HGH TESTING IN THE NFL: IS THE SCIENCE READY?

HEARING

BEFORE THE

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED TWELFTH CONGRESS

SECOND SESSION

DECEMBER 12, 2012

Serial No. 112–192

Printed for the use of the Committee on Oversight and Government Reform

Available via the World Wide Web: http://www.fdsys.gov
http://www.house.gov/reform

U.S. GOVERNMENT PRINTING OFFICE

77–683 PDF WASHINGTON : 2012

For sale by the Superintendent of Documents, U.S. Government Printing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512–1800; DC area (202) 512–1800
Fax: (202) 512–2104 Mail: Stop IDCC, Washington, DC 20402–0001

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

DARRELL E. ISSA, California, *Chairman*

DAN BURTON, Indiana
JOHN L. MICA, Florida
TODD RUSSELL PLATTS, Pennsylvania
MICHAEL R. TURNER, Ohio
PATRICK T. MCHENRY, North Carolina
JIM JORDAN, Ohio
JASON CHAFFETZ, Utah
CONNIE MACK, Florida
TIM WALBERG, Michigan
JAMES LANKFORD, Oklahoma
JUSTIN AMASH, Michigan
ANN MARIE BUERKLE, New York
PAUL A. GOSAR, Arizona
RAÚL R. LABRADOR, Idaho
PATRICK MEEHAN, Pennsylvania
SCOTT DESJARLAIS, Tennessee
JOE WALSH, Illinois
TREY GOWDY, South Carolina
DENNIS A. ROSS, Florida
BLAKE FARENTHOLD, Texas
MIKE KELLY, Pennsylvania
VACANCY

ELIJAH E. CUMMINGS, Maryland, *Ranking Minority Member*
EDOLPHUS TOWNS, New York
CAROLYN B. MALONEY, New York
ELEANOR HOLMES NORTON, District of Columbia
DENNIS J. KUCINICH, Ohio
JOHN F. TIERNEY, Massachusetts
WM. LACY CLAY, Missouri
STEPHEN F. LYNCH, Massachusetts
JIM COOPER, Tennessee
GERALD E. CONNOLLY, Virginia
MIKE QUIGLEY, Illinois
DANNY K. DAVIS, Illinois
BRUCE L. BRALEY, Iowa
PETER WELCH, Vermont
JOHN A. YARMUTH, Kentucky
CHRISTOPHER S. MURPHY, Connecticut
JACKIE SPEIER, California

LAWRENCE J. BRADY, *Staff Director*
JOHN D. CUADERES, *Deputy Staff Director*
ROBERT BORDEN, *General Counsel*
LINDA A. GOOD, *Chief Clerk*
DAVID RAPALLO, *Minority Staff Director*

CONTENTS

HGH TESTING IN THE NFL: IS THE SCIENCE READY?

Wednesday, December 12, 2012

HOUSE OF REPRESENTATIVES,
COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM,
Washington, D.C.

The committee met, pursuant to call, at 10:05 a.m., in Room 2154, Rayburn House Office Building, Hon. Darrell E. Issa [chairman of the committee] presiding.

Present: Representatives Issa, Jordan, Chaffetz, Walberg, Gosar, DesJarlais, Gowdy, Farenthold, Cummings, Towns, Maloney, Tierney, Clay, Connolly, Quigley, and Speier.

Also Present: Representative Lummis.

Staff Present: Alexia Ardolina, Assistant Clerk; Alexa Armstrong, Staff Assistant; Will L. Boyington, Staff Assistant; Molly Boyl, Parliamentarian; Lawrence J. Brady, Staff Director; Sharon Casey, Senior Assistant Clerk; Steve Castor, Chief Counsel, Investigations; John Cuaderes, Deputy Staff Director; Carlton Davis, Counsel; Adam P. Fromm, Director of Member Services and Committee Operations; Linda Good, Chief Clerk; Frederick Hill, Director of Communications and Senior Policy Advisor; Michael R. Kiko, Staff Assistant; Mark D. Marin, Director of Oversight; John Ohly, Professional Staff Member; Ashok M. Pinto, Deputy Chief Counsel, Investigations; Mary Pritchau, Professional Staff Member; Scott Schmidt, Deputy Director of Digital Strategy and Press Secretary; Jonathan J. Skladany, Counsel; Rebecca Watkins, Deputy Director of Communications; Jaron Bourke, Minority Director of Administration; Beverly Britton Fraser, Minority Counsel; Ashley Etienne, Minority Director of Communications; Jennifer Hoffman, Minority Press Secretary; Carla Hultberg, Minority Chief Clerk; Adam Koshkin, Minority Research Assistant; Elisa LaNier, Minority Deputy Clerk; Lucinda Lessley, Minority Policy Director; Dave Rapallo, Minority Staff Director; Rory Sheehan, Minority New Media Press Secretary; and Donald Sherman, Minority Counsel.

Chairman ISSA. The committee will come to order.

The Oversight Committee exists to secure two fundamental principles. First, Americans have a right to know that the money Washington takes from them is well-spent. And, second, Americans deserve an efficient, effective government that works for them. Our duty on the Oversight and Government Reform Committee is to protect these rights.

Our solemn responsibility is to hold government accountable to taxpayers because taxpayers have a right to know what they get from their government. It is our job to work tirelessly in partner-

ship with citizen watchdogs to deliver the facts to the American people and bring genuine reform to the Federal bureaucracy.

Our committee's resources are limited, but in one area we have focused for more than 6 years, and that is taking drugs and dangerous substances out of professional sports. We do so on a bipartisan reason—bipartisan basis, and we do so because, in fact, what professional sports do is what collegiate sports do and it is what children aspire to do. We cannot take professional sports in isolation because ultimately it trickles down to the youngest.

When we began our work on a bipartisan basis on steroids in baseball, steroids had become common at the high school level. Today I believe it is dramatically reduced but not eliminated.

On their own, with some push from Congress, the National Football League signed a historic union agreement that banned human growth hormone from professional football. They did so with a time limit that would have, in fact, put it in play last season. We are now finishing this season, and no such implementation has occurred.

This committee, under Ranking Member Cummings and myself, has met on multiple occasions with the parties, encouraged them to work out their differences, and supported each of their agreements to try to bring the contract into compliance.

We are here today because, in fact, it hasn't happened, because America is watching, and because both the ranking member and myself are personally concerned that the injuries, particularly head injuries, that continue to plague professional sports—professional football and all football played at all levels in no small part is based on the strength of the players hitting each other. Human growth hormones can, in fact—and we will hear testimony to this extent—be a part of this. It is a tough sport when played honestly by people of good, solid training and physical conditioning; we need not make it tougher or more dangerous by the use of banned substances.

This committee is here today to hear from the parties who can, in fact, help us with the science and from one well-known player who knows the science personally, as it impacted on him time and time again.

It is our hope that this hearing will move the parties closer together or at least have the American people clearly understand that, in fact, it needs to happen, that much of the science has been not just done but redone in support of it happening, and that if we are to have the kind of clean game that Americans love, this has to be an element of the testing.

So, with that, I want to thank all of our witnesses, but I particularly want to thank the ranking member. This has been one of those examples in which there has not only been bipartisan behavior but there has been completely nonpartisan behavior. Never have we had a closer tie than the ranking member and I have on this issue, and I want to thank him for his leadership, and yield.

Mr. CUMMINGS. I want to thank you, Mr. Chairman, for your words. And I agree with you totally.

I want to make sure that the league understands this, that our players understand this, that the union understands this: There is no daylight, in the words of the chairman, between his position and

mine. This is a bipartisan effort, and I am very delighted that it is because I think it is so very important.

Thank you, Mr. Chairman, and thanks to all of our witnesses for being here.

Today's hearing is not only about the NFL, it is not only about human growth hormone; this hearing is about millions of young people throughout this country in high school and college who look up to professional athletes and the lengths to which these young people go to emulate their role models.

Let me tell you about some of the young people in my district 40 miles away from here in Baltimore, many of whom come from very challenging backgrounds and from very difficult home situations. They have dreams about making it as lawyers, engineers, teachers, and maybe even a Congressman. I have seen their smiling faces at graduation. I see them at the bus stops at 6 o'clock in the morning trying to get to practice. I see them coming home late from practice. They tell me about burning the late hours doing homework, dead tired. They are dedicated, they are smart, and they have amazing potential.

But that word, "potential," is a very significant word. I have often said that our children are the living messages we send to a future we will never see. The question is whether we will send them there with diabetes, will we send them there with heart disease, will we send them there with mental problems.

Some of these young people dream about becoming ballplayers and succeeding beyond their wildest expectations. And when they see a freshman become the Heisman Trophy winner, they feel that is within reach.

When I meet these young people, I share the same advice my parents gave me; that is, there are no shortcuts in life. If they want to become a successful entrepreneur, a best-selling author, or a Pro Bowl linebacker for the Baltimore Ravens, they have to put in the work to reach their goals.

But when they see their role models in sports using illegal drugs to try to get an edge and when they see the professional leagues looking the other way, refusing to test and going easy on abusers, they start thinking they need to use these substances just to compete.

And so that there will be no confusion, I must credit Commissioner Goodell for his efforts, not only with regard to protecting players, but he has also been one who has been pushing to make sure that this happens. And he said that to the chairman and I, and I want to make sure that is clear, that he has been very adamant about this.

These young people, they start thinking and they have high expectations, and they are reaching.

HGH is a dangerous drug with both short-term and long-term risks. Let me read just a few of the negative health effects of HGH: hypertension, diabetes, arthritis, bone spurs, spinal stenosis, disfigurement, and cardiac dysfunction. These come directly from a scientific journal article published in April of this year.

Mr. Chairman, I ask that this study be placed into the record.

Chairman ISSA. Without objection, so ordered.

Mr. CUMMINGS. Thank you very much.

There is no serious dispute in the scientific community that the test to detect HGH abuse is effective. This test, which has been in place for the past decade, is actually designed to be conservative in order to avoid false positives. As one of our witnesses will testify today, you are more likely to get struck by lightning than to get a false positive on an HGH test.

There is also no dispute that on August 4th, as the chairman has said, 2011, more than a year ago, the NFL Players Association entered into a contract to begin testing NFL players for HGH, quote, "by the first week of the 2011 regular season." As we all know, that season passed without any HGH testing, and now the 2012 season will also pass without it.

Despite their commitment, lawyers for the Players Association now say they do not trust the HGH test. Although it has been used for years on Olympic athletes, Major League Baseball players, and a host of other athletes, they argue that the NFL players are somehow different. They claim that their bodies are not the same as wrestlers, runners, weightlifters, and thousands of other athletes who are tested regularly. They say they need more time to study this issue before doing what they agreed to do.

To me, it seems obvious that the Players Association is simply running out the clock. Although they agreed to the HGH testing, they are now trying to back out of the contract. Well, today we will have the opportunity to hear directly from medical experts, and we will examine the claims of the Players Association under the bright light of science.

Finally, let me address one point that has been raised, which is why Congress is getting involved in this issue. I am sure the chairman agrees with me that this dispute should be resolved by the NFL and the Players Association. We wish it could be or would be. They have a contract, and they should honor it. But when they refuse to do so, that sends exactly the wrong message to the kids we have sworn to protect, and that is when it becomes our business.

Finally, on a personal level, I have worked on this issue for most of my life in public service. I have helped with the formation of a group in Baltimore in 2007 called Powered By Me that has reached more than 30,000 young athletes, coaches, and parents, warning them about the dangers of these substances. The group's director, Mike Gimbel, has spearheaded efforts to prevent young athletes from being brainwashed by the mantra of, quote, "winning at all costs." I am very thankful he is testifying today.

And, again, Mr. Chairman, I cannot tell you how grateful I am to you for the cooperation that we have had on this issue, and I am looking forward to moving forward.

And another thing that keeps coming up, Mr. Chairman, and you may address this later on, people just—I keep being asked the question, well, why are you just having the experts here today? Why don't you have the NFL and the players? And I have told people, and you can expound on this later I guess, that this may be very well the first of several hearings and that we wanted to get the science out and the effect that it is having on our young people.

And with that, Mr. Chairman, I want to thank you for your courtesy, and I yield back.

Chairman ISSA. I thank the gentleman.

Chairman ISSA. I might note, I am not recognizing the only football player here on the dais, but that was only because my understanding is they threw a flag anytime he was hit during his——

Mr. CHAFFETZ. Now, point of clarification. I was a placekicker, not an actual football player.

Chairman ISSA. All the more reason not to recognize him.

Mr. CHAFFETZ. Thank you. We will go win the game at the end, but——

Chairman ISSA. And since we are being very bipartisan, I want to remind the ranking member that we share the Baltimore Ravens since I was born and raised in Cleveland.

