

ES.010 Chemistry of Sports

Illegal manipulation of your body

Schedule of events for today:

1. Update on workout on Thursday – in the pool 4 pm.
2. Drugs in sports
3. Introduction to Wind tunnel testing – preview of next week's class with Kim Blair.

Drugs in Sports

- Blood Doping, Artificial Oxygen Carriers and Erythropoietin (EPO)
- Human Growth Hormone
- Anabolic Steroids
- Insulin-like Growth Factor (IGF-1)
- Cocaine
- Caffeine
- Narcotics
- Cannabinoids
- Amphetamines
- THG
- Human Chorionic Gonadotrophin (HCG)
- Adrenocorticotrophic Hormone (ACTH)
- Beta-2-Agonists
- Hormone Antagonists and Modulators
- Diuretics
- Gene Doping

Why do Athletes Take Drugs?

There are a large number of reasons why an athlete may decide to take drugs. A selection are listed here:

- Pressure to succeed, either from themselves or coaches/family and sponsors (major reason)
- Belief that their competitors are taking drugs
- Pressure from governments/national authorities (as occurred in the eastern bloc countries in the 60's and 70's)
- Financial rewards for outstanding performance
- Lack of access to, or funding for training facilities and additional support (nutrition, psychological support)
- Community and media attitudes and expectations of success

Reference: <http://www.teachpe.com/drugs/drugs.php>.

Drugs in Sports

- Blood Doping and Erythropoietin (EPO)
- Human Growth Hormone
- Anabolic Steroids
- Insulin-like Growth Factor (IGF-1)
- Cocaine
- Caffeine
- Narcotics
- Cannabinoids
- Amphetamines
- THG
- Human Chorionic Gonadotrophin (HCG)
- Adrenocorticotrophic Hormone (ACTH)
- Beta-2-Agonists
- Hormone Antagonists and Modulators
- Diuretics
- Artificial Oxygen Carriers
- Gene Doping

Lance Armstrong

- Prior to 2012, Lance Armstrong was the cyclist who won 7 Tour de France titles, battled back from testicular cancer, started Livestrong foundation to provide support to people with cancer and was known as hardworking, dedicated to training individual



But that changed on between June 2012 to October 10th,
When the USADA (Doping Agency) provided evidence
That he was a doper

Lance Armstrong

- Initially denied all of the charges against him, but eventually came clean to Oprah during a two part interview on Jan 17th and 18th, 2013



Image courtesy of [Paul Coster](#). CC-BY.

<http://www.oprah.com/own/Lance-Armstrong-Confesses-to-Oprah-Video>

What did he do?

- EPO in six blood samples from the 1999 Tour de France that were retested.
- blood transfusions,
- testosterone,
- Corticosteroids
- Masking agents
- Pressured teammates to participate in the illegal drug use

Blood Doping and Erythropoietin (EPO)

Blood Doping:

Increasing the amount of red blood cells in your body (Red blood cells have hemoglobin which carry oxygen to your muscles, more oxygen, more ATP, more energy, better athletic performance)

Erythropoietin (EPO)

is naturally produced in the kidneys to regulate red blood cell production.

The FDA has approved it for medical use in chronic renal failure and certain types of anemia (low red blood cell concentration)

Blood Doping and Erythropoietin (EPO)

How to Blood dope

- Most commonly this involves the removal of two units (approximately 2 pints!) of the athlete's blood several weeks prior to competition. The blood is then frozen until 1-2 days before the competition, when it is thawed and injected back into the athlete. This is known as autologous blood doping. Homologous doping is the injection of fresh blood, removed from a second person, straight into the athlete.

Blood Doping and Erythropoietin (EPO)

Who does it?

Mostly cyclists and Endurance runners

Some say cycling faced a near death following the 1998 doping scandal in which French officials caught an employee of the Festina cycling team with a carload of performance-enhancing drugs, including erythropoietin (EPO)

Festina cycling team was sponsored by the watch manufacturer Festina and was in existence from 1989 to 1998.

Blood Doping and Erythropoietin (EPO)

From the Tour de France 2006: (Washington post)

The drug scandal revolves around a sports doctor, Eufemiano Fuentes, the head of hematology at a Madrid hospital who had worked with several cycling teams. Fuentes allegedly helped riders and athletes from other unidentified sports engage in different kinds of drug use and blood doping to enhance their performance.

The blood doping reportedly involved drawing oxygen rich blood at high altitudes to obtain a concentrate of red blood cells, then injecting them back into riders before a race to boost endurance.

Article on-line: Eufemiano Fuentes Breaks Off Silence (<http://news.softpedia.com/news/Eufemiano-Fuentes-Breaks-Off-Silence-28678.shtml>)

Blood doping

The best way to get around the tests is to take your own blood out of your body, purify the red blood cells (by centrifugation) and transfuse it back into you

So basically you are giving yourself a blood transfusion using your own blood

This does not always work, case in point – Tyler Hamilton

Tyler Hamilton

- Tyler Hamilton (born March 1, 1971, Marblehead, Massachusetts) is a former American professional road bicycle racer and Olympic gold medalist, whose career and reputation were repeatedly marred by doping scandals.
- At the 2004 Summer Olympics in Athens, Hamilton won the gold medal in the men's individual time trial. That medal was placed in doubt on September 20, 2004, after he failed a test for blood doping (receiving blood transfusions to boost performance) at the Olympics. Two days after the announcement of his positive test at Athens, the IOC announced Hamilton would keep his medal because results could not be obtained from the second sample. The Athens lab had frozen the backup, which made it impossible to repeat the test.

Tyler Hamilton

- The positive sample at the Olympics, and the positive test at the Vuelta were not the only indications that Hamilton was manipulating his hematocrit level. In April 2004 his blood was found to have a high ratio of hemoglobin to reticulocytes (young red blood cells), indicative of EPO or blood doping. His score was 132.9; a clean athlete would score 90. The UCI suspends a rider if the score exceeds 133. This sample also showed someone else's blood was in his bloodstream. However, neither piece of evidence in isolation constituted a positive drug test (and the test for a mixed cell population had not yet been adopted), so no action was taken.

Tyler Hamilton

Why the mixed cell population?

