Performance-Enhancing Abuse of Hormones

Dept. of Internal Medicine, AUBMC
Endocrinology Unit
Prepared by: Zaher Ajam(PGY4)
Moderator: Professor Ibrahim Salti
Case Presentation

- A man aged 28 years had taken anabolic-androgenic steroids (mainly methandrostenolone and chlorodehydromethyltestosterone, as well as oxandrolone, Andriol, Proviron, Nolvadex, Sustanon, Decadurabolin, and Parabolan) for extensive bodybuilding since age 15 years.

- As a result, he had arterial hypertension (210/120 mm Hg), substantial obesity, mood disorders with depression, bone fractures, ruptures of various muscles, and secondary hypogonadism.

- Severe disturbances of lipid metabolism, such as decreased high-density lipoprotein cholesterol and raised low-density lipoprotein cholesterol concentrations were repeatedly diagnosed.
Case Presentation

- In 1992, 2 years before his death, echocardiography showed hypertrophy of the septum (18 mm) with a left-ventricular diameter of 60 mm.

- Blood tests showed raised cortisol and decreased testosterone concentrations.

- Symptoms before death included dyspnoea, peripheral oedema, and increases in bodyweight of 3 kg per day.

- Necropsy showed substantial obesity (bodyweight 136 kg, height 178 cm); the body-mass index was 42.9 kg/m² (normal 20–25 kg/m²).

- There was hypertrophy of nearly all inner organs except the brain: heart 800 g; liver 5710 g; kidney 910 g.

THE LANCET • Vol 352 • July 4, 1998
Case Presentation

- **Cardiac findings** included a so-called corbovinum with hypertrophy of the right-ventricular and left-ventricular walls and dilatation of all chambers.

- Histologically, there was disseminated interstitial and perivascular fibrosis in the coronary vessels, with some scarring.

- Extensive signs of **chronic heart insufficiency** were present.

- There was **massive atherosclerosis**.

- Doctors certified the **cause of death** as chronic heart failure due to cor bovinum after long-term abuse of anabolic steroids.
<table>
<thead>
<tr>
<th></th>
<th>Date of test</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Feb, 1992</td>
<td>May, 1994</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>9.7</td>
<td>10.8</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>11.0</td>
<td>10.3</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>7.80</td>
<td>5.75</td>
</tr>
<tr>
<td>β-lipoproteins (U)</td>
<td>680</td>
<td>578</td>
</tr>
<tr>
<td>Total lipids (mg/dL)</td>
<td>1350</td>
<td>1140</td>
</tr>
<tr>
<td>SGOT (U/L)</td>
<td>70</td>
<td>86</td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>98</td>
<td>93</td>
</tr>
<tr>
<td>Creatine kinase (U/L)</td>
<td>2627</td>
<td>3008</td>
</tr>
<tr>
<td>LDH (U/L)</td>
<td>375</td>
<td>513</td>
</tr>
<tr>
<td>Cortisol (μg/L)</td>
<td></td>
<td>736</td>
</tr>
<tr>
<td>Testosterone (μg/L)</td>
<td></td>
<td>3.4</td>
</tr>
</tbody>
</table>

LDL=low-density lipoprotein; HDL-high-density lipoprotein; SGOT=serum glutamine oxaloacetate transaminase; SGPT=serum glutamate pyruvate transaminase; LDH=lactate dehydrogenase.

Blood-test results, 1992–94
Outline

- Historical Overview
- Epidemiology
- Substances Prohibited in Sports
  - Anabolic-Androgenic Steroids
  - Prohormones
  - Growth Hormone
  - Erythropoietin
  - Insulin
  - hCG and Estrogen Blockers
- Prevention
Drug use by athletes to improve performance is not a new practice.

As early as BC 776, the Greek Olympians were reported to use substances such as dried figs, mushrooms, and strychnine to perform better.

However, medical advances now have produced substances that are much more effective toward this end.

A landmark discovery was made in 1889 when Dr Brown-Sequard announced at a scientific meeting in Paris that he had found a substance that reversed his 72-year-old body’s ailments.

He reported having injected himself with the extract of dog and guinea pig testicles under the assumption that these organs had “internal secretions that acted as physiologic regulators.”

*Pediatrics* 2006;117;e577-e589
Historical Overview

- This bold statement was confirmed with the discovery of hormones in 1905 and the isolation of testosterone in 1935.

- Soon thereafter in the 1950s, Russian weightlifters began to outpace American Olympians through performance-enhancing injections.

- In the decades that followed, steroids and stimulants spread throughout sports, and in 1959, the first reported case of a high school football player’s taking steroids surfaced.

- In the 1960s, the International Olympic Committee banned steroid use and began formal drug testing in the ensuing decade.

- During the 1980s, the reported positive test results ranged from 2% to 50%, depending on whether the tests were announced or conducted at random.

- At the 1988 Seoul Olympics, the first gold metal in track and field was stripped when the Canadian sprinter Ben Johnson lost his 100-m victory after failing drug tests.
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Century ago</td>
<td>Incas chewed coca (Erythroxylon spp) leaves to sustain strenuous work; Berserkers, Norse warriors, ate mushrooms containing muscarine before battle</td>
</tr>
<tr>
<td>Ancient Olympians</td>
<td>Bread soaked in opium, mushrooms, strychnine</td>
</tr>
<tr>
<td>Early 1900</td>
<td>Canal swimmers and cyclists taking central stimulants</td>
</tr>
<tr>
<td>World War II</td>
<td>Amphetamine to counter fatigue among soldiers and pilots</td>
</tr>
<tr>
<td>1950</td>
<td>Anabolic androgenic steroids introduced in doping; dianabol synthesis inspired by people in sports</td>
</tr>
<tr>
<td>1959</td>
<td>Classical controlled studies show that amphetamine improves performance in short distance swimming and running</td>
</tr>
<tr>
<td>1960 Olympics</td>
<td>First documented doping fatality—amphetamine induced heatstroke</td>
</tr>
<tr>
<td>1964</td>
<td>The International Olympic Committee (IOC) bans doping for Olympic athletes</td>
</tr>
<tr>
<td>1966–72</td>
<td>East Germany introduces a secret national system for hormone doping of both men and women with methandrostenolone and state manufactured oral-turinabol</td>
</tr>
<tr>
<td>1967</td>
<td>Doping death during Tour de France, IOC adopts a drug-testing policy</td>
</tr>
<tr>
<td>1970</td>
<td>Diuretics used to reach the “right” weight and to dilute urine before drug testing</td>
</tr>
<tr>
<td>1973</td>
<td>Olympic champion Connolly testifies on the common use of anabolic steroids among athletes to US Senate committee</td>
</tr>
<tr>
<td>1974</td>
<td>Anabolic androgenic steroids (AAS) put on the doping list</td>
</tr>
<tr>
<td>Up to 1980</td>
<td>Amphetamine, cocaine, caffeine, and strychnine dominate doping incidents</td>
</tr>
<tr>
<td>1980</td>
<td>AAS spread to many sports</td>
</tr>
<tr>
<td>1980</td>
<td>β-blockers used to improve shooting; misuse of growth hormone appears</td>
</tr>
<tr>
<td>1988</td>
<td>First Olympian gold medal in track and field stripped due to doping with AAS</td>
</tr>
<tr>
<td>2000</td>
<td>Tetrahydrogestrinone (THG or “the clear”), an AAS designed to escape detection in doping analyses, is developed</td>
</tr>
<tr>
<td>2007</td>
<td>Marion Jones admits having taken “the clear”, a performance-enhancing drug listed to the Bay Area Laboratory</td>
</tr>
</tbody>
</table>

Table 1: Historical overview of doping in society and sports

*Lancet* 2008; 371: 1872–82
**Epidemiology**

- Estimates of misuse have to be interpreted with great caution due to the difficulties of reliable studies of illicit drug use.

- In the USA, between 1 million and 3 million people are thought to have misused AAS; the estimate for Sweden is 50,000–100,000, among a population of 9 million.

- These estimates roughly equate to 1% of the respective populations.

*Lancet* 2008; 371: 1872–82
Epidemiology

- Interviews of high-school students in several European countries and the USA reveal that 1–5% have used AAS, but this measure is of doubtful relevance for the population at risk of serious side-effects, which develop during long-term use.

- An investigation of 6000 Swedish people age 16–17 years with an anonymous multiple-choice questionnaire revealed that 3·2% of males had used AAS, but none of the females had.

- Much higher estimates of misuse of AAS have been obtained in groups such as bodybuilders, weight-lifters, and prison populations.

- A German study assessed the use of AAS among visitors to fitness centres by use of anonymous questionnaires.