Mr. CUMMINGS. That was cold.

Chairman ISSA. It was cold. You can keep Modell, though.

We now welcome our witnesses: Mr. Dick Butkus, an NFL Hall of Famer who leads the organization I Play Clean, which encourages student athletes to play sports without performance-enhancing drugs.

Welcome.

Dr. Larry Bowers is the chief science officer of the U.S. Anti-Doping Agency, very important to today's hearing.

Dr. Larry Tabak is the deputy director of the National Institutes of Health and an expert in this field.

Mr. Mike Gimbel is director of Powered By Me at St. Joseph Medical Center.

And Dr. Linn Goldberg is head of the Division of Health Performance and Sports Medicine and director of the Human Performance Laboratory at the Oregon Health and Science University.

Pursuant to our committee rules and because we absolutely want people to know that we treat everyone equally, would you please all rise to take the oath and raise your rights hands?

This is the photo moment you have all waited for.

Do you solemnly swear or affirm that the testimony you are about to give will be the truth, the whole truth, and nothing but the truth?

Please be seated.

Let the record reflect that all witnesses answered in the affirmative.

As the ranking member said, today really is about the science and a lead-in to what will, if necessary, be a series of hearings until in fact this issue is resolved.

So there is a full panel. I would ask that since your entire opening statements will be placed in the record, that if you run short of time, as the former chairman used to say, you know, it is green, we know that means go; yellow, that means go real fast through the intersection; and stop means don't run it anymore. So if you will come as close to that 5 minutes as possible, we would appreciate it.

Dr. Tabak?

STATEMENT OF LAWRENCE A. TABAK, DDS, PH.D.

Dr. TABAK. Good morning, Chairman Issa, Ranking Member——

Chairman ISSA. Oh, the other thing is that these microphones, in order not to get people behind you into the conversation, you have to get them as close as possible. Thank you.

Dr. TABAK. Well, again, good morning, Chairman Issa, Ranking Member Cummings, and distinguished members of the committee. I am here today to describe our understanding of the state of the science pertaining to the nonmedical use of recombinant human growth hormone, which I will refer to as HGH, including its adverse effects, and to discuss the prevailing method for detecting illicit use of recombinant HGH in professional sports.

HGH is a natural product of the pituitary gland with essential roles in human development. Much of our current understanding about the physiological and psychological effects of HGH on the human body comes from decades of studying and treating patients suffering from growth hormone disorders. NIH has a long history of supporting breakthrough research to understand and treat the often devastating effects of deficient or excessive function of the growth hormone system.

Human growth hormone therapies became a mainstay of modern medicine, particularly after development in 1985 of a safe and reliable source of recombinant HGH, a synthetic protein produced by DNA technology that has a sequence identical to that of the primary pituitary-derived HGH.

HGH can stimulate tissue growth, linear growth, and metabolism. It promotes fat loss and increases lean body mass. The FDA has approved recombinant HGH for a number of clinical indications associated with growth hormone deficiency in both adults and children. In patients with growth hormone deficiency, recombinant HGH administration improves aspects of exercise capacity, and some studies have suggested that it improves mood.

Given the well-documented ability of recombinant HGH to spur tissue buildup and burn fat, some athletes began abusing recombinant HGH in an attempt to enhance their performance.

Further increasing the appeal for competitive athletes is the fact that it also stimulates the production of another hormone, insulin-like growth factor-1, that inhibits breakdown of proteins. There are claims that inhibiting protein breakdown can help prevent some of the muscle and tendon damage that results from the chronic abuse of anabolic steroids. This effect is unproven, but it may explain why recombinant HGH is often used in combination with anabolic steroids at high doses for several months, a phenomenon that is bound to complicate our understanding of any potential consequences of the nonmedical use of recombinant HGH.

Studies performed to date have found little or no evidence that increased lean body mass that can result from using unnaturally high doses of recombinant HGH have any effects on boosting strength, power, or aerobic capacity in healthy individuals. Nonmedical use of recombinant HGH might actually decrease performance by increasing exercise-induced buildup of lactic acid in muscles, which promotes muscular fatigue, cramps, and soreness.

Based on well-documented evidence of the side effects of recombinant HGH administration to adults with growth hormone deficiency, athletes who abuse recombinant HGH are putting themselves at serious risk.

Although much of what we know about the adverse effects associated with high-dose recombinant HGH abuse is derived from individual case reports, anecdotal evidence or therapeutic records, what we know about the biology of recombinant HGH, and the long clinical history of treating patients with it points to a worrisome list of possible adverse consequences, including development of some of the features of acromegaly, as well as risks for developing hypoglycemia, diabetes, cardiomyopathy, drug-induced hepatitis, renal failure, soft tissue edema, joint pain, carpal tunnel syndrome, and increased fatigue.

The available information suggests that athletes who dose themselves with recombinant HGH are taking serious risks with their health and may not realize that there is no scientific evidence that the practice will improve their performance or resilience in competition.

Knowledge of the potentially adverse health consequences associated with recombinant HGH abuse has prompted efforts to develop and deploy a sensitive, reliable method for testing of the illicit use. The development of a test provided some formidable challenges, but these technical obstacles have been overcome with the development of several testing approaches.

And I see the time is up, and I will stop at this point.

Chairman ISSA. Thank you. And thanks for being such a good steward of time.

[Prepared statement of Dr. Tabak follows:]

Good morning Chairman Issa, Ranking Member Cummings, and distinguished members of the Committee. My name is Dr. Lawrence Tabak, and I am the Principal Deputy Director of the National Institutes of Health. We understand the public health significance of the issue you are exploring – human growth hormone (hGH) testing in the NFL – and are pleased to participate in this hearing to describe our understanding of the state of the science pertaining to the non-medical use of recombinant hGH (rhGH), including its adverse effects, and to discuss the prevailing method for detecting illicit use of rhGH in professional sports.

HGH is a natural product of the pituitary gland with essential roles in human development. Much of our current understanding about the physiological and psychological effects of hGH on the human body comes from decades of studying and treating patients suffering from growth hormone disorders. NIH has had a long history of supporting breakthrough research to understand and treat the often devastating effects of deficient (*e.g.*, hypogonadism) or excessive (*e.g.*, pituitary tumors) function in the growth hormone system.

Human growth hormone therapies have become a mainstay of modern medicine, particularly after the development, in 1985, of a safe and reliable source of rhGH, a synthetic protein produced by recombinant deoxyribonucleic acid (DNA) technology that has a sequence identical to that of the primary pituitary-derived hGH. The hGH can stimulate tissue growth, linear growth (height), and protein, carbohydrate, lipid, and mineral metabolism. It promotes fat loss and increases lean body mass. The FDA has approved rhGH for a number of clinical indications associated with growth hormone deficiency in both adults and children, including the treatment

of short stature, chronic renal insufficiency, and several genetic or congenital disorders, such as Turner, Noonan, and Prader-Willi syndromes. In patients with growth hormone deficiency, rhGH administration improves aspects of exercise capacity and some studies have suggested that it improves mood, including low energy and psychiatric comorbidities like general anxiety disorder and depression (1-3).

Given the well-documented ability of rhGH to spur tissue build up and burn fat, some athletes began abusing rhGH (non-medical use is defined as abuse) in an attempt to enhance their performance. Further increasing the appeal of rhGH for competitive athletes is the fact that it also stimulates production of another hormone (Insulin-like growth Factor-1 (IGF-1)) that inhibits the breakdown of proteins. There are claims that inhibiting protein breakdown can help prevent some of the muscle and tendon damage that results from chronic abuse of anabolic steroids. This effect is unproven but it may explain why rhGH is reportedly often used in combination with anabolic steroids at high doses and for several months (4, 5), a phenomenon that is bound to complicate our understanding of any potential consequences of non-medical rhGH use.

While the evidence shows that hGH spurs tissue build up and burns fat, the studies performed to date found little or no evidence that the increased lean body mass that can result from using unnaturally high doses of rhGH has any effects on boosting strength, power, or aerobic capacity in healthy individuals (6-8). Non-medical use of rhGH might actually decrease performance by increasing exercise-induced buildup of lactic acid in the muscles, which promotes muscular

fatigue, cramps, and soreness. Based on well-documented evidence of the side effects of rhGH administration to adults with growth hormone deficiency (9), athletes who abuse rhGH are putting themselves at risk of these same adverse consequences. Moreover, it is estimated that athletes are taking doses that are up to 10 times higher than those used therapeutically (10).

Although much of what is known about the adverse effects associated with high-dose rhGH abuse is derived from individual case reports, anecdotal evidence, or therapeutic records, what we know about the biology of rhGH and long clinical history of treating patients with it point to a worrisome list of possible adverse consequences. For example, athletes who chronically use rhGH for non-medical reasons may develop some of the features of acromegaly (or adult onset gigantism) (10). They are also at risk for developing hypoglycemia and diabetes, cardiomyopathy, drug-induced hepatitis, renal failure, soft tissue edema, joint pain, carpal tunnel syndrome, and increased fatigue.

The available information suggests that athletes who dose themselves with rhGH are taking serious risks with their health. Moreover, they may not realize that there is no scientific evidence that the practice will improve their performance or resilience in competition.

Knowledge of a) the potentially adverse health consequences associated with rhGH abuse, b) the "asterisk" epidemic that has compromised the outcomes in sports and c) the use of rhGH and other performance-enhancing drugs among teenagers (8, 11), prompted efforts to develop and deploy a sensitive, reliable method for testing of illicit use of rhGH.

The development of such a test presented a formidable challenge, for several reasons:

1) the predominant naturally-occurring form of hGH and its recombinant version are virtually indistinguishable,
2) normal concentrations of circulating hGH fluctuate widely throughout the day, and
3) hGH concentrations in urine are low and do not necessarily correlate with blood concentrations.

These technical obstacles have been overcome with the development of several testing approaches. The predominant method in use relies on a smart cocktail of specific antibodies that recognize and specifically bind to different versions (isoforms) of hGH and compares their abundance to that of the only isoform (the 22kD) that is identical to the recombinant version relative to all other naturally occurring isoforms. A positive test would be one in which the ratio of the 22kD isoform relative to the other isoform falls above a previously established threshold or reference range based on results from a demographically diverse population.

Based on most published reviews, the scientific validity and robustness of this test has been upheld by numerous studies, carried out around the world by hGH experts and with different populations. Questions can always be raised about whether a given test, even one whose reliability has been established under most circumstances, also has *universal* validity. In this case, the ability of the test to approach universal validity hinges on how the reference range has

been established. In science, universal validity is almost never achievable for reasons I will now explain.

There is a well-known but small inter-individual variability in the hGH system within the athletic population, which could theoretically affect the universal applicability of the reference range (12, 13). However, based on the existing literature, over 90 percent of that variability can be explained just by age and gender differences, making a positive test unlikely to be the result of chance variability (14). And yet, the job of a scientist is to acknowledge the possibility, even if remote, of gaps in our knowledge that could change the prevailing view. For example, greater bone mineral density in adult African American men compared with White males has been associated with greater hGH secretion (15, 16). While this observation does not diminish the rigorously demonstrated and widely accepted validity of the test as currently deployed, it does point to the kind of complexities and confounders that scientists always try to take into account when developing a new clinical test.

I thank you for this opportunity to provide you with testimony.

References

1. Maric NP, Doknic M, Pavlovic D, Pekic S, Stojanovic M, Jasovic-Gasic M *et al.* Psychiatric and neuropsychological changes in growth hormone-deficient patients after traumatic brain injury in response to growth hormone therapy. *J Endocrinol Invest* 2010 Dec; **33**(11): 770-775.

2. Arwert LI, Deijen JB, Muller M, Drent ML. Long-term growth hormone treatment preserves GH-induced memory and mood improvements: a 10-year follow-up study in GH-deficient adult men. *Horm Behav* 2005 Mar; **47**(3): 343-349.

3. Chaplin JE, Kristrom B, Jonsson B, Hagglof B, Tuvemo T, Aronson AS *et al.* Improvements in behaviour and self-esteem following growth hormone treatment in short prepubertal children. *Horm Res Paediatr* 2011; **75**(4): 291-303.

4. Parkinson AB, Evans NA. Anabolic androgenic steroids: a survey of 500 users. *Med Sci Sports Exerc* 2006 Apr; **38**(4): 644-651.

5. Perry PJ, Lund BC, Deninger MJ, Kutscher EC, Schneider J. Anabolic steroid use in weightlifters and bodybuilders: an internet survey of drug utilization. *Clin J Sport Med* 2005 Sep; **15**(5): 326-330.

6. Birzniece V, Nelson AE, Ho KK. Growth hormone administration: is it safe and effective for athletic performance. *Endocrinol Metab Clin North Am* 2010 Mar; **39**(1): 11-23, vii.