- He was getting blood from someone else – it was a mix-up in the blood transfusion – correct type, incorrect person

Tyler Hamilton

- After his suspension, Hamilton came back and became national road race champion in 2008. In 2009, Hamilton failed a doping test again, and this time he was banned for eight years, which effectively caused him to retire. In July 2010, he was subpoenaed to appear before a grand jury revolving around the use of performance enhancing drugs in cycling. In May 2011, Hamilton admitted that he had used banned substances in competition, and returned his gold medal. As of May 2011, the IOC has not removed him from the result, but is studying his confession.

Reference: http://en.wikipedia.org/wiki/Tyler_Hamilton.

How can you naturally boost your red blood cell count?

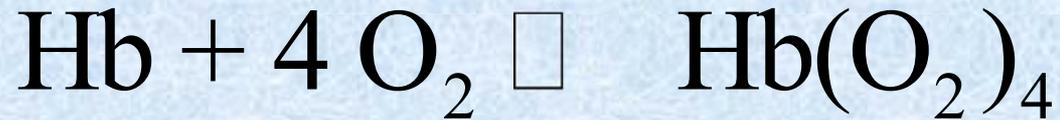
How can you naturally boost your red blood cell count?

Work out at low O₂ levels (I.e. in the mountains) and then race at high O₂ levels (I.e. sea level)

Why do you think that the Olympic training facility is in Colorado?

Biochemically, how does this work?

Binding of O₂ to hemoglobin (Hb)



Remember LeChatelier's principle?

(a system at equilibrium, wants to stay there, so Any change in status quo prompts an opposing reaction in the responding system.)

For our system:

Since this is an equilibrium reaction, if you reduce the O₂, then the system will shift to make more of it (and as a result make more hemoglobin)

Altitude Tent:

Sleep in an altitude chamber (low O₂ levels) 2009 Colorado Altitude Training 150 Tent CAT 9 Generator (Item: CAL800 from the competitive cyclist): cost: 4449.00
URL:

http://altitudetraining.com/main/military/products/uncontrolled_tent/cat150

- From their website: Lance Armstrong was fond of saying that he won the Tour in training. Besides the long miles, the mountain-based training camps, the carefully-weighed food, the guy was sleeping at altitude.



Courtesy of Colorado Altitude Training. Used with permission.

EPO Test

- The adopted by WADA (World Anti-Doping Agency) urine test for EPO is based on a combination of isoelectric focusing on a gel (a semianalytical separation of proteins according to the molecules' net electric charge), the transfer of proteins from gel to a special paper and protein detection by a double immunoblotting.
- The test uses an antibody which reacts with both the human EPO and the rEPO
- This makes it possible to distinguish between artificial rEPO and human EPO, which behave differently in an electric field.

Reference:http://autobus.cyclingnews.com/news.php?id=features/2005/epotest_problems.

EPO Test

- One problem with the test is that it uses antibodies that cross react with both the human EPO and rEPO
- The two proteins have identical amino acid chains, and differ only in the sugars that the cells producing them attach round the protein. The charge on the protein is different because the sugars are different, therefore if you separate on charge, you get different 'ladders' for artificial and natural forms of EPO.
- Then it should not matter if the antibody recognizes both types of EPO.

[http://autobus.cyclingnews.com/news.php?id=features/2005/epotest_problems.](http://autobus.cyclingnews.com/news.php?id=features/2005/epotest_problems)

EPO test

Beullens, Monique, et. al. "False-Positive Detection of Recombinant Human Erythropoietin in Urine Following Strenuous Physical Exercise." *Blood* 107 (2006): 4711-4713.

A new and improved way to blood dope

IOC announced it would retest blood samples from the Beijing Olympics for a new performance enhancing drug.

So far three stage winners of the TDF have tested positive for Continuous Erythropoiesis Receptor Activator ("CERA") a new generation of EPO which stimulates bone marrow to produce more red blood cells and which was developed to treat anemia.

CERA

Roche's new anaemia drug CERA highly effective in dialysis patients with chronic anaemia

Studies have shown that CERA has unique activity at the receptor site. It is postulated this is related to its repeated and rapid attachment and dissociation from the receptor involved in triggering erythropoiesis (red blood cell formation) together with an extended serum half life. This results in more potent stimulation of erythropoiesis, both in magnitude and duration, compared to standard epoetins.

(reference: Roche Website at :

<http://www.roche.com/inv-update-2003-11-17.>)

A new and improved way to blood dope

Links;

http://en.wikipedia.org/wiki/List_of_doping_cases_in_sport.

<http://www.cyclingnews.com/news.php?id=news/2008/oct08/oct08news2>.

<http://www.bikeradar.com/news/article/olympic-riders-bloodsamples-to-be-reanalysed-with-new-epo-cera-tests--18901>.

Who has tested positive for EPO?

The US cycling team at the 1984 Olympics

Swedish cyclist Niklas Axelsson

The Operación Puerto case in 2006 involved allegations of doping and blood doping of hundreds of athletes in Spain.

Tour de France rider Alexander Vinokourov, of the Astana Team, tested positive for two different blood cell populations

19-year-old New York Rangers prospect and Russian hockey player Alexei Cherepanov was engaged in blood doping for several months before he died on October 13, 2008, after collapsing on the bench during a game in Russia.

Reference: http://en.wikipedia.org/wiki/Blood_doping.

Testosterone: why do it?

- allows athletes to rapidly increase muscle mass beyond what their body would normally manage
- reduces their recovery time, meaning they can train hour after hour, day after day, with little need to rest their bodies in between workouts.

<http://www.sfgate.com/giants/article/Testosterone-builds-muscle-but-has-risks-3791601.php>.

Side effects of testosterone abuse

- Liver damage, unsafe cholesterol levels, and heart and circulatory problems. Testosterone abuse may affect the prostate and cause cancer, as well.
- Men who chronically abuse testosterone may experience effects that would seem to be contrary to the hormone's purpose, including breast development, shrunken testicles and infertility.