*Lancet* 2008; 371: 1872–82
Epidemiology

- Although only 34.5% of these were returned, 13.5% in this selected group reported that they had used AAS at some point.

- In this study, only 3.9% of women had used AAS, and studies in Great Britain and the USA have found similar levels of use among women.

*Lancet* 2008; 371: 1872–82
<table>
<thead>
<tr>
<th>Substance being misused (%)</th>
<th>Substance being discussed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAS</td>
<td></td>
</tr>
<tr>
<td>Testosterone</td>
<td>27%</td>
</tr>
<tr>
<td>Methandienone (“Russian”)</td>
<td>26%</td>
</tr>
<tr>
<td>Nandrolone</td>
<td>16%</td>
</tr>
<tr>
<td>Stanozolol</td>
<td>9%</td>
</tr>
<tr>
<td>Others</td>
<td>23%</td>
</tr>
<tr>
<td>Other hormones and related agents</td>
<td>(n=421)</td>
</tr>
<tr>
<td>hCG/tamoxifen</td>
<td>58%</td>
</tr>
<tr>
<td>GH/IGF₁/insulin</td>
<td>42%</td>
</tr>
<tr>
<td>Other substances</td>
<td>(n=1733)</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>23%</td>
</tr>
<tr>
<td>Clenbuterol</td>
<td>12%</td>
</tr>
<tr>
<td>GHB</td>
<td>6%</td>
</tr>
<tr>
<td>Narcotics unspecified</td>
<td>16%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1%</td>
</tr>
<tr>
<td>Creatine</td>
<td>11%</td>
</tr>
<tr>
<td>Dietary supplement</td>
<td>16%</td>
</tr>
<tr>
<td>Prescription drugs not specified here</td>
<td>15%</td>
</tr>
</tbody>
</table>

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

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

- The World Anti-Doping Agency (WADA) publishes a yearly list (panel 1) of substances and practices prohibited at all time in and out of competition.

- When prescribing listed drugs, physicians must be prepared to verify that the drug is medically justified and can be given a therapeutic-use exemption, a decision that requires assessment by the relevant sports organisation.

- There are different rationales for including a drug on the WADA list.

- The original idea was to list drugs known or suspected to improve performance in sports.

- After confrontation with the realities of doping, other reasons were accepted, such as the safety of the athletes, social unacceptability, and attempts to make doping analyses insensitive.

*Lancet* 2008; 371: 1872–82
Substances Prohibited in Sports

- Anti-oestrogens are on the list because they are sometimes used to antagonise the oestrogenic side-effects of AAS and other drugs.

- There is also a list of substances prohibited in competition (panel 2).

- Prohibited practices in sports include:
  - enhancement of oxygen transfer (eg, blood doping),
  - chemical and physical manipulation of samples collected during doping controls,
  - gene doping to administer erythropoietin or other genes that might affect athletic performance,
  - which is a possible future development.

*Lancet* 2008; 371: 1872–82
Panel 1: Substances and methods prohibited in sports at all times according to WADA, 2008

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

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

β2-agonists
- All β2-agonists including their D and L isomers
- Inhalation of β2-agonists requires a therapeutic-use exemption

Hormone antagonists and modulators
- Aromatase inhibitors (e.g., anastrozole, letrozole)
- Selective oestrogen-receptor modulators (e.g., tamoxifen)
- Other anti-oestrogenic substances (e.g., clomiphene)
- Agents modifying myostatin functions (e.g., myostatin inhibitors)

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

*Unless the athlete can prove that the concentration is due to a physiological or pathological disorder.
Panel 2: Substances prohibited in competition according to WADA, 2008

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

*Threshold value of 10 μg/mL.
<table>
<thead>
<tr>
<th>Ergogenic Drug</th>
<th>Category</th>
<th>Goals of Use</th>
<th>Athletic Effect</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anabolic-androgenic steroids</td>
<td>Controlled substance</td>
<td>Gain muscle mass, strength</td>
<td>Increase muscle mass, strength</td>
<td>Multiple organ systems: infertility, gynecomastia, female virilization, hypertension, atherosclerosis, phyleal closure, aggression, depression</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>Controlled substance</td>
<td>Increase testosterone to gain muscle mass, strength</td>
<td>No measurable effect</td>
<td>Increase estrogens in men; overlaps systemic risks with steroids</td>
</tr>
<tr>
<td>DHEA</td>
<td>Nutritional supplement</td>
<td>Increase testosterone to gain muscle mass, strength</td>
<td>No measurable effect</td>
<td>Increase estrogens in men; impurities in preparation</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Controlled substance</td>
<td>Increase muscle mass, strength, and definition</td>
<td>Decreases subcutaneous fat; no performance effect</td>
<td>Acromegaly effects: increased lipids, myopathy, glucose intolerance, phyleal closure</td>
</tr>
<tr>
<td>Creatine</td>
<td>Nutritional supplement</td>
<td>Gain muscle mass, strength</td>
<td>Increase muscle strength gains; performance benefit in short, anaerobic tasks</td>
<td>Dehydration, muscle cramps, gastrointestinal distress, compromised renal function</td>
</tr>
<tr>
<td>Ephedra alkaloids</td>
<td>Possibly returning as nutritional supplement</td>
<td>Increase weight loss, delay fatigue</td>
<td>Increases metabolism; no clear performance benefit</td>
<td>Cerebral vascular accident, arrhythmia, myocardial infarction, seizure, psychosis, hypertension, death</td>
</tr>
</tbody>
</table>
Anabolic-Androgenic Steroids

Kinds and Physiology

- Anabolic-androgenic steroids (AASs) are chemically modified analogues of testosterone.

- First isolated in 1935, AASs have been modified many times to maximize the anabolic effects of the drug and to minimize the androgenic effects by: alkylation of the 17a position or carboxylation of the 17b hydroxyl group on the sterol D ring.

- These analogues are degraded much more slowly than endogenous testosterone is, resulting in a higher prolonged concentration of the analogue.

*J Endocrinol Invest* 2005; 28:81-84
Anabolic-Androgenic Steroids

The AASs used for nontherapeutic purposes are:

1. endogenous androgens (e.g., androstenedione, DHEA);
2. 17β-esters of testosterone (e.g., cypionate, enanthate, heptylate, propionate, undecanoate, bucyclate);
3. 17α-alkyl derivatives of testosterone (e.g., methyltestosterone, fluoxymesterone, oxandrolone, stanozol);
4. 19-nortestosterone (nandrolone);
5. 17β-esters of 19-nortestosterone (e.g., decanoate, phenpropionate);
6. 19-norandrostenedione and 19-norandrostenediol; tetrahydrogestrinone.

More than 100 different AASs have been developed, with most of them being used illegally, synthesized in clandestine laboratories, commercialized without medical prescription or safety controls, and sometimes unknown to the scientific world.

J Endocrinol Invest 2005; 28:81-84
Anabolic-Androgenic Steroids

- Steroids bind to androgen receptors within the cell cytoplasm.

- They then are transported into the nucleus before binding DNA and increasing mRNA transcription, which enhances contractile and structural protein synthesis.

- Steroids have 3 general effects that benefit the athlete.
  - Binding androgen receptors promotes a positive nitrogen balance in muscle, which produces an anabolic state.

*Pediatrics* 2006;117;e577-e589
Anabolic-Androgenic Steroids

- It becomes critical that steroids are also anticatabolic.

- In the overtrained individual, glucocorticoids are increasingly released, which promote the breakdown of muscle glycogen for energy.

- Once available androgen receptors are saturated, exogenous steroids competitively inhibit the binding of catabolic glucocorticoids, thereby preserving muscle mass being gained.

- Anabolic steroids have significant emotional effects.

- This is often manifest in increased aggression, which can push athletes to train more intensely, more often, or longer.

*Pediatrics* 2006;117;e577-e589
Testosterone

Alkylated testosterones

Methyltestosterone

Fluoxymesterone

Oxandrolone

Testosterone esters

Enanthate

Cypionate

Propionate
<table>
<thead>
<tr>
<th>Oral Steroids</th>
<th>Injectable Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anadrol (oxymetholone)</td>
<td>Deca-durabolin (nandrolone decanoate)</td>
</tr>
<tr>
<td>Oxandrin (oxandrolone)</td>
<td>Durabolin (nandrolone phenpropionate)</td>
</tr>
<tr>
<td>Dianabol (methandrosteno)</td>
<td>Depo-testosterone (testosterone cypionate)</td>
</tr>
<tr>
<td>Winstrol (stanozolol)</td>
<td>Equipoise (boldenone undecylenate)</td>
</tr>
</tbody>
</table>

Adapted from the National Institute of Drug Abuse, National Institutes of Health, public domain.
Anabolic-Androgenic Steroids

Dosing

- Oral, injectable, and newer transdermal steroid preparations are available.