7. Liu H, Bravata DM, Olkin I, Friedlander A, Liu V, Roberts B *et al.* Systematic review: the effects of growth hormone on athletic performance. *Ann Intern Med* 2008 May 20; **148**(10): 747-758.

8. Calfee R, Fadale P. Popular ergogenic drugs and supplements in young athletes. *Pediatrics* 2006 Mar; **117**(3): e577-589.

9. Powrie J, Weissberger A, Sonksen P. Growth hormone replacement therapy for growth hormone-deficient adults. *Drugs* 1995 May; **49**(5): 656-663.

10. Holt RI, Sonksen PH. Growth hormone, IGF-I and insulin and their abuse in sport. *Br J Pharmacol* 2008 Jun; **154**(3): 542-556.

11.

11. Rickert VI, Pawlak-Morello C, Sheppard V, Jay MS. Human growth hormone: a new substance of abuse among adolescents? *Clin Pediatr (Phila)* 1992 Dec; **31**(12): 723-726.

12. Erotokritou-Mulligan I, Bassett EE, Cowan DA, Bartlett C, McHugh C, Sonksen PH *et al.* Influence of ethnicity on IGF-I and procollagen III peptide (P-III-P) in elite athletes and its effect on the ability to detect GH abuse. *Clin Endocrinol (Oxf)* 2009 Jan; **70**(1): 161-168.

13. Holt RI, Bassett EE, Erotokritou-Mulligan I, McHugh C, Cowan D, Bartlett C *et al.* Moving one step closer to catching the GH cheats: The GH-2004 experience. *Growth Horm IGF Res* 2009 Aug; **19**(4): 346-351.

14. Erotokritou-Mulligan I, Eryl Bassett E, Cowan DA, Bartlett C, Milward P, Sartorio A *et al.* The use of growth hormone (GH)-dependent markers in the detection of GH abuse in sport: Physiological intra-individual variation of IGF-I, type 3 pro-collagen (P-III-P) and the GH-2000 detection score. *Clin Endocrinol (Oxf)* 2009 Apr; **72**(4): 520-526.

15. Wright NM, Renault J, Willi S, Veldhuis JD, Pandey JP, Gordon L *et al.* Greater secretion of growth hormone in black than in white men: possible factor in greater bone mineral density--a clinical research center study. *J Clin Endocrinol Metab* 1995 Aug; **80**(8): 2291-2297.

16. Bell NH, Gordon L, Stevens J, Shary JR. Demonstration that bone mineral density of the lumbar spine, trochanter, and femoral neck is higher in black than in white young men. *Calcif Tissue Int* 1995 Jan; **56**(1): 11-13.

Chairman ISSA. Dr. Bowers?

STATEMENT OF LARRY BOWERS, PH.D.

Mr. BOWERS. Good morning, Mr. Chairman and members of the committee. My name is Dr. Larry Bowers. I am the chief science officer of the U.S. Anti-Doping Agency. I would like to thank you for this opportunity to testify about the science behind growth hormone testing.

I have been involved in the development of tests for the abuse of growth hormone since 1999. I was the director of the Athletic Drug Testing and Toxicology Laboratory at Indiana University, at the time one of only two International Olympic Committee testing laboratories in the U.S.

USADA has been recognized by Congress as the independent national anti-doping agency for Olympic, Paralympic, and Pan American sport in the United States. USADA's mission is to protect and preserve the health of athletes, the integrity of competition, and the wellbeing of sports through the elimination of doping. Since its inception, USADA has been an advocate for clean athletes.

When Congress approved the medical use of growth hormone, the law expressly stated that it was only to be distributed for conditions specifically authorized by the Secretary of Health and Human Services, making potentially dangerous off-label uses, such as performance enhancement, illegal.

The isoform growth hormone test has been developed by well-respected researchers in the growth hormone research community. It is a blood test that has been used to detect the prohibited use of growth hormone on a limited basis since 2004 and on a worldwide basis since 2008.

The test measures the ratio of the form of growth hormone found in recombinant or synthetic products to other forms of growth hormone that are naturally released by the pituitary gland. The ratio is independent of the amount of growth hormone in the blood. You are just as likely to have a ratio of 0.8 at low concentrations of growth hormone as you are to have a ratio of 0.8 at high concentrations of growth hormone. When you take recombinant synthetic growth hormone, the ratio increases dramatically.

The method has been the subject of four peer-reviewed publications, has been the subject of numerous conferences and working group meetings that have involved growth hormone experts.

WADA has been given the responsibility for harmonizing and improving tests by the World Anti-Doping Code and the UNESCO Convention, which was approved by Congress. A very conservative threshold or decision limit was established for this isoform test. The chances of an athlete who has not used synthetic growth hormone testing positive are comparable to the chance that that same athlete has of being struck by lightning during his or her lifetime.

Mr. Chairman, the conservative nature of the threshold has been borne out by nearly 13,000 growth hormone isoform tests that have been performed globally. There have been 11 positive tests, and 8 of those individuals admitted use. The remaining three cases are in various stages of arbitration and appeal at this time.

In addition, Major League Baseball has conducted approximately 1,700 growth hormone isoform tests in its minor league players

during the season and for the major league players during spring training. One minor league player tested positive and admitted growth hormone use. Since 2008, USADA has conducted 1,387 growth hormone isoform tests. Of these tests, 99 percent were well below the decision limit that has been established.

It has been suggested by the NFL Players Association that NFL players are sufficiently different from other elite athletes with regard to size and ethnicity that an additional population study be done. Mr. Chairman, in my scientific opinion, an additional population study is unnecessary because each of the concerns that have been expressed have already been raised and answered by the growth hormone experts.

Does the current test take the size of athletes into account? Yes. And it was determined that the size of an individual has no relation to the ratio of growth hormone isoforms measured by the test.

Does the test accurately take into account growth hormone isoform ratio differences that may be attributed to an athlete's race or ethnicity? Yes. And the conservative approach that I described reflects that consideration.

Does the test take into consideration the effect of strenuous exercise on growth hormone isoforms? Yes. To the extent growth hormone isoform ratios are affected by exercise, it has been determined that it is minor and it disappears within 30 minutes of the end of exercise.

In conclusion, I would like to point out that the only people who are still questioning the methodology and validity of the growth hormone isoform test are lawyers, not scientists. The test has been not only put into use in Olympic sport but in Major League Baseball as well. The experts who work in the growth hormone field every day, both inside and outside of the anti-doping community, have universally accepted and recognized that the isoform test is scientifically reliable and appropriate for the detection of growth hormone abuse in sport.

Once again, I would like to express my thanks and my appreciation to the committee for having me here to testify.

Chairman ISSA. Thank you.

[Prepared statement of Mr. Bowers follows:]

Good morning, Mr. Chairman and members of the Committee. My name is Doctor Larry Bowers and I am Chief Science Officer of the United States Anti-Doping Agency (USADA). Prior to joining USADA in 2000, I was a professor for 24½ years at the University of Minnesota and Indiana University Medical Centers where I conducted (and published) research on drug metabolism and cutting edge analytical approaches to drug and metabolite detection. From 1992 to 2000, I was also the Director of the Athletic Drug Testing and Toxicology Laboratory at Indiana University, one of only two laboratories in the United States that was accredited by the International Olympic Committee at that time.

USADA has been recognized by Congress as the independent, national anti-doping agency for Olympic, Paralympic and Pan American sport in the United States, and we receive a portion of our funding from an appropriation from the Office of National Drug Control Policy. Our mission, at USADA, is to protect and preserve the health of athletes, the integrity of competition, and the well-being of sport through the elimination of doping. Since its inception, USADA has been an advocate for clean athletes and I would like to thank you, on behalf of USADA and the millions of athletes that USADA represents, for this opportunity to testify about and discuss the science behind growth hormone testing.

Human growth hormone is a performance enhancing drug that has been used by athletes to cheat in sport for over twenty years. Growth hormone is a naturally occurring substance responsible for a number of physiological actions that can be used, in its synthetic form, by athletes to increase skeletal muscle mass, decrease weight, enhance delivery to the tissues of nutrients necessary to build or repair tissue, and alter energy metabolism. There are also indications that growth hormone is frequently used in conjunction with other performance enhancing drugs, like steroids.

Over the last decade, as "anti-aging" clinics and practitioners touting the perceived benefits of growth hormone have become more commonplace, the use of growth hormone by healthy individuals has increased substantially. Interestingly, when Congress approved the medical use of growth hormone, the law expressly stated that it was only to be distributed for indications specifically authorized by the Secretary of Health and Human Services, making potentially dangerous off-label uses, such as performance-enhancement, illegal. Unfortunately, the potential adverse side effects of growth hormone abuse, such as an increased risk of diabetes or glucose intolerance, carpal tunnel syndrome, joint pain, muscle pain, peripheral edema, elevated triglycerides and the potential for long-term growth hormone use to cause cancer, have failed to garner as much attention as its perceived benefits and have led many

members of the public to wrongly conclude that the risks associated with growth hormone abuse are either minor or nonexistent.

There is no question that growth hormone is a drug that has been and continues to be abused by professional athletes. In 2007, the Mitchell Report detailed numerous incidences of established growth hormone abuse among Major League Baseball players going back as far as the late 1990s and up through the release of the report itself. More recently, in 2011, the Canadian sports doctor Anthony Galea pleaded guilty to smuggling unapproved drugs, including human growth hormone, into the United States to treat professional athletes. Dr. Galea's clients in the United States reportedly included NFL and MLB players, as well as professional golfers and other professional athletes.

Of course, the use of performance enhancing drugs by elite athletes is not just an issue for sports leagues, anti-doping agencies and law enforcement; it is also a public health issue for our youth. In 2010, USADA commissioned a survey of nearly 9,000 Americans in order to gain a better understanding of what Americans think about the role and significance of sport in society and to assess their views on sport ethics and values, role models, and aspirations.[1] One of the most notable findings of the study was that nearly 90% of the adults surveyed believed that well-known athletes have a responsibility to be positive role models for young people, whether those athletes like it or not, and that young people who seek to emulate the actions of professional athletes who use performance enhancing drugs will sometimes resort to the use of performance enhancing drugs themselves. Although USADA has always been involved in educational endeavors, the findings of the study prompted USADA to develop the True Sport educational initiative, which is designed to cultivate and champion sportsmanship and the positive ethical life lessons that sports teach.

If there was ever any doubt regarding the serious consequences that can result from the negative influence of elite athletes, it was resolved at the 2005 Congressional Hearings on Steroids in Baseball where witnesses testified about how their young sons lost their lives while trying to emulate the doping practices of the professional athletes they idolized.[2] Like steroids, the adverse health effects of growth hormone are particularly serious in adolescents.

---

[1] *U.S. Anti-Doping Research Report: What Sports Means in America: A Study of Sport's Role in Society* (2010)

[2] *Restoring Faith in America's Pastime: Evaluating Major League Baseball's Efforts to Eradicate Steroid Use: Hearing Before the H. Comm. on Gov't Reform*, 109th Congress. 307 (March 17, 2005) (statement of Dr. Denise Garibaldi and Ray Garibaldi and statement of Donald Hooton).

I have been involved in the development of tests for abuse of growth hormone since 1999. The test that I will be discussing today has been developed during this period by well-respected researchers in the growth hormone research community who had minimal association with sport prior to developing a test for growth hormone abuse. Initial funding for this research came from the International Olympic Committee and the European Union, but funding of subsequent projects was provided by the World Anti-Doping Agency (WADA), USADA, the Partnership for Clean Competition and other national anti-doping organizations and governments. All of these organizations have a peer review process and review the results of the research projects when they are completed.

The current test for growth hormone in sport, the isoforms test, is a blood test[3] that has been used to detect the prohibited use of growth hormone on a limited basis since 2004 and on a worldwide basis since 2008.[4] During that time, almost thirteen-thousand athletes in a variety of sports, including track and field (including throwers), weightlifting, bobsled (in which retired football players have participated), boxing, triathlon, cycling, swimming and wrestling, have been tested globally for growth hormone abuse using this testing method. In addition, Major League Baseball has conducted approximately 1,700 growth hormone tests of its players using the isoforms test over the past two seasons.

Prior to being implemented in drug testing athletes, the isoforms test for the detection of growth hormone abuse in sport was validated and approved by the World Anti-Doping Agency. WADA's validation and approval of the isoforms test is significant because its authority to make that decision is set forth in the World Anti-Doping Code, which by virtue of the UNESCO International Convention against Doping in Sport, was ratified by the United States Senate and signed by President Bush in 2008.

---

[3] Growth hormone is one of several performance enhancing drugs that can only be detected for anti-doping purposes in blood. Although growth hormone can pass through the filter in the kidney, the body has an efficient mechanism in the kidney for recovering the amino acid building blocks of peptides. As a result, only about 0.01% of growth hormone is present in urine.