Testosterone

- Produced mostly in the testes and a small amount of *testosterone* is *produced* from steroids secreted by the outer layer of the adrenal glands
- Lance Armstrong had testicular cancer, so he was going to have low levels of testosterone in his body due to the removal of one of his testes

Corticosteroids

- Any of the steroid hormones produced by the adrenal cortex or their synthetic equivalents, such as
 - cortisol (Its primary functions are to increase blood sugar through gluconeogenesis; suppress the immune system; and aid in fat, protein and carbohydrate metabolism)
- and
- aldosterone (which helps regulates water and salt balance in body)

Corticosteroids

- potent anti-inflammatory and immunomodular agents
- Athletes must use it to reduce the swelling caused by workouts and aid in recovery

Masking agents

- Masking agents are drugs or compounds that are taken with the express purpose of hiding or “masking” the presence of specific illegal drugs that are screened for athletic drug testing .
- Masking agents have the potential to impair or conceal the banned substance in the urine
- The most common masking agents include diuretics, epitestosterone, probenecid and plasma volume expanders

Reference:<http://trackfocus.com/sprints/of-mullings-and-masking-agents>.

Furlanello F, Bentivegna S, Cappato R, and De Ambroggi L. Arrhythmogenic effects of illicit drugs in athletes. Ital Heart J 4: 829-837, 2003.

What is your opinion of Lance
Armstrong?

**Now onto other examples of
illegal substances**

Human Growth Hormone

- See Birkeland, Kåre I. and Peter Hemmersbach. “The Future of Doping Control in Athletes: Issues Related to Blood Sampling.” *Sports Medicine* 28, no. 1 (1999): 25-33.

Human Growth Hormone

Rugby player in UK: Terry Newton

<http://www.nytimes.com/2010/02/28/sports/global/28hgh.html>

In 2007, Patriots safety Rodney Harrison was the first active player in the league to confess to using human growth hormone (HGH). (reference: <http://www.highbeam.com/doc/1P2-8722322.html>)

Andy Pettitte (baseball player): In 2007, admitted that he had taken HGH in 2002 to speed healing from an elbow injury. He was not disciplined.

Bill Romanowski (football player): In 2005, admitted on the TV show 60 Minutes that he'd taken HGH and steroids from 2001 to 2003. Since he'd been retired since 2003, he was not disciplined.

Reference: <http://www.pharmacytechs.net/blog/top-10-performance-enhancing-drugs>

Baseball Scandals

Roger Clemens' s former trainer Brian McNamee said that he injected both Roger Clemens and his wife with HGH (link to the Boston Globe article(http://www.boston.com/sports/baseball/articles/2007/12/14/clemens_implicated_in_steroid_scandal_by_trainer/))

Clemens testified in front of Congress ([see link](#)) and threw his wife under the bus

SI photoshoot

Debbie Clemens

took HGH before
this SI swimsuit
photoshoot

HGH is used to
reduce body fat
(and thus
increase lean
body mass)

[View](#) image of Debbie and Roger Clemens from the *Sports Illustrated Swimsuit* edition from 2003.

Anabolic Steroids

Androstenedione ("Andro")

- A steroid produced in the adrenal glands and the gonads, which is converted in the body to testosterone.

Athletic uses:

To increase muscle strength and mass and to shorten muscle recovery time.

Androstenedione ("Andro")

- Roy Jones, Jr. (boxer): Andro was available in over-the-counter supplements when he tested positive in 2000. He was not disciplined.
- Mark McGwire (baseball player): Admitted using it in 1998, at a time when it was legal not banned by Major League Baseball. He was not disciplined.

Mark McGwire

Between Mark McGwire's andro usage and Ken Caminiti's revelation in Sports Illustrated about steroids in baseball, the sport is having an image crisis.

McGwire went from the svelte American League rookie of the year in 1987 to the heavy-hitting home run king who broke Roger Maris' single-season home run record in 1998.

McGwire said the transformation in his size was the combination of hard work and an over-the-counter testosterone-producing pill called androstenedione, or andro

See [images](#) of Mark McGwire before and after taking steroids.

Mark McGwire

January 11, 2010:

NEW YORK -- Mark McGwire finally came clean, admitting he used steroids when he broke baseball's home run record in 1998, but he also said he didn't need performance-enhancing drugs to hit the long ball.

"I was given a gift to hit home runs," he told Bob Costas on MLB Network

He told Costas that studying pitchers and making his swing shorter led to his increase in home runs and that he could have hit them without PEDs. (performance enhancing drugs)

"I truly believe so," McGwire said. "I believe I was given this gift. The only reason I took steroids was for health purposes."

Reference: <http://sports.espn.go.com/mlb/news/story?id=4816607>

Andro

Andro became controversial because it is banned by the IOC, NFL, NBA and NHL, but not by Major League Baseball.

In May of 2002, Jose Canseco announced his retirement from baseball, and as a parting shot (and perhaps a promo for his tell-all book) he said 85 per cent of all baseball players used steroids. Later, Canseco admitted to taking steroids himself.

Later that month, Sports Illustrated published an investigative report describing professional baseball as "a pharmacological trade show." In the article, former National League MVP Ken Caminiti told the magazine "at least half the guys are using steroids."

More Steroids use: Chinese swim team

Dihydrotestosterone, anabolic steroids, erythropoietin and human growth hormones. All banned substances.

All used by various members of the Chinese national swim team in the last 15 years.

China did not register among the world's swimming powers until the 1990s, and when they did, they did with a bang.

Coincidentally, an East German coach came to China in 1986,

The East Germans

From New York Times, Dec 1991:

OLYMPICS: Coaches Concede That Steroids Fueled East Germany's Success in Swimming

The stunning domination of international swimming by East German women for nearly two decades was built upon an organized system of anabolic steroid use, a group of 20 former East German coaches confirmed yesterday.

The “Women” German swimmers

At the first world swimming championships, in 1973, East German women won 10 of the 14 gold medals available, setting eight world records. Three years later at the Summer Games in Montreal, the East Germans won 10 of the 12 gold medals for individual events. When a rival coach noted with some sarcasm that the voices of many of the East German women were unusually deep -- a telltale sign of the effects of steroid use in females -- an East German coach replied, "We came here to swim, not sing."