- Oral forms are short-acting and eliminated over days, whereas injectable steroids have longer lasting effects but risk positive drug testing up to months after use.

- Steroids are usually used in the off-season, when athletes are strength training and when use is least likely to be detected.

- Steroids are generally taken in 4- to 12-week cycles.

*Pediatrics* 2006;117;e577-e589
Anabolic-Androgenic Steroids

- Athletes often “stack” multiple steroids at the same time and “pyramid” the dosing schedule, taking highest amounts in the middle of cycles.

- Although attempting to maximize results, athletes may consume doses 50 to 100 times the amount that would replace physiologic steroid levels.

- Between dosing cycles, it is typical for users to have a period of abstinence, known as a “drug holiday,” of varying duration.

- The most recent so-called “designer steroids” are steroids that are made with simple chemical modifications to preserve anabolic activity while being undetected during drug testing.

*Pediatrics* 2006;117;e577-e589
Anabolic-Androgenic Steroids

Effects

- Although not every study agrees, the consensus today is that these drugs do increase athletic measures with objective gains in strength and fat-free mass.

- This fact was conceded in the 1980s by the American College of Sports Medicine.

- A recent double-blinded study over a 12-week training cycle confirmed significant gains over placebo in ultrasound-measured muscle pennation and overall strength on a bench press test.

- These drugs increase isokinetic and isometric strength, as well as muscle mass both via muscle hypertrophy and the formation of new muscle fibers.

- Supraphysiologic doses of testosterone, especially when combined with strength training, increase fat-free mass and muscle size and strength in normal men. (N Engl J Med 1996;335:1-7)

Pediatrics 2006;117;e577-e589
THE EFFECTS OF SUPRAHYPOPHYSIOLOGIC DOSES OF TESTOSTERONE ON MUSCLE SIZE AND STRENGTH IN NORMAL MEN

Methods  We randomly assigned 43 normal men to one of four groups: placebo with no exercise, testosterone with no exercise, placebo plus exercise, and testosterone plus exercise. The men received injections of 600 mg of testosterone enanthate or placebo weekly for 10 weeks. The men in the exercise groups performed standardized weight-lifting exercises three times weekly. Before and after the treatment period, fat-free mass was determined by underwater weighing, muscle size was measured by magnetic resonance imaging, and the strength of the arms and legs was assessed by bench-press and squatting exercises, respectively.
Results  Among the men in the no-exercise groups, those given testosterone had greater increases than those given placebo in muscle size in their arms (mean [±SE] change in triceps area, 424±104 vs. −81±109 mm²; P<0.05) and legs (change in quadriceps area, 607±123 vs. −131±111 mm²; P<0.05) and greater increases in strength in the bench-press (9±4 vs. −1±1 kg, P<0.05) and squatting exercises (16±4 vs. 3±1 kg, P<0.05). The men assigned to testosterone and exercise had greater increases in fat-free mass (6.1±0.6 kg) and muscle size (triceps area, 501±104 mm²; quadriceps area, 1174±91 mm²) than those assigned to either no-exercise group, and greater increases in muscle strength (bench-press strength, 22±2 kg; squatting-exercise capacity, 38±4 kg) than either no-exercise group. Neither mood nor behavior was altered in any group.
Table 1. Base-Line Characteristics of the Study Subjects.*

<table>
<thead>
<tr>
<th>GROUP</th>
<th>AGE (yr)</th>
<th>WEIGHT (kg)</th>
<th>HEIGHT (cm)</th>
<th>BODY-MASS INDEX†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>27±5</td>
<td>79.5±13.6</td>
<td>177.5±7.7</td>
<td>25.1±2.9</td>
</tr>
<tr>
<td>Testosterone</td>
<td>26±6</td>
<td>82.2±6.0</td>
<td>177.1±7.2</td>
<td>26.4±3.1</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>26±6</td>
<td>85.5±9.7</td>
<td>181.0±5.8</td>
<td>26.2±3.2</td>
</tr>
<tr>
<td>Testosterone</td>
<td>30±7</td>
<td>76.0±10.0</td>
<td>175.6±6.4</td>
<td>24.6±2.9</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD.

†Calculated as the weight in kilograms divided by the square of the height in meters.
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>NO EXERCISE</th>
<th>EXERCISE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLACEBO</td>
<td>TESTOSTERONE</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>14.9±0.2</td>
<td>15.1±0.2</td>
</tr>
<tr>
<td>10 wk</td>
<td>15.0±0.3</td>
<td>15.5±0.2</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>39±2</td>
<td>37±3</td>
</tr>
<tr>
<td>10 wk</td>
<td>36±3</td>
<td>34±3</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>113±10</td>
<td>133±7</td>
</tr>
<tr>
<td>10 wk</td>
<td>116±11</td>
<td>133±9</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>155±36</td>
<td>147±25</td>
</tr>
<tr>
<td>10 wk</td>
<td>139±27</td>
<td>111±13</td>
</tr>
</tbody>
</table>

*Plasma lipid concentrations were measured in 9 men assigned to placebo with no exercise, 8 men assigned to testosterone with no exercise, 8 men assigned to placebo plus exercise, and 10 men assigned to testosterone plus exercise. HDL denotes high-density lipoprotein, and LDL low-density lipoprotein. To convert values for hemoglobin to millimoles per liter, multiply by 0.62; to convert values for cholesterol to millimoles per liter, multiply by 0.02586; and to convert values for triglycerides to millimoles per liter, multiply by 0.0113. Plus–minus values are means ±SE.

†P = 0.04 for the comparison with the base-line value.
### Table 3. Serum Concentrations of Endocrine Hormones in the Study Subjects before and after the 10 Weeks of Treatment.*

<table>
<thead>
<tr>
<th>Hormone</th>
<th>No Exercise</th>
<th></th>
<th>Exercise</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Testosterone</td>
<td>Placebo</td>
<td>Testosterone</td>
</tr>
<tr>
<td>Total testosterone (ng/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>516±58</td>
<td>502±63</td>
<td>557±45</td>
<td>431±38</td>
</tr>
<tr>
<td>10 wk</td>
<td>453±35</td>
<td>2828±417‡‡</td>
<td>667±117</td>
<td>3244±305‡‡</td>
</tr>
<tr>
<td>Free testosterone (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>74±7</td>
<td>79±7</td>
<td>83±7</td>
<td>90±6</td>
</tr>
<tr>
<td>10 wk</td>
<td>74±13</td>
<td>497±62‡‡</td>
<td>81±9</td>
<td>572±53‡‡</td>
</tr>
<tr>
<td>Luteinizing hormone (mIU/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>3.3±0.4</td>
<td>3.8±0.6</td>
<td>4.0±0.7</td>
<td>3.3±0.5</td>
</tr>
<tr>
<td>10 wk</td>
<td>4.3±0.9</td>
<td>0.4±0.2‡‡</td>
<td>4.4±1.1</td>
<td>0.4±0.2‡‡</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (mIU/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>3.1±0.3</td>
<td>3.1±0.4</td>
<td>3.2±0.6</td>
<td>3.0±0.6</td>
</tr>
<tr>
<td>10 wk</td>
<td>2.7±0.3</td>
<td>0.3±0.2‡‡</td>
<td>4.4±1.1</td>
<td>0.10±0.03‡‡</td>
</tr>
<tr>
<td>Sex hormone–binding globulin (ng/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>224±33</td>
<td>256±34</td>
<td>353±41</td>
<td>271±43</td>
</tr>
<tr>
<td>10 wk</td>
<td>244±53</td>
<td>176±24‡§</td>
<td>320±31</td>
<td>201±34‡¶</td>
</tr>
</tbody>
</table>

*Values at 10 weeks were obtained 1 week after the final injection. To convert values for total testosterone to nanomoles per liter, multiply by 0.0347; to convert values for free testosterone to picomoles per liter, multiply by 3.47; to convert values for sex hormone–binding globulin to nanomoles per liter, multiply by 0.12. Plus–minus values are means ±SE.

†P<0.001 for the comparison with the corresponding base-line value.

‡‡P<0.05 for the comparison of the difference between this value and the base-line value with the corresponding difference in either placebo group.

§P=0.008 for the comparison with the corresponding base-line value.