[4] A second complimentary test, called the biomarkers test, remains under development. This test is based on a score calculated from the concentrations of two compounds produced by the body when growth hormone is present in the blood. These two biomarkers are insulin-like growth factor-1 (IGF-1) and the N-terminal peptide of pro-collagen type III (P-III-NP). The biomarkers test is not intended to replace nor does it undermine the validity of the isoforms test. Rather, the isoforms and biomarkers tests are complementary and intended to be used together as they have different detection windows. The biomarkers test was used at the 2012 London Olympic and Paralympic Games and resulted in positive results for two Paralympic powerlifters. Following their positive tests, the athletes admitted use of growth hormone and were sanctioned. The admissions suggested that the athletes had taken GH about eight days prior to sample collection. Unfortunately, one of the four commercial immunoassays validated for use in the biomarkers test was recently removed from the market by its manufacturer. Although additional assays are in the process of being validated, I estimate that the biomarker test will not be available for worldwide use until at least the fourth quarter of 2013.

There is a broad consensus among the scientific experts who regularly work in the growth hormone field that the isoforms test is a reliable and valid test for the detection of synthetic growth hormone. The method has been the subject of four peer-reviewed publications and has also been the subject of numerous conferences and working groups that met regularly to discuss progress on research, advise on additional scientific work to be conducted and make recommendations regarding important elements of the test such as decision limits, which are the threshold guidelines for the test.

Keeping in mind the obvious limitations of this setting for a more detailed explanation, the principle of the isoforms test is as follows: The body produces many forms of growth hormone in the pituitary gland (as listed in Table 2 of the Baumann review[5] attached to my testimony). The various growth hormone forms (called isoforms) have different molecular weights. One of the major growth hormone isoforms has a molecular weight of 22 kilodaltons and is called 22 kD. Another has a molecular weight of 20 kilodaltons and is called 20 kD, and so on. The typical ratio of the 22 kD isoform relative to the other isoforms in the non-doping population using the isoforms test is approximately 0.8. The isoforms test works by measuring the ratio of 22 kD to the other isoforms secreted by the pituitary. Because recombinant (synthetic) growth hormone is only comprised of 22 kD, in persons who have been doping with recombinant growth hormone, the ratio of 22 kD relative to the other isoforms will be higher than found in the normal population. The analytical methods used to conduct the necessary measurements and analyses for growth hormone are relatively routine and capable of being performed at any WADA accredited laboratory.[6]

The Decision Limit for a positive result under the isoforms test was initially determined in 2009 following a normative study based on samples voluntarily provided by elite track and field athletes at the 2009 IAAF World Championships Berlin and a number of samples provided by the German National Anti-Doping Agency. The Decision Limit has initially been set very conservatively, which ensures that only those athletes who are actually abusing growth hormone will test positive under this testing method. In fact, using the growth hormone isoform test, the chances of an athlete who has not used synthetic growth hormone testing positive are comparable to the chance of that same athlete being struck by lightning during his or her lifetime. This conservative approach is not unusual for newer tests,

[5] Baumann GP. Growth hormone doping in sports: a critical review of use and detection strategies. Endocr Rev. 2012; 33(2):155-86.

[6] The two WADA accredited laboratories in the United States are the UCLA Olympic Analytical Laboratory in Los Angeles, California, and the Sports Medicine Research and Testing Laboratory in Salt Lake City, Utah.

although it increases the likelihood that there will be athletes using growth hormone who will avoid testing positive because their values fall under the Decision Limit. WADA intends to adjust the Decision Limit over time to reduce the likelihood of missed positives.

The isoforms test uses two separate testing kits (Kit 1 and Kit 2) to measure the ratio of 22kD to the other isoforms secreted by the pituitary. The Decision Limit for Kit 1 is a ratio of 1.81 for males and 1.46 for females. The Decision Limit for Kit 2 is a ratio of 1.68 for males and 1.55 for females. The Decision Limit for both Kit 1 and Kit 2 must be exceeded in the sample analysis for the sample to be declared positive for growth hormone.

As of August 28, 2012, WADA records show that 12,764 growth hormone isoforms tests have been performed globally, resulting in 12 positive tests. One positive test was for an athlete known to use growth hormone for therapeutic purposes, whose sample was collected because the agency wanted to demonstrate that the test worked – it did. Eight of the individuals admitted their growth hormone use and accepted a sanction – a rare phenomenon in anti-doping programs. The other three cases are in various stages of arbitration and appeal at this time.

Since 2008, USADA has conducted 1,387 tests, about 90% percent of which were no-notice out-of-competition tests. Of these tests, 99% have had ratios of less than 1.3, which is well below the Decision Limit. One of the above cases where the ratio exceeded the Decision Limit was the result of USADA testing. This athlete, a weightlifter who competed in the above 105 kg (231 lb) classification, admitted growth hormone use and accepted a two-year sanction. In three other tests conducted when this weightlifter was not abusing growth hormone, his ratio was below 1.1. In the two tests collected when he was abusing growth hormone, his ratio was 2.74 (Feb 7) and 2.56 (Feb 27); well above the 1.81 Decision Limit (Kit 1).

I should also point out that Major League Baseball's testing program has resulted in one "positive" test for growth hormone, and the minor league player (Mike Jacobs) admitted growth hormone use. To complete the North American experience with the growth hormone isoforms test, a first-year running back from the University of Waterloo in Canada tested positive for growth hormone in 2010, and was given a three-year ban for use of testosterone and growth hormone.

It has been suggested by the NFL Players Association in the press and their correspondence to WADA that NFL players are sufficiently different from other elite athletes, with regard to size and ethnicity, that an additional population study of 500 NFL players should be conducted in order to

establish alternate reference ranges and decision limits from those that are currently used for growth hormone testing in Olympic sports. In my scientific opinion, an additional population study is unnecessary because each of the concerns that have been raised regarding the applicability of the isoforms test to athletes in the NFL has already been raised and answered by growth hormone scientists.

1. Does the current test take the size of the athletes into account? Yes, and it was determined that the size of an individual has no relation to the ratio of growth hormone isoforms measured by the test.
2. Does the test accurately take into account growth hormone differences that may be attributed to an athlete's race or ethnicity? Yes, and the conservative approach to the Decision Limits reflects that consideration.
3. Does the test take into consideration the effect of strenuous exercise on growth hormone levels and ratio? Yes and to the extent growth hormone levels are affected by exercise, it has been determined that the effect is minor and virtually undetectable within 30 minutes after the conclusion of the physical activity, well short of the testing protocol requiring 2 hours of rest prior to sample collection.

In conclusion, I would like to point out that the only people who are still questioning the methodology and validity of the growth hormone isoforms test are lawyers, not scientists. The test has not only been put into use by Olympic sports, but MLB as well. Considerable resources, of both time and money, have been expended in order to develop this test and the experts who work in the growth hormone field every day, both inside and outside of the anti-doping movement, have universally accepted and recognized that the isoforms test is scientifically reliable and appropriate for the detection of growth hormone abuse in sport.

Once again, I would like to express my appreciation to the Committee for having me here to testify, and for their attention to a somewhat technical presentation.

Chairman ISSA. Mr. Butkus?

STATEMENT OF RICHARD M. BUTKUS

Mr. BUTKUS. Thank you, Representatives Issa and Cummings and members of the committee. I appreciate you holding this hearing on HGH testing.

First, I applaud the NFL and players for taking a bold and decisive position on HGH in their 10-year agreement. Now let's get on with it. The HGH testing process has proven to be reliable. It is time to send a clear message that performance-enhancing drugs have no place in sports, especially the NFL.

Now, as a sports enthusiast, I know you need both a great offense and a great defense to win. The defense is tough league testing and continued crackdown on drug suppliers. The offense is education and practical guidance.

For the last 7 years, my son Matt and I have been playing offense. We have reached out to thousands of active teens across the country, encouraging them to play clean. That means eating well, training hard, and playing with attitude, instead of using performance-enhancing drugs.

Now, we have made some progress, but our work is far from over. Today, we have about 400,000 teens who report that they have experimented with performance-enhancing drugs, many in middle school, and one-third are young women. We also discovered that five of six teens have never received education about performance-enhancing drugs or their consequences. But once teens hear that they are illegal, mess up your body development, and ruin their chances to play at the next level, they make smart decisions.

Now, the work is to equip teenage athletes and their parents and coaches with programs making it easier to train and eat well. We need to make it easier to do the right thing. Plus, every year we have another million or so teen athletes who need to be educated, along with their parents and coaches.

None of our work on offense will matter unless we have a strong defense. The NFL and player agreement on HGH is a great playbook. Now let's get on the field and execute. The wellbeing of our Nation's most active youth is riding on it, and they are paying attention to what happens in the NFL.

Thank you.

Chairman ISSA. Thank you.

Chairman ISSA. Dr. Goldberg?

STATEMENT OF LINN GOLDBERG, M.D., F.A.C.S.M

Dr. GOLDBERG. Mr. Chairman and committee members, thank you for inviting me to this hearing. I am a practicing physician and professor of medicine at the Oregon Health and Science University. I have been researching how to prevent performance-enhancing drug use among young athletes since 1987.

My team of researchers found reasons young men and women use drugs, like growth hormone or steroids, are not the same and, thus, require different approaches. So we developed two NIDA-supported high school programs entitled ATLAS for males and ATHENA for high school females. Both have reduced the use of anabolic

steroids, illicit drugs, and alcohol, and have received national and international recognition for effectiveness.

I was a principal investigator of the NIDA-sponsored SATURN study assessing the effectiveness of drug testing for high school athletes. Because other experts can testify anabolic steroids to the accuracy of the newer growth hormone tests, I will focus my testimony on younger athletes' drug use and the potential messages a robust HGH program in professional sports might send to our youth.

More than 55 percent of high school students participate in school-sponsored sports, and both male and female athletes report using performance-enhancing drugs. There are no reliable estimates as to the prevalence of human growth hormone use among adolescents. Also, the potential harmful effects of high doses of HGH are not known, although the disease may mimic the disease—excuse me—the intake may mimic the disease acromegaly, where excess growth hormone is produced by a pituitary tumor.

Furthermore, it is not yet not clear that human growth hormone by itself is an athletic enhancer. However, many athletes believe it works and use it alone in combination with anabolic steroids or other drugs.

If the NFL has a reliable, robust testing program for HGH and the analysis is accurate, testing could make professional football fairer, if not healthier. However, the message to young athletes may not only show that the NFL does not tolerate drug use, but other messages may be present as well: one, that HGH actually enhances athletic performance; and, two, there is a need to test elite athletes because so many are users. Teens don't always respond to adult messages as they are intended.

The CDC estimates that over one-half million high school students report steroid use. This means that there are more high school steroid users than the total number of athletes in the NFL, Major League Baseball, the NBA, and NHL combined multiplied by 100. Thus, the most profound performance-enhancing drug problem, by numbers of users, is among high school students, not the pros.

While drug testing may weed out users in professional sports, for young athletes it is critical to prevent drug use. In our own study of student athlete drug testing, there was no deterrent effect. So if drug testing in an athlete's own school does not deter his or her use, why would testing in professional sports deter high school drug use?

The way to reduce performance-enhancing drug use by young athletes is to implement programs proven to work. Recognizing this, the NFL is doing just that. The NFL Youth Football Fund has sponsored ATLAS and ATHENA to over 40,000 young athletes throughout the United States. Moreover, the NFL has provided funds to both the Taylor Hooton and Efrain Marrero Foundations to better inform students and parents about these drugs.

It is important to stress that Congress passed the Anabolic Steroid Control Act in 2004, authorizing $15 million per year for 6 years to enable DHHS to distribute science-based education programs in elementary and secondary schools to prevent steroid use.

Although funds were authorized, Congress did not appropriate funding.

Consequently, in 2009, the NFL, MLB, USADA, USOC, and the National Federation of State High Schools sent a joint letter to all Members of Congress requesting appropriation of funds to educate children about steroids. However, not one penny was appropriated.

Instead, there have been multiple high-profile hearings on steroids and prominent steroid court cases, costing the government tens of millions of dollars, in failed attempts to convict just two Major League Baseball players. Additionally, according to the GAO, well over $1 billion was wasted on the Federal antidrug campaign, where greater campaign exposure appeared to make things worse.

Drug testing may be needed in an effort to keep professional sports more drug-free and fair, but testing elite athletes will not prevent drug use among teens. If Congress thinks adolescent use of performance-enhancing drugs is a problem, then do something about it. The notion that HGH testing in professional sports will trickle down to young athletes, causing them to be drug-free, without strong science-based education is not only naive, it may send a message that you need to use drugs to succeed.

