
 - Advantage detect up 84days after injection
 - Direct Method: Isoform detection
 - Disadvantage 1-2 days only
- No urine test!



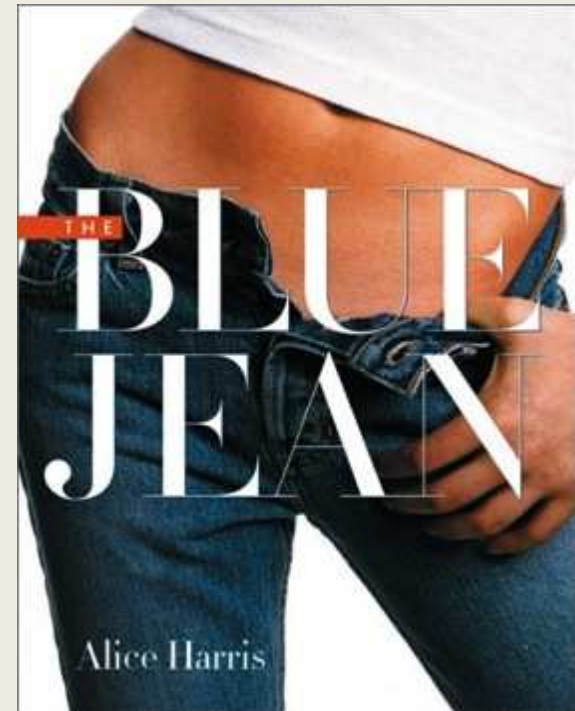
Terry Newton (7 November 1978 – c. 26 September 2010)



- 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.

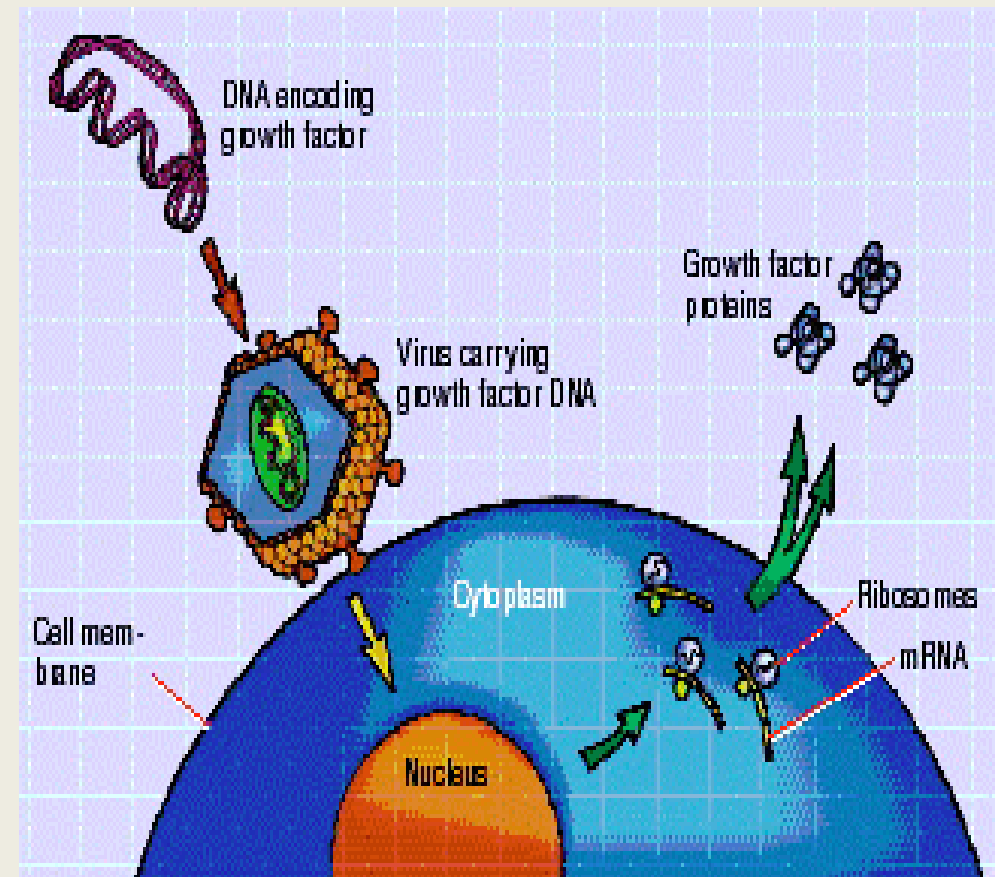
Gene Doping

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 the 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.



Mary Noyes artist

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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

- In December 2005 → World Anti-Doping Agency: Stockholm.
 - 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 **Reproxygen**



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)

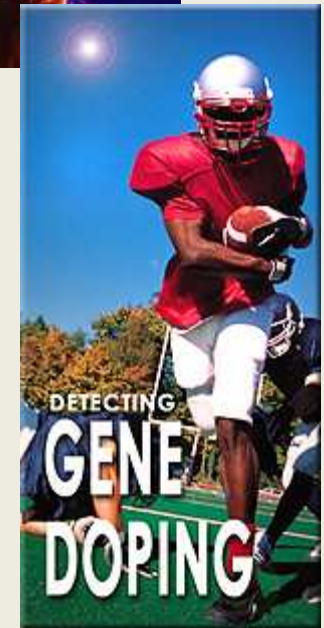
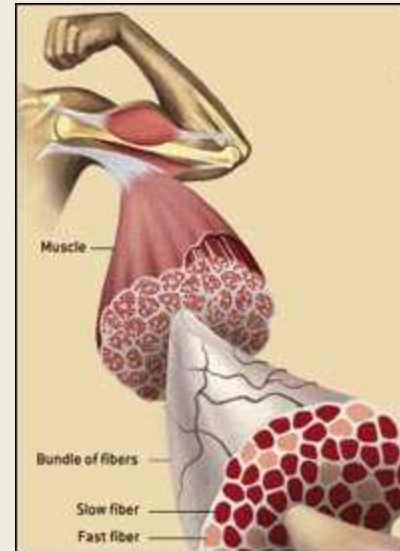


bioMed

Oxford Biomedica

Testing *Gene Doping?*

- Gene doping may be undetectable?



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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?

- sachar@ucsd.edu
- Want to help with research?



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