The “Women” German swimmers

The victims all received Oral-Turinabol - an anabolic steroid containing testosterone made by Jenapharm. The "blue bean" had astonishing powers - accelerating muscle build-up and boosting recovery times - but its subsequent side effects were catastrophic: infertility among women, embarrassing hair growth, breast cancer, heart problems and testicular cancer. An estimated 800 athletes developed serious ailments.

Intriguingly, some of the world records set by East German athletes while using Oral-Turinabol have not been bettered.

Back to the Chinese swim team

The country won four swimming gold medals at the 1992 Barcelona Olympics and then took 12 of 16 women's titles at the 1994 world championships.

The team's sudden success fuelled suspicion of drug use, and by the next big competition, those hunches proved true.

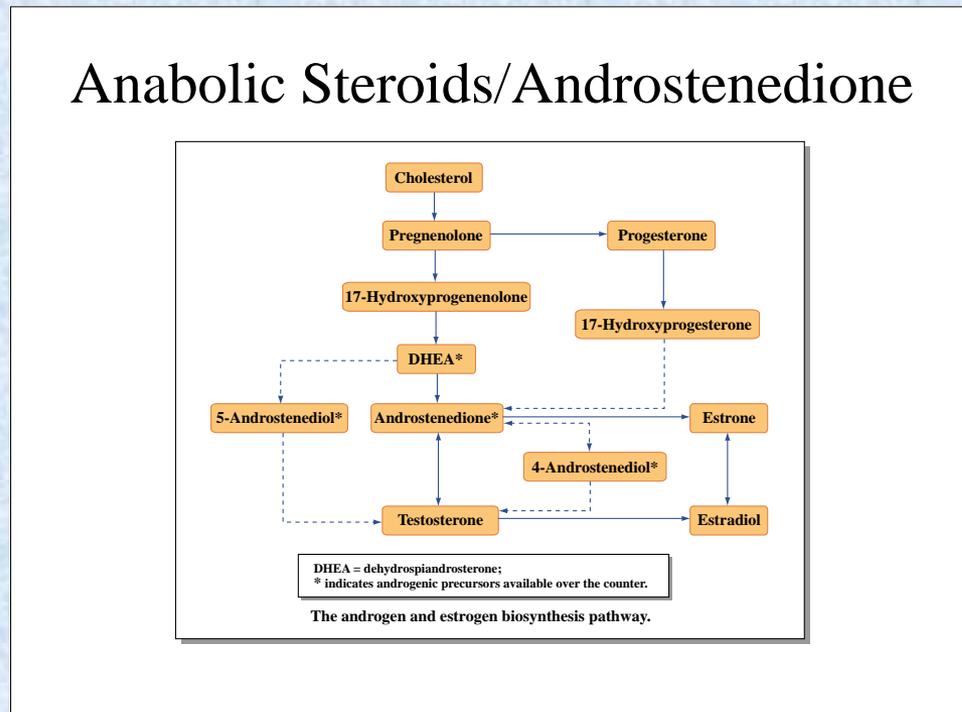
Eleven athletes tested positive for dihydrotestosterone at the 1994 Asian Games. The big bust decimated the swim squad for the 1996 Olympics (they won just one gold), but soon enough the Chinese were back on top again. Not for long, however.

Anabolic Steroids/Androstenedione

Used because it increases muscle mass and strength

Either take testosterone or one of its precursors,
dehydroepiandrosterone (DHEA),

androstenedione or dihydrotestosterone (DHT)



Back to the Chinese swim team coached by the East German coach

Four positive tests before the 1998 world championships along with the vials of the human growth hormone found in breast stroker Yuan Yuan's luggage before the worlds signaled that doping was still thriving in China's pools.

Though the country maintained there was no systemic doping on its swim teams, the statistics say otherwise.

Over 40 Chinese swimmers since 1990 have failed drug tests. That's triple the amount of any other swimming country during the same period of time.

Chinese swim team

After pressure from FINA, swimming's governing body, China's swim association promised stricter drug testing and higher penalties for cheats.

Just before the 2000 Sydney Olympics, China removed four swimmers from its team because of "suspicious" drug test results.

Chinese swimmers were rarely on the podium in major competitions until the 2003 world aquatic championships in Barcelona. There, the women's team collected seven swimming medals, including three gold.

More Cycling and illegal drugs

- Floyd Landis won the Tour de France in 2006
- Landis allegedly tested positive for a skewed testosterone-epitestosterone (T/E) ratio following his remarkable come-from-behind performance in the 17th stage of the 2006 Tour.
- Read all about Landis:
- NY times ([here](#)) or at his website:



Image courtesy of colinedwards99. CC BY.

The test:

From C& E news article

Despite the speculation about its origin, the one thing certain about the high T/E ratio is that it prompted the doping-control lab to pursue the matter further and retest the sample by gas chromatography/combustion/isotope-ratio mass spectrometry, which is considered foolproof for identifying synthetic testosterone. This method determines the percent difference between the ratio of ^{13}C to ^{12}C in CO_2 from the combustion of testosterone or its metabolites in the urine sample and the ^{13}C to ^{12}C ratio of an internal CO_2 standard. When synthetic testosterone is used, the percent difference is reduced, by a few percent, relative to baseline isotope ratios of natural steroids, their precursors, and their metabolites in urine. According to doping-control authorities, Landis flunked the test. (his ratio was 11:1, the normal is 4:1)

- Reference:
<http://pubs.acs.org/subscribe/journals/cen/84/i35/html/8435sci4.html>

The test:

From C& E news article

The isotope-ratio test is possible because synthesized steroids are made from starting compounds (diosgenin or stigmasterol) obtained from soybean or other plant oils. Soybeans and most agricultural crops are C₃ plants, which means they first form a three-carbon molecule (3-phosphoglyceric acid) from CO₂ during photosynthesis. Other plants that are integral to the human diet, such as corn and sugarcane, are C₄ plants, which first form four carbon molecules (oxaloacetate, malate, and aspartate). Because the human diet consists of a mix of C₃ and C₄ plants, naturally produced steroids will have a slightly higher amount of ¹³C than synthetically derived steroids, hence the decrease in the percent difference observed for a positive testosterone doping test.