Programs that actually work are available. Because Congress approved but did not appropriate funds, we would like to give our ATLAS and ATHENA programs back to the Federal Government so schools can use them for free.

Thank you.

[Prepared statement of Dr. Goldberg follows:]

Testimony of Linn Goldberg, M.D., F.A.C.S.M.
U.S. House of Representatives
Committee on Oversight and Government Reform
"HGH Testing in the NFL"
Washington, D.C. 20515-6413
December 12, 2012

Mr. Chairman and Committee members:

Thank you for inviting me to this hearing concerned with Human Growth Hormone (hGH) testing within the National Football League. I am a practicing physician, Professor of Medicine and Head of the Division of Health Promotion & Sports Medicine at the Oregon Health & Science University. I, along with colleagues, co-developed two evidence-based health promotion and drug prevention programs for teen athletes: ATLAS for males, and ATHENA for females (1-5). I was the principal investigator of the SATURN study, the first NIDA funded drug-testing study of high school athletes (6). In addition, I co-edit the Endocrine Society's Hormone Foundation website concerned with both anabolic steroid and hGH use and abuse and am a former U.S. Olympic Committee Crew Chief and Doping Control Officer for the United States Anti-Doping Agency.

This is the third time I have testified to the House of Representatives concerning use performance enhancing drugs (PEDs). I would like to focus much of my testimony on high school athletes' use of PEDs, and comment on the potential impact a "robust HGH testing program in professional sports," as described in the letter requesting my testimony.

Adolescent athletes and performance enhancing drugs
More than 55% of high school students participate in school-sponsored sports. While both young male and female athletes report use performance enhancing drugs, there are unique, sex-specific reasons for use, thus requiring a different prevention approach. Some use these substances because of 1) social pressures; 2) to enhance athletic performance; 3) improve their body image; 4) impulsivity and risk-taking (especially young males); 6) depression and disordered eating practices (especially young women); and 7) modeling use by older, accomplished athletes. Teen performance-enhancing drug users are more likely to use alcohol and other drugs (8), thus performance enhancing drug prevention should target other substances of abuse, as well.

Unfortunately, no national data estimates include the use of human growth hormone among adolescents. One report published twenty years ago suggested 5% of high school athletes had used hGH during their lifetime (9). However, In our study of over 3200 male high school football players, less than 1% reported using hGH (1,2).

The laboratory derived human growth hormone sold commercially has eliminated

a once critical risk that existed when cadaver pituitary glands were used as the source of hGH, when some developed a devastating degenerative brain disease known as Creutzfeldt–Jakob, due to a virus found in some hormone samples (10). HGH has been on the list of forbidden substances in collegiate, professional sports, and banned from Olympics since 1989.

Use of physiological doses of rhGH has been shown to be relatively safe and can increase in bone mass, lower body fat, enhance growth rate and muscle mass and improve cholesterol levels among children with a growth hormone deficiency (11,12). However, athletes use recombinant (rhGH) at higher doses than amounts used to replace normal growth hormone production (13). Although the ability to enhance athletic abilities is not proven (8), many athletes believe rhGH works, and use it alone or in combination with other drugs (14,15).

Potential risks of human growth hormone use

Like any injectable drug, if vials or needles are shared, there is a risk of disease transmission of HIV, hepatitis or other infections. Also, since a prescription is needed, those who may sell the drug on the "black market" or buying what they believe to be human growth hormone from a website, may be getting something other than rhGH, with potential impurities.

Although long-term risks of high dose rhGH have not been studied, pituitary tumors producing high levels of hGH can cause the disease, acromegaly. This is a potential model of the hormone's long-term toxicity. Signs of acromegaly include enlargement and broadening of facial features and a protruding jaw, features present in the French born professional wrester Maurice Tillet, who some believe was the inspiration for the appearance of the cartoon character, Shrek. There can be swelling of the limbs, joint pains, and an increased risk of developing diabetes, high blood pressure, and premature cardiovascular disease. Over years, peripheral nerve damage and muscle weakening can occur.

Athlete drug testing

The primary aim of drug use in collegiate, professional and Olympic sport is to identify the user and remove them from competition or sanction the athlete and expunge their record. This contributes to fairness in sports, by eliminating the advantage performance enhancing drugs.

Reasons to drug test at the youth athlete level may be somewhat different. Among those in middle and high school, drug testing has been used in an attempt to 1) prevent use and potential harm of drugs, 2) identify early abuse or addiction and 3) to identify and provide treatment. In addition it may lead to fair competition. Although some states have tested for anabolic-androgenic steroids (AAS), most high school athletes subject to drug testing are not being tested for steroids, let alone, hGH. Student athlete drug testing most often includes a group of illicit drugs, such as marijuana, phencyclidine, cocaine and opiates, while other substances of abuse, such as club drugs or alcohol are not regularly assessed.

Does drug testing prevent drug use, even among elite athletes?
Despite the best efforts sports' drug testing policies, a number of high profile athletes have never failed a test, yet have been identified by sports authorities or self-admitted their use of performance enhancing drugs. The use of THG (tetrahydrogestrinone or 'the clear'), is an anabolic steroid created in a laboratory, designed to avoid detection (16). Use was successfully masked until a sample of THG was sent to the Olympic laboratory for analysis and a number of athletes were identified as steroid users when their urine samples were reexamined. For those athletes, drug testing did not deter use, but resulted in searching for methods to beat the test.

No randomized, prospective evaluation of drug testing, has been performed among collegiate, professional or Olympic athletes. Thus the question is, does drug testing at the elite level deter use, or just reveal use? If drug testing were a strong deterrent to an athlete's drug use, one would suspect there would be few, if any positive tests because the policy would prevent use. If drug testing deterred but did not eliminate performance enhancing or other drug use, we might expect fewer positive tests the longer a drug-testing program was in place, as identification of drug positive athletes would discourage others from using. However, the data does not provide much evidence of a strong deterrent.

- Anabolic steroid testing has been in the Olympics since 1976, yet positive drug tests occur prior to and during every Olympics. During the six months prior to the 2012 London Olympics, 117 athletes received sanctions for drug offenses and nine additional positive drug tests occurred during the 'Games' (17).
- Major League Baseball drug suspensions in 2012 were the most since 2007 (18).
- National Football League testing reported 21 tests positive for performance enhancing drugs in 2012, which is a 75% increase over the 12 suspensions issued last year (19).
- The World Anti-Doping Agency's drug testing data reports a reduction in 15,000 tests from 2010 to 2011. Despite fewer tests during 2011, the percentage of overall "Adverse Analytical Findings," were the highest since 2008 (20).
- For the combined years of 2007 and 2008, USADA performed 17,133 tests of which 44 were positive. During the subsequent two years of 2009 and 2010, USADA performed 5% less tests yet positive tests increased 54% (21).

Thus, recent WADA, USADA, MLB and NFL data suggest a higher percentage of athletes using drugs who are subject to testing. Although this also implies that drug testing policies may be improving and keeping the competition cleaner, they do not support a strong drug prevention component of testing by itself. Rather than send a message that human growth hormone testing or any other drug is not tolerated because there is testing in elite sports, the message may be interpreted that "the professionals they admire" use or have used hGH to achieve

their elite status and drug testing is needed in order to keep them honest.

Drug testing and high school athletes
The first-ever drug testing study of high school athletes, funded by the National Institute on Drug Abuse, entitled SATURN (Student Athlete Testing Using Random Notification) (6), was a suspicionless, no-advance warning program to I helped design, to mirror elite athlete programs. Testing was in and out of season, and steroids and alcohol tests were included. After two years, no drug or alcohol deterrent effects were present for past month use at any of the four follow-up periods. In addition, athletes at testing schools, had an increase in risk factors for future substance use. Although a U.S. Department of Education (DOE) one-year study of student drug testing found some reductions in drug use, there were no spillover prevention effects among other students not subject to testing (22). Unlike SATURN, the DOE study could not track students, thus the reduction in reported drug use, may have been an artifact of their volunteer sample from pre to post testing. In the largest epidemiological national study of school drug testing performed by the staff at Monitoring the Future at the University of Michigan (23), investigators found drug testing not to be associated with students' reported illicit drug use; and drug testing of athletes was not associated with lower illicit drug use among male high school athletes.

What about the penalties for college players who test positive during their tryouts for the NFL?
The reason given for avoiding drug use in elite sport is sanctions, loss of earning power and the shame of being recognized as a drug user. At the invitation-only NFL Scouting Combine, college football players perform physical and mental tests and drug tests are administered. When I last testified to this committee in 2005, a Northwestern University football player tested positive for anabolic steroids at the NFL Scouting Combine (24). Despite using steroids, this athlete was drafted by the San Diego Chargers in the first round of the 2005 NFL Draft. During the most recent 2012 Scouting Combine, several college players tested positive for drugs. Three prominent athletes testing positive for drugs are playing in the National Football League (25). What message does this send to collegiate and high school athletes about toleration of their drug use?

What has not worked in drug prevention?
Effective drug prevention principles are based on decades of study, determining how drug abuse starts and how it progresses (26). The types of interventions without proof of evidence of effectiveness include:

- Use of fear arousal or "scare tactics," only emphasizing the negative effects of drugs. Among male athletes, this resulted in an increase desire to use anabolic steroids (27).
- Use of national media campaigns. The GAO report found that not only was ONDCP's 1.2 billion dollar "Youth Anti-Drug Media Campaign" was not only ineffective, but it may have increased marijuana initiation among some youth (28). Another analysis, confirmed the ineffectiveness of

ONDCP's media campaign (29).
- Student-athlete drug testing (6,23).
- Knowledge only approaches (explaining risks and benefits of PEDs (30)
- Pamphlets or written materials, only (30)

Successful Prevention of Performance Enhancing Drugs
I, along with my colleagues, at the Oregon Health & Science University and Arizona State University, developed performance and body shaping drug prevention programs tailored to adolescent male and female athletes risk and protective factors, involving over 4,000 high school athletes (1-5). ATLAS, for high school male athletes and ATHENA for high school female athletes are multi-component programs that are peer-led in small groups of approximately 5 athletes within a team structure. The programs feature positive peer pressure and promote healthy role modeling. Students learn why and how to counter drug offers, including use of steroids, growth hormone and other drugs. Sports nutrition and strength training techniques, were used to naturally enhance athletic abilities. These sport team-centered programs were found to do the following, as compared to control schools:

After ATLAS (1) athletes reported;
- 50% decrease in new anabolic steroid use
- 50% reduction in new alcohol and illicit substance use
- 50% lowering of sport supplement use
- 24% decline in drinking and driving occurrences
- Improved nutrition and exercise behaviors
- Reduced desire to use steroids
- The belief they were better athletes

After ATHENA athletes reported;
- Less use of athletic enhancing substances (steroids, amphetamines, supplements)
- Less use of diet pills
- Less riding in a car with a drinking driver
- Greater seatbelt use
- Reduced sexual activity
- Improved nutrition behaviors
- Reduced long-term use of alcohol, marijuana and tobacco

After reviewing the scientific evidence, a 2007 GAO report (31) reported: "assessments of the ATLAS and ATHENA prevention programs and in general suggested that the programs may reduce abuse of anabolic steroids and other drugs among high school athletes immediately following participation in the programs." The World Anti-Doping Agency's sponsored evaluations of worldwide anti-doping programs (32,33) reported that ATLAS and ATHENA "provide the only high quality evidence available on the best way to educate adolescents about doping." ATLAS and ATHENA are listed in the U.S. Department of Health

& Human Services' National Registry of Evidence-Based Programs and listed as evidence-based by other federal departments.

ATLAS and ATHENA have been disseminated to more than 80,000 young athletes in the United States during the past 6 years, spearheaded by the National Football League's Youth Football Fund, Sports Illustrated the National Football League's Youth Football Fund, the Hanley Center in Florida, the Professional Baseball Strength & Conditioning Coaches Society, and other foundations. However, there are over 7.5 million high school athletes in the United States, with an additional 2 million entering sports programs each year. If Congress thinks prevention of performance enhancing drugs among our nation's youth is important, it should go beyond support of testing professional athletes.

In 2004, Congress passed the Anabolic Steroid Control Act, to eliminate prohormone steroids sold over-the-counter, making them a schedule III drug of the Controlled Substances Act (34). The Act authorized $90 million, or $15 million per year to the Department of Health & Human Services for "...science-based education programs in elementary and secondary schools..." to prevent steroid use. Because Congress did not appropriate funding over subsequent years, in 2009, the last year of the Act's educational fund authorization, the National Football League, Major League Baseball, United States Anti-Doping Agency, United States Olympic Committee and the National Federation of State High Schools sent letters to all members of Congress, requesting funds to educate children and adolescents about steroids. No funds were appropriated. However, since that time there have been two high profile steroid court cases, costing the government millions of dollars in a failed attempt to convict two Major League Baseball players.