¶P=0.05 for the comparison with the corresponding base-line value.
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>NO EXERCISE</th>
<th>EXERCISE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PLACEBO</td>
<td>TESTOSTERONE</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>79.5 ± 4.3</td>
<td>82.2 ± 1.9</td>
</tr>
<tr>
<td>10 wk</td>
<td>80.8 ± 4.4</td>
<td>85.7 ± 1.5</td>
</tr>
<tr>
<td>P value</td>
<td>—</td>
<td>0.004</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>65.1 ± 2.5</td>
<td>69.9 ± 1.3</td>
</tr>
<tr>
<td>10 wk</td>
<td>65.9 ± 2.7</td>
<td>73.1 ± 2.2</td>
</tr>
<tr>
<td>P value</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Triceps area (mm²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>3621 ± 213</td>
<td>3579 ± 260</td>
</tr>
<tr>
<td>10 wk</td>
<td>3539 ± 226</td>
<td>4003 ± 229§</td>
</tr>
<tr>
<td>P value</td>
<td>—</td>
<td>0.003</td>
</tr>
<tr>
<td>Quadriceps area (mm²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>8796 ± 561</td>
<td>9067 ± 398</td>
</tr>
<tr>
<td>10 wk</td>
<td>8665 ± 481</td>
<td>9674 ± 472§</td>
</tr>
<tr>
<td>P value</td>
<td>—</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bench-press exercise (kg lifted)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>88 ± 5</td>
<td>96 ± 8</td>
</tr>
<tr>
<td>10 wk</td>
<td>88 ± 5</td>
<td>105 ± 8§</td>
</tr>
<tr>
<td>P value</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Squatting exercise (kg lifted)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Base line</td>
<td>102 ± 6</td>
<td>103 ± 8</td>
</tr>
<tr>
<td>10 wk</td>
<td>105 ± 6</td>
<td>116 ± 5</td>
</tr>
<tr>
<td>P value</td>
<td>—</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*P values are shown for the comparison of the 10-week values with the base-line values when P≤0.05. Plus–minus values are means ± SE.

†P<0.05 for the comparison of the change from base line with that in either placebo group.

‡P<0.05 for the comparison of the change from base line with that in either no-exercise group.

§P<0.05 for the comparison of the change from base line with that in the group assigned to placebo with no exercise.

¶P<0.05 for the comparison of the change from base line with that in the other three groups.
Figure 1. Changes from Base Line in Mean (± SE) Fat-free Mass, Triceps and Quadriiceps Cross-Sectional Areas, and Muscle Strength in the Bench-Press and Squatting Exercises over the 10 Weeks of Treatment.

The P values shown are for the comparison between the change indicated and a change of zero. The asterisks indicate P<0.05 for the comparison between the change indicated and that in either no-exercise group; the daggers, P<0.05 for the comparison between the change indicated and that in the group assigned to placebo with no exercise; and the double daggers, P<0.05 for the comparison between the change indicated and the changes in all three other groups.
Anabolic-Androgenic Steroids

AAS and Chronic Diseases

- Androgenic anabolic steroids (AAS) are widely prescribed for the treatment of male hypogonadism.

- They may play a significant role in the treatment of other conditions as well, such as cachexia associated with HIV, cancer, burns, renal and hepatic failure, and anemia associated with leukemia or kidney failure.

- Although the threat of various side effects is present, AAS therapy appears to have a favorable anabolic effect on patients with chronic diseases and muscle catabolism.

- Studies suggest that Testosterone and its analogs, regardless of the route of administration, result in an increase in weight and LBM in AIDS patients.

*J Clin Endocrinol Metab 86: 5108–5117, 2001*
Anabolic-Androgenic Steroids

- In a 4-month randomized, placebo-controlled study of oxandrolone (15 mg/d) in 63 AIDS patients with more than 10% body weight loss, oxandrolone resulted in significant weight gain, increase in appetite, and improvement in physical activity.

- At wk 16, patients taking oxandrolone had an increase of 0.6 kg in mean body weight, whereas the placebo patients lost 1.1 kg.

- Further studies would be welcomed to determine the exact nature of the relationship between factors such as dosage, route, and preparation used and the resultant changes in body composition in HIV patients, including women.

*J Clin Endocrinol Metab* 86: 5108–5117, 2001
Recent studies indicate a potential use for AAS therapy in COPD-associated wasting.

A regimen of exercise, 250 mg im T administration at the baseline visit, and then 12 mg/d oral stanozolol for 27 wk showed significant improvement in weight, body mass index, LBM, and muscle size compared with exercise alone in patients with COPD.

However, there was no increase in maximum inspiratory pressure or measures of physical endurance.

Caution is recommended when treating COPD patients with androgens due to the risk of developing polycythemia.

J Clin Endocrinol Metab 86: 5108–5117, 2001
Anabolic-Androgenic Steroids

- AAS also have a role in treating patients with hepatitis-related malnutrition.

- In a study of 271 patients with alcoholic hepatitis, oxandrolone along with a high calorie supplement was compared with placebo and a low calorie supplement.

- Significant improvement in liver function and overall survival was observed in the oxandrolone and high calorie supplement group.

- Although the preliminary studies hold promise, the use of AAS in these patients is not considered a standard of care and may be potentially dangerous.

J Clin Endocrinol Metab 86: 5108–5117, 2001
Anabolic-Androgenic Steroids

- The anabolic effects of T may also have a place in the process of wound healing and surgical recovery.

- The 17-alkylated agent stanozolol has been shown in vitro to significantly enhance collagen synthesis when applied to human dermal fibroblasts.

- Amory et al. have recently shown that the positive effects of AAS on muscle strength lead to early mobilization and, hence, alleviates the postoperative debilitation associated with knee replacement surgery.

- Until more research is available AAS should not be used on a routine basis to expedite the process of wound healing.

- There is a significant decrease in T levels in patients with severe burn injuries.

J Clin Endocrinol Metab 86: 5108–5117, 2001
Anabolic-Androgenic Steroids

- As these patients are catabolic, the anabolic effects of AAS may play an important role in weight gain in these patients.

- Oxandrolone (20 mg/d) administered during the immediate postburn period to patients with burns covering 40–70% of their body surface area produced a decrease in net weight loss, an increase in nitrogen retention, and a decrease in healing time compared with placebo.

- Physicians recommend judicious use of AAS in patients who have major burn injuries and are severely catabolic.

*J Clin Endocrinol Metab* 86: 5108–5117, 2001
Anabolic-Androgenic Steroids

- The cachexic/anorexic effects of cancer lead to malnutrition and contribute to androgen deficiency.

- AAS may have a role to play in the treatment of cancer cachexia.

- Only a few controlled trials have been performed to ascertain whether this represents an influence of hormones on nutritional intake or vice versa.

- Preclinical trials with nandrolone decanoate in rats did not support the former hypothesis.

*J Clin Endocrinol Metab 86: 5108–5117, 2001*
Anabolic-Androgenic Steroids

- Clinical studies show that the treatment with stanozolol during the induction phase of chemotherapy results in a positive effect on the duration of remission.

- Malnutrition and sarcopenia are commonly seen in patients with end-stage renal disease receiving dialysis.

- In addition to the increase in LBM, patients with chronic renal failure benefit from the stimulation of erythropoiesis resulting from the administration of AAS.

*J Clin Endocrinol Metab* 86: 5108–5117, 2001
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Generic name</th>
<th>Trade name</th>
<th>Route</th>
<th>Indications</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>T propionate</td>
<td>Testex</td>
<td>im</td>
<td>T replacement</td>
<td>10–25 mg 2–3 ×/wk</td>
</tr>
<tr>
<td></td>
<td>T enanthate</td>
<td>Delatestryl, Everone, Durathate</td>
<td>im</td>
<td>T replacement</td>
<td>50–400 mg every 2–4 wk</td>
</tr>
<tr>
<td></td>
<td>T cypionate</td>
<td>Virilon im, Depotest, Andro-Cyp</td>
<td>im</td>
<td>T replacement</td>
<td>50–400 mg q 2–4 wk</td>
</tr>
<tr>
<td></td>
<td>T patches</td>
<td>Androderm, Testoderm TTS</td>
<td>Top</td>
<td>T replacement</td>
<td>5 mg/day</td>
</tr>
<tr>
<td></td>
<td>T Gel</td>
<td>Androgel</td>
<td>Top</td>
<td>T replacement</td>
<td>5 g/day</td>
</tr>
<tr>
<td>AC</td>
<td>Nandrolone decanoate</td>
<td>Deca-Durabolin</td>
<td>im</td>
<td>Renal insufficiency-associated anemia</td>
<td>50–200 mg/wk</td>
</tr>
<tr>
<td></td>
<td>Nandrolone, phenpropionate</td>
<td>Durabolin</td>
<td>im</td>
<td>Renal insufficiency-associated anemia</td>
<td>50–200 mg/wk</td>
</tr>
<tr>
<td>B</td>
<td>Methyltestosterone</td>
<td>Testred, Android, Virilon</td>
<td>PO</td>
<td>T replacement; endometriosis</td>
<td>10–50 mg/d 800 mg/d initially</td>
</tr>
<tr>
<td>BC</td>
<td>Danazol</td>
<td>Danocrine</td>
<td>PO</td>
<td>HAE</td>
<td>400–600 mg/d initially</td>
</tr>
<tr>
<td></td>
<td>Fluoxymesterone</td>
<td>Halotestin</td>
<td>PO</td>
<td>T replacement</td>
<td>5–20 mg/d</td>
</tr>
<tr>
<td></td>
<td>Methandrostenolone</td>
<td>Methandienone</td>
<td>PO</td>
<td>Wt loss</td>
<td>5–10 mg/d</td>
</tr>
<tr>
<td></td>
<td>Oxandrolone</td>
<td>Anavar, Oxandrin</td>
<td>PO</td>
<td>Anemia</td>
<td>1–5 mg/kg·d</td>
</tr>
<tr>
<td></td>
<td>Oxymetholone</td>
<td>Anadrol</td>
<td>PO</td>
<td>HAE attack prevention</td>
<td>6 mg/d</td>
</tr>
<tr>
<td></td>
<td>Stanozolol</td>
<td>Winstrol</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HAE, Hereditary angioedema; PO, taken orally.
### TABLE 2. Efficacy of AAS therapy in chronic diseases associated with catabolic states