- Reference:

<http://pubs.acs.org/isubscribe/journals/cen/84/i35/html/8435sci4.html>

The Results

Floyd Landis was be stripped of his Tour de France crown and banned from the sport for two years for testing positive for synthetic testosterone after an arbitration panel on September 20, 2007 which affirmed the finding by the US Anti-Doping Agency.

Insulin-like Growth Factor (IGF-1)

- Insulin-like growth factor is the most predominant somatomedin or growth factor hormone, with a very similar structure to insulin although it is released by the liver. It plays an important role in growth and development in children and is thought to have anabolic effects in adults.
- Due to perceived anabolic effects, athletes use IGF-1 to increase muscle mass and strength, although clinical studies have not shown any increases. It is thought that it is actually the IGF binding protein-3 which is responsible for growth rather than the growth factor itself. IGF-1 does, however, inhibit cell death and so may have a role in reducing recovery times.

Insulin-like Growth Factor (IGF-1)

- From: <http://insulin-growth-factor.com/Why-Athletes-Buy-IGF-1-Supplements.html>

IGF 1 has been reported to decrease the percentage of body fat in body builders, athletes and fitness enthusiasts who use the supplement for enhancement of their workouts. This is a good reason to buy IGF. The hormone stimulates the release of fats from fatty cells. The fats are therefore used as a source of energy in the muscle cells as opposed to using carbohydrates. Therefore, more energy is produced and the athlete burns a greater percentage of fat than they normally would during a workout.

Insulin-like Growth Factor (IGF-1)

- Study out of Italy showed that top level male rowers had higher levels of IGF-1 levels and increased cardiac output when compared to sedentary control
- They looked at cardiac output and IGF-1 serum levels, but reported no other effects
- Shocking that the heart muscle had expanded in elite rowers who had high levels of physical exercise.

Vitale et al., 2008. Circulating IGF-1 levels are associated with increased biventricular contractility in top-level rowers. *Clinical Endocrinology*, 69, 231-236

Insulin-like Growth Factor (IGF-1)

Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 15603–15607, December 1998
Medical Sciences

Viral mediated expression of insulin-like growth factor I blocks the aging-related loss of skeletal muscle function

ELISABETH R. BARTON-DAVIS*, DARIA I. SHOTURMA*, ANTONIO MUSARO†, NADIA ROSENTHAL†,
AND H. LEE SWEENEY*‡

© National Academy of Sciences. All rights reserved. This content is excluded from our Creative Commons license. For more information, see <http://ocw.mit.edu/help/faq-fair-use/>.

- This involved the injection of a recombinant adeno-associated virus directing overexpression of insulin-like growth factor I (IGF-I) in differentiated muscle fibers. We demonstrate that the IGF-I expression promotes an average increase of 15% in muscle mass and a 14% increase in strength in young adult mice, and remarkably, prevents aging-related muscle changes in old adult mice, resulting in a 27% increase in strength as compared with uninjected old muscles.

Insulin-like Growth Factor (IGF-1)

Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 15603–15607, December 1998
Medical Sciences

Viral mediated expression of insulin-like growth factor I blocks the aging-related loss of skeletal muscle function

ELISABETH R. BARTON-DAVIS*, DARIA I. SHOTURMA*, ANTONIO MUSARO†, NADIA ROSENTHAL†,
AND H. LEE SWEENEY*‡

© National Academy of Sciences. All rights reserved. This content is excluded from our Creative Commons license. For more information, see <http://ocw.mit.edu/help/faq-fair-use/>.

- During the aging process, mammals lose up to a third of their skeletal muscle mass and strength. Although the mechanisms underlying this loss are not entirely understood, we attempted to moderate the loss by increasing the regenerative capacity of muscle. This involved the injection of a recombinant adeno-associated virus directing overexpression of insulin-like growth factor I (IGF-I) in differentiated muscle fibers. We demonstrate that the IGF-I expression promotes an average increase of 15% in muscle mass and a 14% increase in strength in young adult mice, and remarkably, prevents aging-related muscle changes in old adult mice, resulting in a 27% increase in strength as compared with uninjected old muscles.

Insulin-like Growth Factor (IGF-1)

Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 15603–15607, December 1998
Medical Sciences

Viral mediated expression of insulin-like growth factor I blocks the aging-related loss of skeletal muscle function

ELISABETH R. BARTON-DAVIS*, DARIA I. SHOTURMA*, ANTONIO MUSARO†, NADIA ROSENTHAL†,
AND H. LEE SWEENEY*‡

© National Academy of Sciences. All rights reserved. This content is excluded from our Creative Commons license. For more information, see <http://ocw.mit.edu/help/faq-fair-use/>.

- Muscle mass and fiber type distributions were maintained at levels similar to those in young adults. We propose that these effects are primarily due to stimulation of muscle regeneration via the activation of satellite cells by IGF-I. This supports the hypothesis that the primary cause of aging-related impairment of muscle function is a cumulative failure to repair damage sustained during muscle utilization. Our results suggest that gene transfer of IGF-I into muscle could form the basis of a human gene therapy for preventing the loss of muscle function associated with aging and may be of benefit in diseases where the rate of damage to skeletal muscle is accelerated.

Insulin-like Growth Factor (IGF-1)

The molecular responses of skeletal muscle satellite cells to continuous expression of IGF-1: implications for the rescue of induced muscular atrophy in aged rats.

Chakravarthy MV, Booth FW, Spangenburg EE.

Collaborators (1)

Department of Integrative Biology, University of Texas Medical School, Houston 77030, USA.

Abstract

Approximately 50% of humans older than 85 years have physical frailty due to weak skeletal muscles. This indicates a need for determining mechanisms to combat this problem. A critical cellular factor for postnatal muscle growth is a population of myogenic precursor cells called satellite cells. Given the complex process of sarcopenia, it has been postulated that, at some point in this process, a limited satellite cell proliferation potential could become rate-limiting to the regrowth of old muscles. It is conceivable that if satellite cell proliferative capacity can be maintained or enhanced with advanced age, sarcopenia could potentially be delayed or prevented. Therefore, the purposes of this paper are to describe whether IGF-I can prevent muscular atrophy induced by repeated cycles of hindlimb immobilization, increase the in vitro proliferation in satellite cells from these muscles and, if so, the molecular mechanisms by which IGF-I mediates this increased proliferation. Our results provide evidence that IGF-I can enhance aged muscle regrowth possibly through increased satellite cell proliferation. The results also suggest that IGF-I enhances satellite cell proliferation by decreasing the cell cycle inhibitor, p27Kip1, through the PI3'-K/Akt pathway. These data provide molecular evidence for IGF-I's rescue effect upon aging-associated skeletal muscle atrophy.