The CDC estimates (35) over 500,00 high school students report using anabolic steroids and it is likely these and other students have tried human growth hormone and other PEDs. This level of use is more than all the players in the NFL, NBA, NHL and MLB combined, multiplied by over 100. If the NFL does effective rhGH testing, it may improve fairness in professional football. However, effective youth programs are needed to help ensure that young athletes have the tools to resist performance enhancing drugs and hormones in order that sports promote safety, health and fairness. That is the message Congress could send.

References:

1. Goldberg L, MacKinnon DP, Elliot DL, Moe EL, Clarke G, Cheong J. The adolescents training and learning to avoid steroids program: preventing drug use and promoting healthy behaviors. Arch Pediatrics Adolescent Medicine 2000;154:332-338.
2. Goldberg L, Elliot DL, Clarke GN, et al. Effects of a multidimensional anabolic steroid prevention intervention. The Adolescents Training and Learning to Avoid Steroids (ATLAS) program. JAMA 1996;276:1555-62.
3. MacKinnon DP, Goldberg L, Clarke GN, Elliot DL, Cheong J, Lapin A, Moe EL, Krull JL. Mediating mechanisms in a program to reduce intentions to use anabolic steroids and improve exercise self-efficacy and dietary behavior. Prevention Science 2001;2:15-28.
4. Elliot DL, Goldberg L, Moe EL, DeFrancesco CA, Durham MB, Hix-Small H. Preventing substance use and disordered eating: initial outcomes of the ATHENA (athletes targeting healthy exercise and nutrition alternatives) program. Arch Pediatr Adolesc Med. 2004 Nov;158(11):1043-9.
5. Elliot DL, Goldberg L, Moe EL, DeFrancesco CA, Durham MB, McGinnis W, Lockwood C. Long-term outcomes of the ATHENA (Athletes Targeting Healthy Exercise & Nutrition Alternatives) program for female high school athletes. J Alcohol & Drug Educ 2008;52: 73-92.
6. Goldberg L, Elliot DL, MacKinnon DP, et al. Outcomes of a prospective trial of student-athlete drug testing: the Student Athlete Testing Using Random Notification (SATURN) study. J Adol Health 2007;41:421-9.
7. Koebler, J. High school sports participation increases for 22nd straight year. September 2, 2011. U.S.news.com. http://www.usnews.com/education/blogs/high-school-notes/2011/09/02/high-school-sports-participation-increases-for-22nd-straight-year
8. Kersey RD, Elliot D L, Goldberg L, Kanayama G, Leone JE, Pavlovich M, Pope HG. National athletic trainers' association position statement: Anabolic-androgenic steroids. J Athl Train. 2012;47(5):567-88.
9. Rickert V I, Pawlak-Morello C, Sheppard V. *et al* Human growth hormone: a new substance of abuse among adolescents? Clin Ped 1992. 31723–726.726.
10. Souza FM. Collett-Solberg PF. Adverse effects of growth hormone replacement therapy in children. Arq Bras Endocrinol Metabol. 2011 Nov;55(8):559-65.
11. Curtis VA, Allen DB. Boosting the late blooming male: Use of growth promoting agents in the athlete with constitutional delay of growth and puberty. Sports Health. 2011 Jan;3(1):32-40
12. Boot AM, Engels MA, Boerma GJ, Krenning EP, De Muinck Keizer-

Schrama SM. Changes in bone mineral density, body composition, and lipid metabolism during growth hormone (GH) treatment in children with GH deficiency. J Clin Endocrinol Metab. 1997 Aug;82(8):2423-8.
13. Saugy M, Robinson N, Saudan C, Baume N, Avois L, Mangin P. Human growth hormone doping in sport. Br J Sports Med. 2006 July; 40(Suppl 1):135-139.
14. Ho KK, Nelson AE. Growth hormone in sports: detecting the doped or duped. Horm Res Paediatr. 2011;76 Suppl 1:84-90.
15. Brennan BP, Kanayama G, Hudson JI, Pope HG Jr. Human growth hormone abuse in male weightlifters. Am J Addic. 2011 Jan-Feb;20(1):9-13.
16. Levesque JF, Templeton E, Trimble L, Berthelette C, Chauret N. Discovery, biosynthesis, and structure elucidation of metabolites of a doping agent and a direct analogue, tetrahydrogestrinone and gestrinone, using human hepatocytes. Anal Chem. 2005 May 15;77(10):3164-72.
17. http://www.dailymail.co.uk/sport/olympics/article-2190409/London-2012-Olympics-Drug-cheats-prospering--Dick-Pound.html#ixzz2DvYAL96v
18. http://sportsillustrated.cnn.com/2012/baseball/mlb/wires/11/28/2000.ap.bbo.players.union.drug.testing.0204/index.html
19. http://www.nytimes.com/2012/12/02/sports/football/adderall-a-drug-of-increased-focus-for-nfl-players.html?pagewanted=all&_r=0
20. http://www.wada-ama.org/en/Resources/Testing-Figures/Laboratory-Testing-Figures/
21. http://www.usada.org/rule-violation-statistics/
22. James-Burdumy S, Goesling B, Deke J, Einspruch E. The effectiveness of mandatory random student drug testing: a cluster randomized trial. J. Adolesc Health. 2012 Feb;50(2):172-8.
23. Yamaguchi R, Johnston LD, O'Malley PM. Relationship between student illicit drug use and school drug-testing policies. J Sch Health. 2003 Apr;73(4):159-64.
24. King, P. The real draft surprise. April 25, 2005. SI.com. http://sportsillustrated.cnn.com/2005/writers/peter_king/04/25/mmqb.draft/index.html
25. Six players tested positive at the NFL Combine in 2012. http://profootballtalk.nbcsports.com/2012/04/25/six-total-players-tested-positive-at-scouting-combine/
26. Preventing drug use among children and adolescents. A research-based guide. U.S. Department of Health and Human Services; National Institutes of Health; National Institute on Drug Abuse. NIH Publication No. 99-4212. Reprinted April, 1999.
27. Goldberg L, Bents R, Bosworth E, Trevisan L, Elliot DL. Anabolic steroid education and adolescents: Do scare tactics work? Pediatrics 1991;87:283-6.

28. United States Government Accountability Office. Contractor's national evaluation did not find that the youth anti-drug media campaign was effective in reducing youth drug use. August 2006. GAO-06-818 http://www.gao.gov/new.items/d06818.pdf
29. Magura S. Failure of intervention or failure of evaluation: a meta-evaluation of the national youth anti-drug media campaign evaluation. Substance Use Misuse. 2012 Nov;47(13-14):1414-20
30. Goldberg L, Bosworth EE, Bents RT, Trevisan L. Effect of an anabolic steroid education program on knowledge and attitudes of high school football players. J Adolesc Health Care. 1990 May;11(3):210-4.
31. United States Government Accountability Office. Federal efforts to prevent and reduce anabolic steroid abuse among teenagers. GAO-08-15, Oct 31, 2007. http://www.gao.gov/products/GAO-08-15
32. Backhouse S, McKenna J, Robinson S, Atkin A. Social Science Research Fund: International literature review: Attitudes, behaviours, knowledge and education-drugs in sport: past, present and future. 2007. http://www.wada-ama.org/rtecontent/document/backhouse_et_al_full_report.pdf
33. Backhouse S, McKenna J, Patterson L. Prevention through education: a review of current international social science literature. Prepared for World Anti-Doping Agency. 2009. http://www.wada-ama.org/rtecontent/document/backhouse_Prevention_through_Education_final_2009.pdf
34. http://www.gpo.gov/fdsys/pkg/PLAW-108publ358/pdf/PLAW-108publ358.pdf
35. Youth Risk Behavior Surveillance-United States, 2011. Morbidity and Mortality Weekly Report. Surveillance Summaries. Vol.61, No.4. June 8, 2012. http://www.cdc.gov/mmwr/pdf/ss/ss6104.pdf

Chairman ISSA. Mr. Gimbel?

STATEMENT OF MICHAEL GIMBEL

Mr. GIMBEL. Thank you, Mr. Chairman. Thank you for inviting us, Congressman Cummings. My name is Mike Gimbel. I am director of the University of Maryland St. Joseph Medical Center Powered By Me antidrug athlete program. We have been around for 5 years.

More than that, I come from a different place here today. I am also a recovering addict, being clean 40 years. I am also a competitive marathon runner. I am proud to say I have run the Boston Marathon 8 years out of the last 10. I work with kids every day. I love sports, I love working with kids, and I hate what drugs are doing to these kids.

We are addicted in our society. We have an addiction to winning—winning at all cost. The kids I work with tell me that they will do anything to win. That means play injured, that means cheat, and it means take drugs. Because the goal, the addiction is to win, and we have an obsession in our Nation to win.

And these children are starting at an early age, following the same pattern of addiction that we see with other drugs. We have 9-, 10-year-old kids who are drinking gallons of energy drinks in order to get an edge. Kids when they are 12 or 13 will spend thousands of dollars on unregulated supplements—muscle supplements, diet supplements—in order to get bigger and stronger and faster. And then when they get to high school, where it is really competitive and winning is really important, they go to the hard stuff. And that is when they start looking for HGH, anabolic steroids, anything they can get their hands on because they have to win.

And we have enablers—coaches, parents—who support this, who watch this, who need to get involved. And we are in denial, as we are with other addictions, because we love winners. The message to our kids is that you have to win.

Now, we have seen with other addictions that we have to have an attack that is three-pronged of education and treatment and enforcement. The education you have heard; there are programs out there that work. What we haven't talked much about is treatment. People that use these supplements will get addicted, whether it is just psychologically or whether it is physically as well. We have to get them help.

And, finally, in enforcement, what we have certainly found in other drug issues is that drug testing is important. Drug testing does two things: It helps to deter some athletes from using, and it also helps us identify those who are chronic users who then we can identify and get help. So testing is critical, not just for HGH but for any substance that we can identify that will help us make our sports and our athletes play safer and fairer and drug-free. That is the message.

We look at the message that these kids get from their role models. We know that professional athletes are role models; they know that they are role models. Just in the last couple of weeks, we have watched tragedy after tragedy in the NFL. There are lots of other people who have died in car crashes, in domestic violence cases, and carry weapons, but it wasn't on the news the way it was with

the NFL and professional sports. That is how powerful it is. That is the message that goes to our children.

So we need to attack this the way we have attacked every other addiction because winning can't be everything because there aren't all winners all the time. Sometimes you lose. We have to teach that.

What you heard up here with the panel, everyone agrees we have to work with parents, we have to work with coaches. And we have to send a new message, not a mixed message, but a new message that you play safe, you play fair, you play drug-free, you do the best you can, you use your God-given talents, and if you win, great, and if you lose, great. You tried; you did your best. And that is the message we need to send.

We are proud of the work we have done. We certainly thank our Congressman Cummings, who has helped us and gave us guidance and support for 5 years. We have reached 30,000 kids, but there are a lot out there that we need to reach. And I think what Mr. Butkus said is true, that we just have to get to as many kids as possible.

I want to thank you for inviting me and supporting our efforts. Thank you.

Chairman ISSA. Thank you.

[Prepared statement of Mr. Gimbel follows:]

Mr. Chairman and Members of the House Oversight and Government Reform Committee:

First I would like to thank you for inviting us here to speak with you today about the impact that the use of Performance Enhancing Substances by professional athletes have on our youth.

My name is Mike Gimbel; I am the Director of the University of Maryland St. Joseph Medical Center's "Powered by Me!" Anti-Drug Education program. I am also a recovering addict with 40 years of sobriety and I am an 18 time marathon runner including finishing the Boston Marathon 8 times. I love sports and I love working with our young athletes. I am deeply worried about the use of Performance Enhancing Substances in sports and its impact on our young athletes.

Five years ago under the encouragement of Congressman Elijah Cummings the University of Maryland St. Joseph Medical Center made a commitment to develop a program to educate our young athletes in the state of Maryland and across the country about the dangers of using Performance Enhancing Substances, from energy drinks to anabolic steroids. This was the beginning of the "Powered by Me!" program. We are very proud of our efforts and feel like we are beginning to make a difference in changing the attitudes among our young athletes. Over these past 5 years "Powered by Me!" has reached over 30,000 young athletes, coaches and parents with our message of "Playing Safe, Fair and Drug Free".

It became very clear at the beginning of our program that young people were following in the footsteps of our professional athletes by using more and more Performance Enhancing Substances, both legal and illegal. Our young athletes have also embraced the professional athlete's mantra of "WINNING AT ALL COSTS." This "Winning at All Costs" mentality has led to a behavior that believes, "If Winning is everything, you will do anything to win..." And that is just what our young athletes are doing. Whether it's playing injured to prove they are tough or taking some type of performance enhancing drug to bulk up... to our youth, the ends justify the means.