<table>
<thead>
<tr>
<th>Condition</th>
<th>Wt gain efficacy</th>
<th>Disease-specific efficacy</th>
<th>Safety comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Yes</td>
<td>Conflicting&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Liver failure</td>
<td>Yes</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Hepatic dysfunction associated with 17α-alkylated analogs</td>
</tr>
<tr>
<td>Postoperative recovery</td>
<td>Yes</td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Burns</td>
<td>Yes</td>
<td>Yes&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>Not studied&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Yes&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>Yes</td>
<td>Yes&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Sodium retention may exacerbate edema</td>
</tr>
</tbody>
</table>

<sup>a</sup> Studies examining AAS effects on maximal inspiratory pressure (Pmax) have yielded conflicting results.

<sup>b</sup> Oxandrolone treatment in alcoholic hepatitis has yielded significant improvement in liver function.

<sup>c</sup> AAS has beneficial effects in preliminary studies.

<sup>d</sup> The efficacy of AAS therapy for weight gain in cancer patients has not yet been examined in a clinical trial.

<sup>e</sup> AAS therapy has been shown to have positive effects on remission rates in leukemia patients.

<sup>f</sup> In addition to increasing lean body mass in dialysis patients, AAS also improves erythropoietin synthesis.
Anabolic-Androgenic Steroids

Anabolic Steroids and Osteoporosis

- Androgen inhibits osteoclastic bone resorption with increase of bone formation thru the androgen receptor in bone tissue.

- Some of the anabolic steroids have been approved for treating osteoporosis.

- They have revealed the increased bone mineral content or BMD at the radius, and the lumbar spine in osteoporosis patients.

- They also lessened bone pain in osteoporosis patients having bone fracture.

- Recently, few clinical trials about the effect of anabolic steroids on osteoporosis have been reported, and prospective study for bone fracture using anabolic steroids has not been reported yet.

Clin Calcium 2008;18(10):1451-9
Anabolic-Androgenic Steroids

Side Effects

Suppression of endogenous testicular function:
- All androgens suppress gonadotropin secretion and therefore suppress endogenous testicular function.
- Spermatogenesis and fertility are greatly diminished by high doses of androgens, although the sperm count usually returns to normal within four months after discontinuation.
- Testicular size may decrease if androgen administration continues for many years.
- Gonadotropin and testosterone secretion remain suppressed for a few months after androgens are discontinued.

Gynecomastia:
- Gynecomastia occurs because testosterone is converted to estradiol via the action of the aromatase enzyme complex, so that high doses of testosterone result in high serum estradiol concentrations.
- Androgens that have been 5 alpha-reduced, such as dihydrotestosterone and synthetic androgens in which the A ring has been modified, cannot be aromatized and therefore cannot be converted to estrogens and do not cause gynecomastia.

Erythrocytosis:
- Erythrocytosis is a common side effect of pharmacologic doses of all androgens, probably due largely to direct androgen stimulation of erythropoiesis.

Anabolic-Androgenic Steroids

Hepatotoxicity:
- Hepatic side effects occur only with oral 17-alpha-alkylated androgens and include high serum concentrations of liver enzymes, cholestatic jaundice, and peliosis hepatitis, characterized by blood-filled hepatic cyst.
- Hepatomas have also been reported, but the number of cases is few and causality is uncertain.

Serum lipids:
- Physiologic doses of testosterone have no consistent effects upon serum lipid concentrations.
- Pharmacologic doses of androgens, especially 17-alpha-alkylated androgens, decrease serum high-density-lipoprotein (HDL) cholesterol and increase low-density-lipoprotein (LDL) cholesterol concentrations.

JAMA 1989 Feb 24;261(8):1165-8
Anabolic-Androgenic Steroids

**Coagulation activation:**
- Androgen administration is associated with activation of the hemostatic system.

**Virilization:**
- Because men are maximally virilized by physiologic amounts of testosterone, only women athletes are virilized by taking androgens.
- Specifically, they have facial and body hirsutism, temporal hair recession in a male pattern, acne, and clitoral enlargement.

Anabolic-Androgenic Steroids

**Premature epiphyseal fusion and stunting of growth:**
- Pharmacologic doses of testosterone or other androgens that can be aromatized to estrogens hasten epiphyseal closure if taken by adolescents whose epiphyses have not yet closed naturally.

**Infections:**
- Sporadic case reports describe infections due to injection of androgens, including local abscess at the site of injection, septic arthritis, hepatitis B and C, and HIV infection from sharing of needles.

*J Community Health* 1999 Apr;24 (2):131-45

*Drug Alcohol Depend.* 2002 Feb 1;65(3):303-8
Anabolic-Androgenic Steroids

Cardiac Disease:

- The effect of high doses of androgens on cardiac function is uncertain.

- Several case reports describe sudden death in young athletes who had no previously known heart disease but who were taking androgens; cardiac hypertrophy or myocarditis were found at autopsy.

- There are also reports of left ventricular hypertrophy in body builders and power lifters, but most of these studies have not been randomized or controlled for degree of exercise, which itself can affect the degree of cardiac hypertrophy.

*Int J Legal Med* 1998;111(5): 261-4
Anabolic-Androgenic Steroids

- Whether of local or systemic origin, endogenous steroid hormones appear to drive LV growth.

- Systemic glucocorticoid excess is associated with significant hypertrophy.

- This action is more likely to be direct, rather than mediated through an elevated pressor burden, with aldosterone having similar effects.

- Local myocardial renin-angiotensin systems (RAS) play a role in regulating LV growth, and at least part of the hypertrophic responses to steroid hormones may be mediated through upregulation of local RAS expression.

*Heart* 2004;90:473–475
Anabolic-Androgenic Steroids

- Anabolic/androgenic steroids (AAS—primarily comprising testosterone and its synthetic derivatives) are likely to share such influences on the LV hypertrophic response through actions on the androgen receptor (AR), a transcriptional regulator.

- ARs are almost ubiquitously expressed, being found not only in skeletal muscle cells, but also on cardiac myocytes.

- Several lines of evidence also implicate endogenous androgenic pathways in the development of cardiac hypertrophy, including the demonstration of raised 5a reductase, aromatase, and AR expression in hypertrophic hearts of both humans and mice.