© Human Kinetics, Inc. All rights reserved. This content is excluded from our Creative Commons license. For more information, see <http://ocw.mit.edu/help/faq-fair-use/>.

Reference: Int J Sport Nutr Exerc Metab. 2001 Dec;11 Suppl:S44-8.

Insulin-like Growth Factor (IGF-1)

Muscle cells do not divide (they are inhibited), so the way that the muscle cells increase in girth is to recruit new nuclei to the already existing cells

IGF-1 can help this process

But another way is to inhibit the inhibitor to allow the muscle cells to divide

Cheating or just good genes?

Regulation of myostatin activity and muscle growth

Se-Jin Lee* and Alexandra C. McPherron

Department of Molecular Biology and Genetics, Johns Hopkins

Published in

PNAS(2001):
98(16):9306-
9311

Myostatin is a transforming growth factor- β (TGF- β) family member that plays an essential role in regulating skeletal muscle growth (1). Myostatin is expressed initially in the myotome compartment of developing somites and continues to be expressed in the myogenic lineage throughout development and in adult animals. Mice carrying a targeted deletion of the myostatin gene have a dramatic and widespread increase in skeletal muscle mass. Individual muscles of myostatin null mice weigh approximately twice as much as those of wild-type mice as a result of a combination of muscle fiber hyperplasia and hypertrophy. The myostatin sequence has been highly conserved through evolution (2). Remarkably, the human, rat, murine, porcine, turkey, and chicken myostatin sequences are identical in the biologically active C-terminal portion of the molecule following the proteolytic processing site. The function of myostatin also appears to be conserved across species, as mutations in the myostatin gene have been shown to result in the double muscling phenotype in cattle (2-5).

These findings have raised the possibility that pharmacological agents capable of blocking myostatin activity may have applications for promoting muscle growth in human disease settings as well as in livestock animals. To identify novel strategies for blocking myostatin activity, we investigated the regulation of myostatin signaling. Here, we present evidence that myostatin, like TGF- β , may normally exist *in vivo* in a latent complex with the propeptide (the portion of the precursor protein upstream of the proteolytic processing site) and that on activation, myostatin may signal by binding to activin type II receptors.

Source: Lee, S-J, and A. C. McPherron. "Regulation of Myostatin Activity and Muscle Growth." *PNAS* 98, no 16 (2001): 9306-11. Courtesy of National Academy of Sciences, U. S. A. Used with permission.

Follistatin

- Inhibits myostatin

The most dramatic effects on skeletal muscle were obtained by using the follistatin construct. We obtained two founder animals (F3 and F66) that showed increased muscling (Table 1, Figs. 2 and 3b). In one of these animals (F3), muscle weights were increased by 194–327% relative to control animals, resulting from a combination of hyperplasia (66% increase in fiber number to 13,051 in the gastrocnemius/plantaris) and hypertrophy (28% increase in fiber diameter to 55 μm). Although we have not analyzed muscle weights of myostatin knockout mice in a hybrid SJL/C57BL/6 background, the increases in muscle mass observed in the F3 founder animal were significantly greater than the increases we have seen in myostatin null animals in other genetic backgrounds (unpublished

Similarly, our data do not show definitively that follistatin is blocking myostatin activity *in vivo* to promote muscle growth. In this regard, the extraordinary degree of muscling seen in one of the follistatin-expressing founder animals suggests that other follistatin-sensitive ligands may be involved in regulating muscle growth. One obvious candidate is GDF-11, which is highly related to myostatin (1, 18–20) and also expressed in skeletal muscle (unpublished results). Moreover, it is known that GDF-11 activity in *Xenopus* can be blocked by follistatin (18). Other candidate ligands would also include the activins, which have been shown to be capable of inhibiting muscle cell differentiation *in vitro* (33).

FOLLISTATIN



Myostatin deficiency

- See images of people/animals affected by myostatin deficiency:
 - Dog
 - Human-adult
 - Human-child
 - Cow
 - Mice

Cocaine

- Used as a topical anesthetic to numb the surface of a body part -- most often for eye, ear, nose, throat, neck and head injury.
- the energy boost and self-confidence it creates can aid in short-term athletic activity.

Is it legal? May be prescribed under special restrictions. Otherwise, illegal to possess or use.

Who has tested positive for Cocaine?

- Dwight Gooden (baseball player): 1987
- Thomas "Hollywood" Henderson (football player): 1979
- Lawrence Taylor (football player): Tested positive in 1988 and was suspended by the National Football League for 30 days
- Darryl Strawberry (baseball player): In 1995, tested positive for cocaine and was suspended by Major League Baseball for 60 days. Arrested in 1999 for cocaine possession, sentenced to 18 months' probation and received a 120-day suspension from baseball. Tested positive again for cocaine in 2000 and was suspended for a year.

Reference: <http://www.pharmacytechs.net/blog/top-10-performance-enhancing-drugs>

Who has tested positive for Cocaine?

- Martina Hingis (tennis player): In 2007, during the Wimbledon tennis tournament, tested positive for cocaine and was banned from tennis for two years. She retired shortly after the results were announced.
- Diego Maradona (soccer player): Was suspended from soccer for 15 months in 1991 for testing positive for cocaine.
- Michael Irvin (football player): Was arrested in 1996 for cocaine possession and sentenced to four years' probation. He was suspended by the National Football League for five games

Caffeine

- Caffeine is a naturally occurring substance, found in over 60 different plants and is a stimulant and mild diuretic. It is the most commonly used drug in the world as it is found in coffee, tea, chocolate (and chocolate based drinks) and many carbonated and energy drinks.
- Up until 2004 caffeine was on the prohibited substances list, with athletes being limited to a urine level below 12 micrograms per millilitre. This is equivalent to 6-8 cups of coffee (600-800mg). Performance enhancing effects have since been proven at a much lower intake, between 2-4 cups of coffee (200-400mg).