A recent study published by the "American Academy of Pediatrics", shows that the use of Performance Enhancing Substances is growing and effecting both athletes and non athletes. This study, which surveyed over 2,800 middle and high school teens, showed that 1 out of every 3 teenage boys used a dietary supplement to help build muscle and 6% used steroids. The girls surveyed showed that 1 in every 5 teen girls used a diet supplement and 5% used steroids.

This shows that many of our teens, are willing to take a variety of supplements in order to get "Bigger, Stronger and Faster." And because teens often feel invincible, they are convinced that nothing bad will happen. But as educators, parents and coaches, we know better and have an obligation to educate and convince our young people that taking any form of dietary supplements is like playing Russian Roulette.....

But how do we get our message of playing safe, fair and drug free to these young athletes when their professional athlete role models are doing the very behavior we're trying to teach them not to do? It makes our work and the work of good coaches and loving parents very hard because taking these dangerous Performance Enhancing Substances work and as we know, teens only see the immediate results and not the long-term danger.

Eliminating all Performance Enhancing Drugs from Recreation, high school, college and professional sports would be the best of all worlds and it would send a clear and positive message to our teens. We have come a long way, but we are not there yet. We certainly applaud all the professional sports organizations, the NCAA and the Olympics for working so hard to making their sports drug free.

It is important for all of us to continue our quest to eliminate the use of all Performance Enhancing Drugs from sports. This includes the use and abuse of Human Growth Hormones (HGH). The University of Maryland St. Joseph Medical Center Powered by Me! program supports the use of drug testing as a major tool in confronting the illegal use of HGH from all sports. The use of drug testing for other Performance Enhancing Drugs have helped to reduce the use and abuse of these substances and we believe the same will happen if we institute drug testing for Human Growth Hormone. It's safe, it's accurate and it's needed.

Again, we have come a long way in a short period of time in confronting the issue of Performance Enhancing Substances in sports. We can't stop now. Our kids are depending on us to make sports as safe, fair and drug free as possible.

On behalf of the University of Maryland St. Joseph Medical Center Powered by Me! program, we ask this committee to encourage all sports to educate their athletes about the dangers of all Performance Enhancing Substances and to include testing for Human Growth Hormones.

I would like to thank the committee for inviting me here today and especially to our Congressman Elijah Cummings, whose commitment to our program and our youth never stops. We appreciate him and all the work he does to improve the quality of life of our youth and families.

I would be happy to answer any questions.

Respectfully Submitted by:

Mike Gimbel

Chairman ISSA. I now ask unanimous consent that the gentlelady from Wyoming be allowed to attend and participate in this hearing, Ms. Lummis.

Without objection, so ordered.

Mrs. LUMMIS. Thank you.

Chairman ISSA. By the way, she will be joining the committee in the next Congress, so this may be the only time I have to wave her on.

I will now recognize myself for a brief round of questions.

First of all, Dr. Goldberg, I share with you your concern that we have to do all these other things. I hope today that we can all focus on this portion of it. It is not uncommon that Congress authorizes and then doesn't appropriate. Hopefully, Mr. Butkus and others can illuminate us on an awful lot of things that the NFL—players, owners—are doing in which they are spending far greater money. And hopefully that makes up for the stinginess of Congress, which is not famous right now, but a trillion dollars of deficits from now it might become famous.

Dr. Bowers, you have certainly looked at the decades of the testing of human growth hormones and other substances. And when people say it is like being struck by lightning, I want to make sure I understand. Is there a chance that we will get a false positive on the margin on a football player if we begin testing all of them?

Mr. BOWERS. Well, no test is perfect, but, again, in 1,400 tests that we have done at USADA, there hasn't been a single false-positive test. So the odds are extraordinarily low.

Chairman ISSA. And my understanding of the contract is that there is an appeal process and union protection if, in fact, somebody claims to have a false positive. You have looked at other athletes and so on. Are the protections, in your opinion, sufficient if there is an accusation of a false positive?

Mr. BOWERS. Yes. I think the adjudication process is the appropriate place to discuss a particular test result, and there is opportunity to deal with the issues there, yes.

Chairman ISSA. Thank you.

Mr. Butkus, a lot has changed since your time on the gridiron, but I suspect you are acutely aware of all of the physicians, trainers, people who administer both on and off the field in professional sports.

In your opinion, is that well-regulated and, in fact, already, if you will, creating an environment in which there is tremendous enhancement of the players?

And I ask this for a reason. This committee is also concerned about the injuries, both at the professional and collegiate level. Isn't it true that, in fact, without human growth hormones, if we really eradicate it, and steroids, don't we also have in the NFL probably the greatest level of legal enhancement that anyone could possibly imagine, whether it is fluids or it is the actual training or every other piece of science that is available but legal?

Mr. BUTKUS. Well, I would hope so. I can only go back to the years when I was playing. You have to understand——

Chairman ISSA. Well, you were pretty enhanced. We have to know how.

Mr. BUTKUS. Well, the thing inside my chest, I think it was.

But you would think that the owners and the NFL, with the money, the amount of money that they are paying today, would have the best doctors available for their people. Unfortunately, I don't think that was true back in the sixties when I played because it was a lot of friendships. And I don't know, I would go as far to say if I maybe went to a different doctor, I might have played a couple more years.

So you have to understand what they are doing today. With all the advancements of nutrition and training techniques and everything else, you would think that each NFL team would make the—you know, would make the effort to get the best possible. I mean, you know, when I was playing, we could never go to another doctor. The people, the players today, they can go anywhere they want, any specialist they want, and, you know, they usually do.

So I would think that to avoid injuries and everything else, they are going to happen, but if you train properly and eat well, like we tell the kids from I Play Clean, you can get just as much out of the sport as you can.

Chairman ISSA. Well, now, Dr. Goldberg made an opening statement that I think is worth asking you to respond to. If, in fact, the NFL lives up to its contract, the players live up to their contract, do we send a powerful message, in your opinion, that could reduce or eliminate the pretense, if you will, at the college level and hopefully at the high school level for using these kinds of drugs, knowing that the testing will prevent it for sure when they get to the pros?

Mr. BUTKUS. Well, absolutely. I mean, where have you been? The NFL is a very powerful group. I mean, I am in front of the public a lot this past couple years. And why would a kid come to me and ask for an autograph or talk about the Bears? I am 70 years old. You mean to tell me that my playing in the NFL doesn't have an effect on the kids today? Come on.

Chairman ISSA. Thank you.

Mr. BUTKUS. What they do in the NFL by testing—and believe me, I believe a lot of them want it. Nobody wants to be playing and have that shadow hanging over, "Well, did he or didn't he take the juice? Did he or didn't he?" I think they all want—a majority of them want to do the testing. So why it is held up, I don't know.

Chairman ISSA. I might only make one comment, and you can respond. And I will give equal time to the ranking member.

The value of graduating from high school as a star and going to college, if there is testing in the college for steroids and human growth hormone, and you get cut from the team because you can't perform the next year the way you did before is pretty minimal, isn't it? Basically, 1 year in college doesn't get you there. And the same is true if you get to the pros and suddenly you are being tested and you can't perform the way you did the year before.

Could you comment a little bit on, essentially, the disincentive, if you know you are going to be tested at the next level, to even try to use it at the previous level to get that 1 year?

Mr. BUTKUS. Well, I testified in Texas for high school testing, and a lot of the results were, "Well, you know, there was 100,000 kids tested and only 2 turned up positive." Well, it could have been

maybe more but because of the testing. So I believe it is good for high school kids to be tested. It is a deterrent, I would think.

Now, I got to be educated, and that is what we try to do, is educate these kids that, listen, you know, you want to try this stuff? Like, you girls, you want to try this stuff and end up with a mustache and talking like a guy? Think about it. And the guys, do you want to play at the next level? Because you might get by here in high school, but they are going to nab you in college. Why would you risk that if this is your real goal?

And so, again, I go back to educating them. I mean, who is to say if I was a player back then and I thought, well, this is going to give me an edge and everything else, that I wouldn't do it? I mean, I hear about it all the time in different sports. They do it to have a great year. Lo and behold, it happens to be their last year of the contract, and then the next year they sign a big one, and they go right in the toilet as they get off of it.

So I think it is a deterring factor for high schools.

Chairman ISSA. I thank you.

I now recognize the ranking member for his questions.

Mr. CUMMINGS. Mr. Butkus, I want to follow up on the chairman's questions.

First of all, I want to thank you. You said you are 70 years old?

Mr. BUTKUS. Right.

Mr. CUMMINGS. And there are so many things you could be doing, but you decided to touch the future. And I just want you to know I really—we all appreciate that.

And that leads me to this. You know, in my district, the kids—I live in the inner city of Baltimore. And most of the kids in my neighborhood, they will never get to an NFL game. You know why? Can't afford it.

And when you hear about these players—and, I mean, more power to them—making millions upon millions of dollars, agree to take a test, agree now, and 2 years later no tests and complaining about the science—and you just heard the doctors, what they said about the science—you know, I mean, what do you think that sends to—I mean, and you are trying to convince kids not to go that route. But what message do you think that sends to those very kids that you are trying to help?

Mr. BUTKUS. Well, the message is that, like they have stated, it is in the hands of lawyers instead of scientists.

I mean, I really believe that the majority of the players, if not all of them, welcome the test. I mean, I would, not because I—I wouldn't take the stuff, but it is just that I want them to know that I am playing on an even field here. Because there are big rewards, like you say, with the money and endorsements and everything else.

I mean, when I see a mother talking about her kid and I am trying to talk to the 10-year-old kid and the mother is saying, "Ask him how to be a pro, ask him what to eat," and I turn to her and I say, "Ma'am, I don't want to bust your bubble here, but little Johnny here has got about one chance in a million to make it. Why don't you just let him play for fun?" "Oh, no, he is going to make it." So you got to educate not only the kids, the players, the coaches, and the parents—whew, the parents, we all know that.

But getting back to your question, I think the majority of them want to be tested. They agreed to the agreement. So whatever the ramifications are that they are worried about, the reliability, I think these gentleman up here have, you know, certainly made it clear. Other than that, I don't know. I really think they want to play on an even field. I know I would.

Mr. CUMMINGS. Mr. Gimbel, part of our goal here today is to ensure the health and safety of professional athletes while ensuring fairness and integrity in the game. But we are also concerned about the millions of young people that participate in middle school, high school, college athletics across the country.

What message does it send to young athletes that play the sports when the NFL players don't get tested? I mean, what do you—what does that say?

Mr. GIMBEL. Well, I think we——

Mr. CUMMINGS. You talked about being addicted to winning. Are you—and from what you know and listening to the doctors, and I am sure you have done your own research on this, I mean, do you have doubts about the accuracy of the test?

Mr. GIMBEL. No, I don't have any doubts about the accuracy of the test. I think we have all done our homework to know about it. The same with other testing that is done.

And I think the importance, you know, when Dick was saying about reaching parents and the attitude of parents who believe that every child is going to be a star, and the reality is that kids have lost the fun of playing sport because it is about winning. And that pressure starts so young that these kids are looking for an edge. The little skinny kid is looking for an edge because he has been told by his parents or the coach, You better bulk up.

And then they look up at the colleges and they look up at the pros, and they see their role models, one, getting busted; you know, two, getting in trouble; you know, three, getting injured over and over. And they look at that, and, yeah, that has an impact, but they also look at the fact that their way of getting there might be through drugs because that is going to get them the scholarship, that is going to get them out of the ghetto, that is going to get them out of the neighborhood, that is going to get them their chance.

And they are willing—and this is what they say—you know, if winning is everything, they will do anything to win. And that is the scary part.

Mr. CUMMINGS. Just one last question.

Dr. Bowers, I keep going back to what you said about lightning and the chances of being—what did you say? The chances of an athlete who has not used synthetic growth hormone testing positive are comparable to the chance of that same athlete being struck by lightning.

Mr. BOWERS. Correct.

Mr. CUMMINGS. That is incredible. So what you are saying is, then—and I think you said 11 folks have been found——

Mr. BOWERS. That is correct. There have been 11 positive tests out of 13,000.

Mr. CUMMINGS. And so, are there any other tests—I know there are two tests now—are there any other tests, Dr. Tabak or Dr.

Bowers, in the pipeline that could even be more accurate? Just curious.

Mr. BOWERS. I wouldn't make the distinction of accurate. All of the tests are accurate.

The isoforms test that I described, the limitation of it is it has a very short detection window. Basically, 2 days after you take the drug, it is undetectable again. The other test that has been in development, the biomarkers test, probably detects the use of growth hormone out to 8 to 10 days afterwards.