*Heart* 2004;90:473–475
Panel 3: Physical signs in patients using megadoses of AAS

Vital signs
Increased blood pressure (relatively uncommon)

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

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

Chest
Gynaecomastia with tenderness in men

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

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

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

Extremities
Oedema due to water retention for which diuretics may be used
Neuroendocrine and behavioral effects of high-dose anabolic steroid administration in male normal volunteers

R.C. Daly *, T.-P. Su, P.J. Schmidt, M. Pagliaro, D. Pickar, D.R. Rubinow

Behavioural Endocrinology Branch, National Institute of Mental Health, Building 10, Room 3N238, 10 Center Drive MSC 1277, 20892-1277 Bethesda, MD, USA
Objective: Despite widespread abuse of anabolic-androgenic steroids (AAS), the endocrine effects of supraphysiologic doses of these compounds remain unclear. We administered the AAS methyltestosterone (MT) to 20 normal volunteers in an in-patient setting, examined its effects on levels of pituitary-gonadal, -thyroid, and -adrenal hormones, and examined potential relationships between endocrine changes and MT-induced psychological symptoms.
Subjects received MT (three days of 40 mg/day, then three days of 240 mg/day) or placebo in a fixed sequence with neither subjects nor raters aware of order. Samples were obtained at the ends of the baseline, high-dose MT and withdrawal phases. Potential relationships between hormonal changes and visual analog scale measured mood changes were examined.
 Significant decreases in plasma levels of gonadotropins, gonadal steroids, sex hormone binding globulin, free T3 and T4, and thyroid binding globulin (Bonferroni \( t, p < 0.01 \) for each) were seen during high-dose MT; free thyroxine and TSH increased during high-dose MT, with TSH increases reaching significance during withdrawal. No significant changes in pituitary-adrenal hormones were observed. Changes in free thyroxine significantly correlated with changes in aggressiveness (anger, violent feelings, irritability) \( (r = 0.5, p = 0.02) \) and changes in total testosterone correlated significantly with changes in cognitive cluster symptoms (forgetfulness, distractibility) \( (r = 0.52, p = 0.02) \). Hormonal changes did not correlate with plasma MT.
Table 1
Effect of MT on behavioral symptom and symptom cluster scores ($n = 20$) between baseline and high-dose phases

<table>
<thead>
<tr>
<th>Behavioral symptoms* and symptom clusters</th>
<th>Baseline rating</th>
<th>High dose rating</th>
<th>$t$, $p^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td><strong>Cognitive symptom cluster</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>4.6 (4.7)</td>
<td>9.3 (8.8)</td>
<td>$t = 2.3$, $p = 0.03$</td>
</tr>
<tr>
<td>Distractibility</td>
<td>3.8 (4.6)</td>
<td>7.2 (9.8)</td>
<td>$t = 1.56$, $p = 0.13$</td>
</tr>
<tr>
<td><strong>Activation symptom cluster</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy</td>
<td>24.8 (20.7)</td>
<td>31.5 (16.9)</td>
<td>$t = 4.2$, $p = 0.001$</td>
</tr>
<tr>
<td>Sexual arousal</td>
<td>37.5 (30.8)</td>
<td>42.0 (28.5)</td>
<td>$t = 2.24$, $p = 0.04$</td>
</tr>
<tr>
<td>Disturbed sleep</td>
<td>27.3 (29.8)</td>
<td>35.3 (31.1)</td>
<td>$t = 4.09$, $p = 0.001$</td>
</tr>
<tr>
<td><strong>Aggressiveness symptom cluster</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger</td>
<td>9.5 (11.4)</td>
<td>17.2 (16.8)</td>
<td>$t = 1.83$, $p = 0.08$</td>
</tr>
<tr>
<td>Violent feelings</td>
<td>14.6 (9.9)</td>
<td>18.5 (12.3)</td>
<td>$t = 2.8$, $p = 0.01$</td>
</tr>
<tr>
<td>Irritability</td>
<td>5.4 (8.9)</td>
<td>7.4 (11.6)</td>
<td>$t = 1.93$, $p = 0.07$</td>
</tr>
<tr>
<td></td>
<td>23.9 (18.4)</td>
<td>27.1 (20.3)</td>
<td>$t = 2.00$, $p = 0.06$</td>
</tr>
<tr>
<td></td>
<td>14.6 (12.5)</td>
<td>20.9 (19.8)</td>
<td>$t = 2.25$, $p = 0.04$</td>
</tr>
</tbody>
</table>

* Measured by visual analogue scale ratings.

$^b$ Paired $t$-test, df = 19.
<table>
<thead>
<tr>
<th>Hormones</th>
<th>B (Mean±SD)</th>
<th>HD (Mean±SD)</th>
<th>W (Mean±SD)</th>
<th>F</th>
<th>p</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gonadal axis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total testosterone (ng/dl)</td>
<td>748.8 (246.0)</td>
<td>290.4 (251.7)**</td>
<td>398.5 (181.4)**</td>
<td>50.4</td>
<td>0.001</td>
<td>2.38</td>
</tr>
<tr>
<td>Free testosterone (pg/ml)</td>
<td>203.6 (57.3)</td>
<td>98.0 (87.8)**</td>
<td>132.2 (52.7)**</td>
<td>23.8</td>
<td>0.001</td>
<td>2.38</td>
</tr>
<tr>
<td>DHT (ng/dl)</td>
<td>139.2 (72.6)</td>
<td>54.5 (33.0)**</td>
<td>71.5 (35.0)**</td>
<td>24.6</td>
<td>0.001</td>
<td>2.38</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>41.8 (15.1)</td>
<td>25.8 (14.4)**</td>
<td>30.3 (16.3)**</td>
<td>10.5</td>
<td>0.001</td>
<td>2.38</td>
</tr>
<tr>
<td>SHBG (nmol/l)</td>
<td>30.6 (9.6)</td>
<td>17.2 (6.4)**</td>
<td>16.8 (6.8)**</td>
<td>53.7</td>
<td>0.001</td>
<td>2.38</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>8.8 (1.1)</td>
<td>7.3 (0.7)**</td>
<td>8.7 (2.0)</td>
<td>9.7</td>
<td>0.001</td>
<td>2.38</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>8.4 (1.9)</td>
<td>5.4 (1.6)**</td>
<td>9.2 (2.5)</td>
<td>27.6</td>
<td>0.001</td>
<td>2.38</td>
</tr>
<tr>
<td><strong>Thyroid axis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triiodothyroxine (ng/dl)</td>
<td>131.6 (17.9)</td>
<td>96.0 (9.6)**</td>
<td>107.4 (11.3)**</td>
<td>83.6</td>
<td>0.001</td>
<td>2.38</td>
</tr>
<tr>
<td>T4 (ug/dl)</td>
<td>6.5 (0.8)</td>
<td>5.8 (1.0)**</td>
<td>6.0 (1.0)*</td>
<td>7.6</td>
<td>0.005</td>
<td>2.38</td>
</tr>
<tr>
<td>TBG (ug/ml)</td>
<td>18.2 (2.9)</td>
<td>13.2 (3.5)**</td>
<td>14.2 (3.2)**</td>
<td>48.0</td>
<td>0.001</td>
<td>2.38</td>
</tr>
<tr>
<td>TSH (uIU/ml)</td>
<td>1.9 (1.0)</td>
<td>2.3 (1.4)*</td>
<td>3.2 (2.0)**</td>
<td>18.6</td>
<td>0.001</td>
<td>2.38</td>
</tr>
<tr>
<td>FT4 (ng/dl)</td>
<td>1.2 (0.2)</td>
<td>1.4 (0.2)**</td>
<td>1.3 (0.2)*</td>
<td>8.1</td>
<td>0.005</td>
<td>2.38</td>
</tr>
</tbody>
</table>

B, baseline; HD, high-dose; W, withdrawal; ANOVA-R, analysis of variance with repeated measures. All Bonferroni t-test p-values represent comparisons with baseline (***p < 0.01, *p < 0.05).
Table 4
Effects of MT on pituitary-adrenal hormones

<table>
<thead>
<tr>
<th>Hormones</th>
<th>B (Mean±SD)</th>
<th>HD (Mean±SD)</th>
<th>W (Mean±SD)</th>
<th>ANOVA-R</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F</td>
</tr>
<tr>
<td><strong>Plasma (n = 20)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>41.9 (21.6)</td>
<td>37.7 (14.9)</td>
<td>59.2 (51.9)*</td>
<td>3.7</td>
</tr>
<tr>
<td>DHEA (ng/dl)</td>
<td>1167 (525)</td>
<td>962 (420)</td>
<td>999 (434)</td>
<td>2.4</td>
</tr>
<tr>
<td>Cortisol (ug/dl)</td>
<td>18.6 (4.8)</td>
<td>17.1 (3.7)</td>
<td>18.8 (4.7)</td>
<td>NS</td>
</tr>
<tr>
<td>β-Endorphin (pg/ml)</td>
<td>30.1 (7.7)</td>
<td>31.8 (8.7)</td>
<td>32.9 (15.3)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Urine (n = 19)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h Cortisol (ug/dl)</td>
<td>78.11 (30.2)</td>
<td>74.3 (35.7)</td>
<td>83.9 (37.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS, non-significant for all three treatment conditions. Bonferroni *t*-test *p*-values represent comparisons with baseline (*p < 0.1).
Comments

- High-dose AAS administration acutely and profoundly affects hormonal balance in the pituitary-gonadal and -thyroid axes, with little impact on the HPA axis.