Caffeine

- WADA (World Anti-Doping Agency) are currently monitoring the usage of caffeine by athletes, as it has been suggested that since it was removed from the prohibited list, its use has dramatically increased. If this is the case, WADA must decide whether to reinstate the ban and if the permitted threshold should be lowered.
- Of course the other option is to put a complete ban on the use of caffeine, this would however be impossible due to caffeine staying in the system up to 48 hours. Therefore an athlete would not be able to have a cup of coffee or an energy drink within 48 hours of a competition. Random drug testing makes this even less feasible.

Caffeine

- WADA (World Anti-Doping Agency) are currently monitoring the usage of caffeine by athletes, as it has been suggested that since it was removed from the prohibited list, its use has dramatically increased. If this is the case, WADA must decide whether to reinstate the ban and if the permitted threshold should be lowered.
- Of course the other option is to put a complete ban on the use of caffeine, this would however be impossible due to caffeine staying in the system up to 48 hours. Therefore an athlete would not be able to have a cup of coffee or an energy drink within 48 hours of a competition. Random drug testing makes this even less feasible.

Who would not test positive for Caffeine?

Narcotics

- Narcotics are derived from the opium poppy and include the commonly known painkillers morphine, diamorphine and pethidine.
- Narcotics are used in medicine to reduce moderate to severe pain.

Narcotics

- Narcotics have no ergogenic or performance enhancing qualities. Athletes use Narcotics to mask pain caused by musculoskeletal injury, allowing them to compete
- it is for this reason that they are listed as banned substances in competition but are permitted when out of competition.

Snail Venom Inspires Powerful Pain Reliever

The new drug could be the most promising painkiller since morphine was introduced.

In the nervous system, communication can be stopped by blocking certain ion channels. These channels open to let a chemical signal travel from neuron to neuron. Eventually the signal reaches a muscle cell that tells it to contract. This is how you can bend your finger and kick a ball. Cone snail toxins, called conotoxins, block these channels. When the channels are blocked, communication in the nervous system stops. This causes paralysis.



PRIALT

PRIALT contains ziconotide, a synthetic equivalent of a naturally occurring conopeptide found in the piscivorous marine snail, *Conus magus*. Ziconotide is a 25 amino acid, polybasic peptide

PRIALT is the only non-opioid intrathecal (IT) therapy approved for severe chronic pain.

Athletes are using to mask the pain due to injuries

Reference: <http://www.prialt.com/>

Cannabinoids

- Cannabinoids are a compound contained in the Marijuana plant and its products. The cannabinoid compound contains a substance called THC which has psychoactive properties. Due to the fast absorption rate of THC by the lungs, cannabinoids have a rapid onset, with the effect on the central nervous system being obvious within 20 minutes with duration lasting 4-6 hours.
- Cannabinoids can be detected in the urine of an occasional user for up to a week following use, and much longer for regular users.

Cannabinoids

- Cannabinoids have no positive effects on performance and in fact can be detrimental. Prolonged use can cause 'amotivational' syndrome causing the user to lose focus and determination to succeed.
- It is their analgesic (pain relief) properties which make Cannabinoids prohibited in competition.
- But prior to 1998 it was not on the list of performance enhancing substances
- What happened in 1998?

Canadian Snowboarder Retains Olympic Gold Medal After Testing Positive For Marijuana



Image courtesy of [Rachael Ashe Photo](#). CC-BY

Canadian snowboarder Ross Rebagliati, 26, won the men's giant slalom on February 8 in the Olympic Winter Games in Nagano, Japan. After Rebagliati tested positive for marijuana -- 17.8 nanograms of metabolite per milliliter -- the International Olympic Committee (IOC) stripped him of his gold medal on February 10. The following day, the IOC returned the medal, saying it did not have the power to take it

Amphetamines

- A nervous system stimulant and appetite suppressant.
- Used to to treat hyperactive children, sleep disorders and depression.
- To increase energy and focus.

Tour de France: Whatever it takes

Enthusiasts say the Tour de France is the biggest, hardest, most grueling race there is, a prize so precious that cyclists will do anything to win. And they have.

In the past, riders have scattered broken glass and fans have tossed nails on the road to confound rivals. And that's just for starters.

In the 1960s, riders attempted to gain a competitive edge with amphetamines and alcohol. In doing so, Britain's Tim Simpson lost his life during the 1967 Tour.

Who has been caught using Amphetamines?

- Barry Bonds (baseball player): In 2006, tested positive for amphetamines.
- Jason Giambi (baseball player): In 2007, it was reported that he failed a drug test for amphetamines. He was subjected to counseling and increased testing.
- *It should be noted that since the 1960s, widespread, open use of amphetamine pills ("greenies") has been reported in professional baseball. Stories of bowls of pills in locker rooms and "special" pots of coffee spiked with amphetamines were common, and player usage was estimated by some as high as 85%. However, it wasn't until 2006 that Major League Baseball began testing for amphetamines.

THG: Tetrahydrogestrinone ("the Clear")

- A "designer" anabolic steroid (a steroid that acts as the hormone testosterone), created at the Bay Area Laboratory Co-operative (BALCO) to be undetectable by drug tests. Used in combination with a testosterone ointment called "the cream" to avoid detection.
- Athletic Use: To increase muscle strength and promote muscle growth.

Who has tested positive for THG?

- Barry Bonds (baseball player):
- Jason Giambi (baseball player):
- Marion Jones (track athlete):
- Shane Mosley (boxer): Used the BALCO products before his 2003 fight with Oscar De La Hoya but claims that he thought they contained legal vitamins. He has not been disciplined.
- Bill Romanowski (football player): In 2005, admitted on the TV show 60 Minutes that he'd taken "the cream" and "the clear" and HGH from 2001 to 2003. Since he'd been retired since 2003, he was not disciplined.
- Gary Sheffield (baseball player): Similar to Bonds, admitted in 2004 that in 2002 he'd applied a cream to his injured knee, unaware that it contained steroids. He was not disciplined.