- When the relationships between changes in hormonal and adverse psychological measures were examined, changes in testosterone and FT4 were associated with the emergence of cognitive, aggressiveness and activation symptoms.
Anabolic-Androgenic Steroids

Detection of Use
- All known AASs can be detected via urinalysis (gas chromatography–mass spectrometry) for a period of time following the last dose.

- The detection of these drugs depends on several factors, including their chemical structures, metabolism, the form in which they were administered, pattern of dosing, and concomitant use of other drugs.

- The assessment of illegal testosterone use is based on the urinary ratio of testosterone to epitestosterone, with a ratio of six being the upper legal cutoff limit.

Clin Chem 1997; 43:1280-1288
Anabolic-Androgenic Steroids

- Because testosterone is not readily converted to epitestosterone, exogenous use of testosterone will increase this ratio.

- Some athletes inject epitestosterone before drug testing in an effort to mask exogenous testosterone use.

- To counteract this strategy, urine epitestosterone concentrations above 200 ng/mL are considered proof of epitestosterone manipulation.

- Short-lasting forms of testosterone can raise serum testosterone for only a few hours, after which the testosterone-to-epitestosterone ratio may return rapidly to baseline.

- Detection of testosterone use represents a significant challenge for doping control laboratories.
Anabolic-Androgenic Steroids

A Gateway to Opioid Dependence?

- Athletes who abuse anabolic–androgenic steroids may go on to abuse opioid agonist–antagonists such as nalbuphine or even classic opioids such as heroin.

- Among 227 men admitted for dependence on heroin or other opioids in 1999, they found that 21 (9.3 percent) had a history of anabolic–androgenic steroid use.

NEJM 2000;342:1532
Anabolic-Androgenic Steroids

- In contrast, among 197 men admitted for opioid dependence in 1990, only 1 (0.5 percent) reported prior use of anabolic–androgenic steroids (P<0.001 by two-tailed Fisher's exact test).

- These findings suggest an alarming trend: that anabolic–androgenic steroids may serve as "gateway" drugs to opioid dependence, with substantial associated morbidity and even mortality.

- Progression from anabolic–androgenic steroid use to opioid dependence deserves further exploration as a public health problem.

*NEJM 2000;342:1532*
Prohormones

Physiology

- Androstenedione and closely related dehydroepiandrosterone (DHEA) are 2 popular steroid precursors, or prohormones.

- DHEA is a weak androgen that is produced in the adrenal cortex, whereas androstenedione, a more potent anabolic-androgenic steroid, is made in the adrenal glands and gonads.

- DHEA is converted in the body to androstenedione, which then can be transformed into either testosterone or estrone.

- Athletes use these substances with the belief that they will boost testosterone levels, thereby having ergogenic effects similar to anabolic steroids.

*Pediatrics* 2006;117;e577-e589
Prohormones

Dosing

- DHEA’s recommended dosing is in a range of 50 to 100 mg/day for up to 1 year.

- The number of adverse effects increases at doses that exceed this amount, although athletes may well take more than the recommended amounts.

- Androstenedione’s upper limit for dosing was 100 to 300 mg/day; it’s now off the supplement market.
Effect of Oral Androstenedione on Serum Testosterone and Adaptations to Resistance Training in Young Men
A Randomized Controlled Trial
Context: Androstenedione, a precursor to testosterone, is marketed to increase blood testosterone concentrations as a natural alternative to anabolic steroid use. However, whether androstenedione actually increases blood testosterone levels or produces anabolic androgenic effects is not known.

Objectives: To determine if short- and long-term oral androstenedione supplementation in men increases serum testosterone levels and skeletal muscle fiber size and strength and to examine its effect on blood lipids and markers of liver function.

Design and Setting: Eight-week randomized controlled trial conducted between February and June 1998.

Participants: Thirty healthy, normotestosterogenic men (aged 19-29 years) not taking any nutritional supplements or androgenic-anabolic steroids or engaged in resistance training.

Interventions: Twenty subjects performed 8 weeks of whole-body resistance training. During weeks 1, 2, 4, 5, 7, and 8, the men were randomized to either androstenedione, 300 mg/d (n = 10), or placebo (n = 10). The effect of a single 100-mg androstenedione dose on serum testosterone and estrogen concentrations was determined in 10 men.
Results

- Serum free and total testosterone concentrations were not affected by short- or long-term androstenedione administration.

- Serum estradiol concentration (mean [SEM]) was higher ($P<.05$) in the androstenedione group after 2 (310 [20] pmol/L), 5 (300 [30] pmol/L), and 8 (280 [20] pmol/L) weeks compared with presupplementation values (220 [20] pmol/L).

- The serum estrone concentration was significantly higher ($P<.05$) after 2 (153 [12] pmol/L) and 5 (142 [15] pmol/L) weeks of androstenedione supplementation compared with baseline (106 [11] pmol/L).

- Knee extension strength increased significantly ($P<.05$) and similarly in the placebo (770 [55] N vs 1095 [52] N) and androstenedione (717 [46] N vs 1024 [57] N) groups.
Results

- The increase of the mean cross-sectional area of type 2 muscle fibers was also similar in androstenedione (4703 [471] vs 5307 [604] mm²; \( P < 0.05 \)) and placebo (5271 [485] vs 5728 [451] mm²; \( P < 0.05 \)) groups.

- The significant \( (P < 0.05) \) increases in lean body mass and decreases in fat mass were also not different in the androstenedione and placebo groups.

- In the androstenedione group, the serum high-density lipoprotein cholesterol concentration was reduced after 2 weeks (1.09 [0.08] mmol/L [42 (3) mg/dL] vs 0.96 [0.08] mmol/L [37 (3) mg/dL]; \( P < 0.05 \)) and remained low after 5 and 8 weeks of training and supplementation.
Figure 1. Serum Androstenedione, Luteinizing Hormone (LH), and Follicle-Stimulating Hormone (FSH) Concentrations With 100 mg of Androstenedione or Placebo

Data are mean (SEM) for n = 10. Asterisk indicates significantly different from time zero for androstenedione (P<.05).

Figure 2. Serum Free and Total Testosterone Concentrations With 100 mg of Androstenedione or Placebo

Data are mean (SEM) for n = 10.
**Figure 3.** Serum Androstenedione, Luteinizing Hormone (LH), and Follicle-Stimulating Hormone (FSH) Concentrations With 300 mg/d of Androstenedione (n = 9) and Placebo (n = 10)

Data are mean (SEM). Asterisk indicates significantly different from time zero for androstenedione (*P* < .05).

**Figure 4.** Serum Free and Total Testosterone Concentrations With 300 mg/d of Androstenedione (n = 9) and Placebo (n = 10)

Data are mean (SEM). Serum free testosterone was significantly higher in the androstenedione group vs placebo group (significant main effect, *P* < .01).
Figure 5. Serum Estradiol, Estriol, and Estrone Concentrations With 300 mg/d of Androstenedione (n = 9) and Placebo (n = 10).

Data are mean (SEM). Asterisk indicates significantly different from week zero for androstenedione (P < .05). Dagger indicates androstenedione significantly different from placebo (P < .05).
Comments

- Androstenedione administration during resistance training did not significantly alter the serum testosterone concentration in normotestosterogenic young men.

- The increased muscle size and strength observed with resistance training were also not augmented with androstenedione administration.

- The use of androstenedione increased the serum concentrations of estradiol and estrone, suggesting an increased aromatization of the ingested androstenedione and/or testosterone derived from the exogenous androstenedione.

- The use of androstenedione was associated with decreased levels of HDL-C.

- These data provide evidence that androstenedione does not enhance adaptations to resistance training and may result in potentially serious adverse health consequences in young men.
Growth Hormone

- GH has been used as a drug of abuse in sport since the early 1980s, although the first scientific studies demonstrating a clear cut physiologic role for GH in adults was only published in the peer-reviewed medical literature in 1989.

- There are currently no proper scientific studies providing GH to be performance enhancing in normal subjects, but GH has been shown to have a very important role in regulating body composition in adult humans and in other species.

- GH-deficient (GHD) adults have reduced lean body mass and increased fat mass, especially at the abdominal level.

- Physiologic replacement therapy with recombinant GH (rhGH) in GHD adults results in significant changes in body composition with, on average, a 5-kg increase in lean body mass within the first month and a comparable loss of 5 kg of fat.

Growth Hormone

- There is a lack of general agreement whether GH replacement improves physical performance in GHD patients.

- Exercise capacity is reported to increase in some but not all placebo-controlled trials conducted in hypopituitary adult patients.

- GH replacement therapy in GHD patients has been shown to increase lean body mass but not aerobic capacity.