Marion Jones

- Athlete profile
- Jones pleads guilty, admits lying about steroids
- Marion Jones had her gold medals stripped from her (as well as her relay teammates).

Human Chorionic Gonadotrophin (HCG)

- A hormone produced in pregnant women by the placenta.
- Used in conjunction with cycles of anabolic steroid intake to maintain levels of testosterone after the steroids cause the body to shut down testosterone production. Also helps restore testicular size after steroid cycles.

Who has been caught using HCG

- Jose Canseco (baseball player): Was caught in 2008 trying to smuggle HCG across the border from Mexico without a prescription, claiming he needed it to jump-start the testosterone in his body that had been drained from years of steroid abuse. He was sentenced to probation and was not disciplined by Major League Baseball, since he'd been retired since 2002.
- Manny Ramirez (baseball player): Tested positive in 2009, claiming he was given it for a "personal health issue." Since it was added to Major League Baseball's banned substances list in 2008, he was suspended for 50 games.

Adrenocorticotrophic Hormone (ACTH)

- Adrenocorticotrophic hormone is a polypeptide hormone produced by the pituitary gland. It is sometimes also known as Corticotrophin or Adrenocorticotrophin.
- ACTH stimulates the release of corticosteroids, glucocorticoids and steroid hormones (or androgens) from the adrenal glands.

Adrenocorticotrophic Hormone (ACTH)

- ACTH is mainly used in tests to diagnose conditions of the adrenal and pituitary glands such as: Cushing's syndrome (an endocrine disorder caused by high levels of cortisol in the blood)
- Addison's disease (an endocrine disorder where the adrenal glands produce only limited amounts of glucocorticoids)
- Congenital adrenal hyperplasia (refers to a group of inherited adrenal gland disorders)
- Nelson's syndrome (sometimes occurs following the removal of both adrenal glands as performed to treat Cushing's syndrome and is the rapid development of growths on the pituitary gland)

Adrenocorticotrophic Hormone (ACTH)

- ACTH is used by athletes in order to increase the amount of androgens secreted by the adrenal glands as these are converted to testosterone. However, use also raises cortisol levels which increases gluconeogenesis (the production of glucose) and hence raises blood glucose levels. This is achieved by the use of amino acids, transported from muscle to the liver to be converted into glucose and also a reduction in the use of glucose by the cells.
- All of this means that the positive androgenic effects are cancelled out by the catabolic effect (breakdown of muscle tissue to release amino acids) and so ACTH has no benefit and may even be detrimental to performance

Reference: <http://www.teachpe.com/drugs/acth.php>

Beta-2-Agonists

- Beta-2-Agonists are dilators which cause dilation (widening) of vessels by relaxing the smooth muscle surrounding them.
- Inhaled forms of Beta-2-agonists (including salmeterol, salbutamol, formoterol and terbutaline) are used for the treatment of Asthma and exercise-induced bronchospasm (EIB).
- Injected forms are most commonly used in the prevention of premature labour, as they act to relax the smooth muscle of the uterus and so inhibit contractions.

Beta-2-Agonists

- Inhaled forms used for the treatment of Asthma and EIB have no performance-enhancing effect and so are permitted for use by WADA (world anti-doping agency). The athlete must however be in receipt of an abbreviated therapeutic use exemption (aTUE).
- When administered by injection or tablet form they are thought to have anabolic effects (increased muscle mass, reduced body fat percentage and faster recovery rates) and so their use is prohibited.

Reference: <http://www.teachpe.com/drugs/beta2.php>

Hormone Antagonists and Modulators

- Hormone antagonists and modulators, sometimes known as anti-oestrogenic substances act to either decrease the amount of oestrogen in the body or block the oestrogen receptors.
- Some forms of Anti-oestrogenic drugs have been used in the treatment of breast cancer, contraception, osteoporosis and anovulatory infertility (infertility through cessation of ovulation).

Reference: <http://www.teachpe.com/drugs/antagonists.php>

Hormone Antagonists and Modulators

- The anti-oestrogenic drugs Tamoxifen and Clomiphene are used by both male and female athletes. Males use Tamoxifen in conjunction with Anabolic Steroids in an attempt to prevent gynecomastia (the development of oversized mammary glands in males). It is also used to increase testosterone levels.
- Female body-builders and weight lifters have been known to use Tamoxifen as blocking the oestrogen receptors leaves testosterone unopposed, leading to an increase in masculine features.

Reference: <http://www.teachpe.com/drugs/antagonists.php>

Diuretics

- Diuretics (sometimes called water pills) are drugs including Frusemide, Chlorothiazide and Hydrochlorothiazide. Their purpose is to remove excess water from the body although each type of diuretic does this in a different way.
- Diuretics are not used to enhance performance. If anything they have a detrimental effect on performance as they cause dehydration. Diuretics are used for two reasons..

Reference: <http://www.teachpe.com/drugs/diuretics.php>

Diuretics

- Firstly to loose weight rapidly in sports which require the athlete to be within a set weight limit. For example boxers and jockeys.
- Secondly, to dilute the presence of illegal substances and aid their excretion.

Gene Doping

- Gene doping or transfer is based on the principles of gene therapy. Here a healthy gene is transplanted into cells or directly into the genome to replace a mutated or absent gene. Currently this process is still in the research and trial stage.
- In future, athletes could use this process to influence their health. For instance transfer the genes which produce the hormone **IGF-1**, transported into the cells and causing the body to produce higher levels of IGF-1, important in the growth and development of musculoskeletal structures.

Gene Doping

- The detection of gene doping will be difficult, but **WADA** believe it will be possible. The detection process is likely to look for the consequences of gene doping in blood samples, rather than the gene transfer itself. For example increased presence of certain enzymes and proteins. A second possibility is the use of MRI scans to detect areas of unusual gene expression.

Reference: <http://www.teachpe.com/drugs/genes.php>

MIT OpenCourseWare

<http://ocw.mit.edu>

ES.010 Chemistry of Sports

Spring 2013

For information about citing these materials or our Terms of Use, visit: <http://ocw.mit.edu/terms>.