*Clin Endocrinol* 1999; 51:53-60
*Clin Endocrinol* 1994; 41:615-620
Growth Hormone

- The mechanisms through which GH acts on exercise performance are more complex than the simple increase in lean body mass.

- GH stimulates erythropoiesis under various conditions and exerts significant cardiovascular effects, increasing plasma volume and peripheral blood flow and enhancing left ventricular stroke volume and cardiac output.

- All these factors may well contribute to improve aerobic capacity.

- Evidence suggests that GH therapy alone, in the absence of some form of exercise program, may increase the lean body mass but not its functional capacity, thus indicating that training may have to be combined with GH replacement in these patients to increase physical performance.
Growth Hormone

- The only controlled studies on the effects of GH on muscle function in experienced weight lifters or power athletes have not been able to show a significant positive effect of GH on muscular protein biosynthesis or strength.

- Only one study has demonstrated an increase in fat-free mass and a decrease in fat mass in healthy men and women undergoing intensive exercise.

- Two recent studies in obese men and women found that GH treatment augmented fat loss in conjunction with dietary restriction and/or exercise.

_J Appl Physiol_ 1993; 74:3073-3076

_J Clin Endocrinol Metab_ 1997; 82:727-734
Growth Hormone

- Physiologic doses of GH given for 6 months to healthy older men with well-preserved functional abilities have been shown able to improve body composition, increasing lean tissue mass and decreasing fat mass.

- However, functional ability was not improved, while frequent side effects were reported.

- Two different strategies have been proposed to detect GH doping in sports: parameters of the IGF system such as IGF-I, IGFBP-3, and ALS are suitable markers of GH use in combination with procollagen cleavage products; the “GH isoform method” exploits the difference in isoform composition between recombinant and endogenous growth hormone.


*Lancet* 1999; 353:895
### Table 5. Key Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event*</th>
<th>Studies Reporting Outcome, n</th>
<th>Events in Growth Hormone-Treated Group, n (%)</th>
<th>Events in Non-Growth Hormone-Treated Group, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue edema</td>
<td>8</td>
<td>33 (44)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>11 (35)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>2</td>
<td>4 (25)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>2</td>
<td>3 (15)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sweating</td>
<td>1</td>
<td>3 (30)</td>
<td>2 (20)</td>
</tr>
</tbody>
</table>

* Participants may have reported more than 1 adverse event.
**Erythropoietin**

- EPO is an **essential growth factor** for the erythrocytic progenitors in the bone marrow.

- Once released, it serves to stimulate an increase in hemoglobin thus increasing the **oxygen-carrying capacity** of the blood.

- EPO increases **hematocrit** when administered in a recombinant form.

- **RhEPO** has been imputed to be **abused by athletes** in **aerobic sports** early after its marketing as an erythropoiesis-stimulating drug.

- Artificially raising hemoglobin levels can have dangerous consequences.

- The administration of **rhEPO** produces a selective increase in red cell mass.

- The main risk of **erythrocytosis** include heart failure, myocardial infarction, seizures, peripheral thromboembolic events, and pulmonary embolism.

*J Endocrinol Invest* 2003; 26:832-837
Erythropoietin

- The use of recombinant erythropoietin should be suspected in athletes if the hematocrit is above 50 percent in males and above 47 percent in females.

- There is substantial overlap with healthy controls.

- As a result, tests for confirming erythropoietin use have been proposed.

- Elevation of the serum ratio of the soluble transferrin receptor to ferritin is one of the tests.

- The glycosylation pattern of commercially available recombinant erythropoietin differs from that of human serum erythropoietin, and can be detected by a combination of electrophoretic and immunologic techniques.

*Lancet* 2002 Jul 13;360 (9327):99-100
Insulin

- Anabolic steroid users self-administer insulin.
- Insulin promotes anabolic processes and inhibits catabolism in muscle, liver, and adipose tissue.
- Insulin increases the synthesis of glycogen, fatty acids, and proteins.
- Insulin promotes the entry of glucose and amino acids into the muscle and fat cells.

JAMA, May 27, 1998—Vol 279, No. 20
Insulin

- Twenty self-identified anabolic-androgenic steroid injectors, recruited from local gyms, were interviewed regarding their injection practices.

- Five (25%) of the 20 anabolic-androgenic steroid injectors reported insulin use to increase muscle mass.

- None of the anabolic-androgenic steroid injectors reported insulin use to treat a medical condition.

- Those using insulin reported injecting a dose of 10 IU of regular insulin a mean of 44 times (range, 20-60) in the 6 months prior to the interview.

- Information regarding insulin administration and dosage reportedly was disseminated by “word-of-mouth.”

- Most reported consuming sugar-containing foods or drinks after injection.
- None of the individuals reported hypoglycemia.
- Individuals reported obtaining insulin from “black-market” dealers and from pharmacies.

JAMA, May 27, 1998—Vol 279, No. 20
**hCG and Estrogen Blockers**

**hCG**

- hCG is a dimeric glycoprotein consisting of an a- and b-subunit normally produced by the human placenta.

- **Endogenous hCG** is produced by the normal placenta in pregnancy or placental trophoblastic (hydatidiform mole, choriocarcinoma), gonadal (ovarian, testicular or extragonadal teratoma), or ectopic and nontrophoblastic tumors.

- In **clinical practice**, the identification of hCG immunoreactivity in blood or urine is used for early pregnancy diagnosis as well as a tumor marker.

- Biologically active **heterodimeric hCG** is manufactured pharmaceutically as a biological product either purified from human pregnancy urine or as a recombinant glycoprotein purified from genetically engineered mammalian cells.

  *J Clin Endocrinol Metab* 91: 1646–1653, 2006
hCG and Estrogen Blockers

- Clinically, hCG is used as a naturally occurring long-acting and potent LH analog.

- The only legitimate clinical indication for hCG is to restore endogenous testosterone production and normalize blood testosterone concentrations in gonadotrophin-deficient men including delayed male puberty.

- hCG is misused by male athletes in two settings.
hCG and Estrogen Blockers

- In one scenario, men who have developed sustained inhibition of their hypothalamo-pituitary testicular axis from prolonged high-dose androgen abuse seek to rectify this by increasing testicular testosterone production using hCG.

- The other setting is that of androgen abusers seeking to avoid detection of synthetic androgens or exogenous testosterone by stimulating endogenous testosterone production.
hCG and Estrogen Blockers

Estrogen Blockers

- There are no valid clinical indications for estrogen blockers in men.

- Accepted off-label use for estrogen blockers would be limited to men with breast cancer, an exceptionally rare tumor.

- Some limited experimental uses for estrogen blockade in men have included delayed puberty, short stature, gynecomastia, spinal growth, and idiopathic male infertility.

J Clin Endocrinol Metab 91: 1646–1653, 2006
hCG and Estrogen Blockers

- There is abundant and consistent evidence that estrogen blockers increase blood testosterone concentrations in men.

- It is well established that in normal men antiestrogens such as clomiphene, tamoxifen, and raloxifene cause a reflex rise in pituitary gonadotrophin secretion and consequently in blood testosterone concentrations.

- This is attributable to their inhibition of testosterone-negative feedback on the hypothalamus, a process that involves local aromatization of testosterone within the brain.

*J Clin Endocrinol Metab*
91:
1646–1653, 2006
hCG and Estrogen Blockers

- A similar increase in blood testosterone concentrations ranging from 5 to 20 nmol/liter is reported with aromatase inhibitors such as testolactone, exemestane, and anastrozole.

- By virtue of their common mechanism of action in inhibiting that part of testosterone’s negative hypothalamic feedback due to aromatization, it is highly likely that all estrogen blockers would have similar class-wide effects, proportional to their estrogen-blocking effectiveness.

*J Clin Endocrinol Metab 91: 1646–1653, 2006*
Prevention

- Preventive measures include increased awareness among physicians, proper doping analyses, pedagogic interventions, and updated legislation.

- Doping in sport must be combated with much longer disqualifications of athletes using AAS, a proposal that has scientific support.

- The introduction of doping analyses has held back doping in elite sports.
- In Sweden, the proportion of positive doping tests among athletes has declined from 2% to below 0.5% during the past 5 years.

- Between 1981 and 2005, hormones (62%) were the most commonly detected, stimulants accounted for 7% and narcotics for 5%.
- 23% of athletes refused to participate and were disqualified.

*Lancet* 2008; 371: 1872–82
Prevention

- School children need to be taught about the risks of doping, and athletes and their attending coaches and doctors need more comprehensive education about which substances are banned and why they appear on the prohibited list.

- More research should be done to develop more sophisticated techniques for detecting banned substances, which should include blood tests as well as urine sampling.

- And much tougher measures should be introduced for athletes caught doping.