So the two tests are complementary. They are both accurate. They just test for different times after the person takes the drug.

Mr. CUMMINGS. Thank you very much, Mr. Chairman.

Chairman ISSA. Thank you.

We now recognize the "I wasn't a player, just a placekicker" for 5 minutes, Mr. Chaffetz.

By the way, you haven't looked at George Blanda at the end of his season. You are still always on the roster.

Mr. CHAFFETZ. Well, the most important statistic for a kicker is we never lost a game by the margin of my missed kicks. Otherwise, I would be in Arizona or California at this point in my life. But it was a great experience, and it is a great sport and America loves it. And there are a lot of kids that look up to the people that engage.

And to Mr. Butkus and the others that have gone through a lot of pain in playing the roughest—one of the roughest sports around, the public enjoys it, but we have to send the right message to the youth.

Mr. CHAFFETZ. So, Mr. Chairman, Ranking Member Cummings, and to the five members who are testifying here today, I appreciate your passion and your willingness to testify on this issue. The importance of this issue is that we as a country make sure that our youth, in particular, and others don't go down the wrong direction.

I do want to make sure, though, that we inform the public of the distinction between the synthetic recombinant human growth hormone injections that artificially raise growth hormone levels and keep them unnaturally elevated for periods of long time versus perhaps a dietary supplement that provides nutritional support to the pituitary to produce optimum youthful levels of natural HGH release that flows to the body's natural rhythms. And I think the testimony here today does reflect in part the difference and the distinction between the synthetic recombinant human growth hormones and maybe some of the other more natural levels of HGS. In fact, I would ask unanimous consent, there is a company that is in my State of Utah that wants to make sure that we are distinguishing the differences. And I ask unanimous consent to insert into the record their letter.

Chairman ISSA. Without objection, so ordered.

Mr. CHAFFETZ. Thank you.

Dr. Bowers, two things. One is, in your testimony, you said that an additional population study is needed. My understanding is that the Players Association and the NFL have agreed to do this population study. So I don't think that that is necessarily applicable. My other part of it is a question. The tests that you are performing,

have those been peer-reviewed? By whom have they been peer reviewed? And how were they peer reviewed?

Mr. BOWERS. So peer review takes a number of forms. One of the ways can be publication. And I mentioned that the test—there have been four publications about this test that are in the literature. That is one form of peer review. Another form of peer review is to get a group of scientific experts together around the table, present data, have them talk about it, and then go forward with their recommendations. And that also has been done with growth hormone over the last—like I said, since 1999, we started——

Mr. CHAFFETZ. But specific to the test that you are doing?

Mr. BOWERS. Yes. All of those things have happened specific to the test that I have talked about.

Mr. CHAFFETZ. And have you given all of that to the NFL and to the Players Association? Do they have access to that? All of it?

Mr. BOWERS. Yes, they do.

Mr. CHAFFETZ. My understanding is that perhaps they don't. So, just as a point of clarification for the record, my understanding is you will provide all of that information that we just talked about to both the Players Association and to the NFL.

Mr. BOWERS. We offered, USADA offered to go talk with the player representatives and show them all the data that USADA has, answer any questions that they have, and they never took us up on it.

Mr. CHAFFETZ. Is there anything that you wouldn't show them?

Mr. BOWERS. That I have accessible?

Mr. CHAFFETZ. Uh-huh.

Mr. BOWERS. No.

Mr. CHAFFETZ. Okay. All right.

I thank you all, again. I appreciate this. I think it is an important topic. And I hope they continue to execute.

Thank you, Mr. Chairman.

Chairman ISSA. Would the gentleman yield?

Mr. CHAFFETZ. Sure. Sure.

Chairman ISSA. I just want to sort of come back to what Mr. Cummings had started on. If you were to look below the current levels, the threshold, the very conservative threshold, is it likely that some of those who would not test positive are in fact doping? In other words, I want to understand, not only is it a lightning question, but isn't it true that, in some cases, because it is such a short window, basically somebody dopes 3 days before, you are seeing it, but you are not considering it a false. Is that correct?

Mr. BOWERS. That is correct. I mean, the threshold has been set intentionally very high. And when you do that, you are accepting a number of what would be false negatives. So the people are actually using it, but you are saying I am willing to exclude that just so we don't get anyone having a false positive.

Chairman ISSA. Just one follow up. It also means that, under the current testing, they could juice in the off off-season and get away with it. This is a relatively limited testing period in which they are really only being tested during the playing season, if you will. Isn't that correct? In other words, it is not year-round testing.

Mr. BOWERS. Yeah. I am not totally familiar with what the NFL does. Certainly, for USADA, 90 percent of our growth hormone tests have been no notice, out of competition.

Chairman ISSA. Right, your random tests.

Mr. BOWERS. Right.

Chairman ISSA. Though this one, as I understand it, is less aggressive.

With that, we go to the gentleman from Missouri who was patiently not leaving the dais, Mr. Clay.

Mr. CLAY. Thank you so much, Mr. Chairman.

And thanks for conducting this hearing. Recently, the NFL Players Association raised questions about the science that underlies the HGH test, arguing that it should not be applied to NFL athletes. This HGH test has been used at the Olympics since 2004.

Dr. Tabak, correct me if I am wrong, but WADA is recognized as a scientific leader in this field. Is that correct?

Dr. TABAK. Yes, that is correct.

Mr. CLAY. And despite the variations in size and body types that exist among NFL players, there are Olympic equivalents that span the full range. For example, six-time Pro Bowl wide receiver Randy Moss is 6'4" and weighs 215 pounds. Gold medallist sprinter Usain Bolt stands at 6'5" and 210 pounds. In fact, the sports reporters in this room may remember that Bolt was flirting with the idea of trying out for the NFL.

Mr. Butkus, I don't know about you, but I don't see any conceivable relevant difference between these two athletes. Do you?

Mr. BUTKUS. Nope. Not really.

Mr. CLAY. So what is it that the NFL players are talking about here? I mean, why are they saying there is a distinction or that they have—that size and body types are different?

Mr. BUTKUS. I really don't know. I am just saying that they are being represented by their union, and one false positive can mean a guy's reputation. But again, like I say, I bet you the majority or all of them want to be tested.

Mr. CLAY. Another example is 2012 weightlifting bronze medalist Ruslan Albegov, who at 6'4", 324 pounds, is roughly the same size as 11-time Pro Bowl lineman Larry Allen, who is 6'3", and 324 pounds. Dr. Bowers, again, I don't see any relevant difference between these two athletes. What do you think?

Mr. BOWERS. I agree. And I can even add a little more to that. If I look at the top 1 percent, the highest growth hormone test results that we have seen, the three sports that were involved were bobsled, a driver; cycling; and three track and field sprinters. None of them are particularly big individuals. So the highest test isn't correlated at all to body size.

Mr. CLAY. Can you talk about the test for growth hormone in sport and the research that went into its development?

Mr. BOWERS. I can. The search for a test for growth hormone abuse started back in 1996. It split into two different paths, one of which is the test we are discussing today, which is the isoforms test. And that test was based on the fact that when people were given growth hormone, this test could discriminate or classify people correctly into users and nonusers.

The other test, having recognized that a 2-day window was probably not going to be the best solution for us, the other test is a biomarkers test. And that basically is an indication of the effect of growth hormone on the body. And so since those effects last much longer than growth hormone is actually there, the window of detection is much broader. And those are the two tests that are currently under development.

Mr. CLAY. And did the trials include a wide range of individuals with a wide range of body types?

Mr. BOWERS. Yes, it did.

Mr. CLAY. And has the test also gone through the peer-review process? And what were the results of that process?

Mr. BOWERS. So as I mentioned, the isoforms test has had four publications related to the test itself. They are published in the peer-reviewed literature. The biomarkers test has had more than 33 publications laying the background for the test. And again, those are all in the peer-reviewed literature. So quite a bit of research has been done over the last, what, 15 years.

Mr. CLAY. Thank you so much.

And Mr. Chairman, just yesterday, in fact, the committee received a letter from Scott Blackmun, the CEO of the U.S. Olympic Committee, stating, quote, "Given the stringent review process, the USOC has the utmost confidence in the WADA-approved testing methods to detect HGH." And I ask unanimous consent to enter this letter into the record.

Chairman ISSA. Without objection, so ordered.

Chairman ISSA. I thank the gentleman.

We now go to the distinguished gentleman from Tennessee, Dr. DesJarlais.

Mr. DESJARLAIS. Thank you, Mr. Chairman.

Thank you, gentlemen, for joining us today. I want to take this just in a little different direction than we have gotten to so far. As a practicing physician for 20 years before coming to Congress, I think that we are kind of overlooking, to some extent, the source of the problem here. And to my knowledge, HGH is not something you can go down to GNC and get. HGH is going to have to be prescribed by a physician.

I know from my experience, and I have had patients come in who were undersized, off the growth chart at young ages when they are hitting puberty, and those discussions have occurred, whether it is appropriate to use this hormone. And generally, that is a problem that is referred to on to an endocrinologist.

Now, I guess what is confusing to me here is why is this so readily accessible? And who are the doctors who are providing this for the wrong reasons? And why is the punishment not starting there? And then maybe we don't have to worry as much about it.

I know bad things will happen as long as there is bad people or bad players in the game. Can anyone enlighten me on what the punishment history has been for physicians prescribing HGH?

Dr. Goldberg?

Dr. GOLDBERG. Many of the kids who get both HGH or think they are getting HGH, or anabolic steroids, get them from the Internet. If you put in "buy HGH" or "buy steroids," you can get many, many thousands and thousands of hits, and you can send

away for vials of steroids or human growth hormone. Whether they are, in reality, human growth hormone or steroids is questionable. And they have been looked at. Many of them are phony. But from Eastern Europe, you can get those. They are readily available.

Mr. DESJARLAIS. That is without a doctor's prescription, or do they just forge them?

Dr. GOLDBERG. Oh, without a doctor's prescription.

Mr. DESJARLAIS. Okay. So there is a certain—yes, Mr. Gimbel?

Mr. GIMBEL. The other issue here is the fact that many athletes, pro, college, certainly high school, are going to health food stores, GNC stores, buying tons of muscle supplements, which are not regulated. The FDA does not regulate that industry.

In surveys that have been done randomly over the years, many of these products have had HGH and anabolic steroids in them. We just don't know. You know, the fact is that these products are working, and they are working so well, my assessment, and many other professionals, is something is not right. And it needs to be regulated.

So we have got a whole industry, from energy drinks up to what you buy in these stores or on the Internet, it is not regulated. So it is a real kind of a Russian roulette crapshoot when it comes to what these kids are buying, which they are probably getting more from the Internet and these stores than they are from their doctors.

Mr. DESJARLAIS. Dr. Goldberg?

Dr. GOLDBERG. Well, you can't get HGH from a pill. You can get anabolic steroids. The IOC did a study of U.S. supplements; in 2003, it was published that 18.6 percent of supplements, of 240 supplements analyzed, had true anabolic steroids in them. Of course, that wasn't on the label. But because they are not regulated, they can put those in to make them work.

Mr. DESJARLAIS. Okay. And I know creatine has become a big problem as an over-the-counter supplement. I know I have a son, Mr. Butkus, who played linebacker and in his senior year this year was 140 pounds. As you said, he is not going to the next level. But as much as he and his other teammates wanted to continue to use creatine, I told them the perils of this, and yet, at halftime or all throughout the game, they are laying on the sideline getting their cramps stretched out, whether it is their calves or hamstrings.

In college football, we see players routinely going into the locker room at halftime getting IV fluids. That is probably not something that was as common in your day. And this is because this dehydrates and causes these muscles to cramp.

So it shows even as a physician and a father, I could not influence my own son from going off to GNC and taking this. So that is a big challenge. How do we do a better job? I know that you have been working on it.

Mr. BUTKUS. I guess we just got to keep on pounding the pavement and educating them. The parents, I mean, I come across a Pop Warner coach, he comes up to me, and he says, you know what, I finally had to have a meeting with my parents of my 9-year-olds.

I said, really? I said, about what?

He said, just before the game, the parents make them go back in the parking lot and they chug down energy drinks at 9 years old.

I am saying, I am trying to reach high school kids. You mean to tell me I got to go to grammar school now?

Or the case of telling that story to another Pop Warner coach that came by, and he said that is nothing, Dick. I actually caught a mother giving a 9-year-old a laxative so he could make his weight at 9 years old.

Mr. DESJARLAIS. Wrestling that happens for sure.

Just as a point of personal privilege, I have to tell you that I have gotten over my grudge against you. Growing up in South Dakota, I was an avid Viking fan. And I was not upset when you retired in 1973. But that has been 40 years ago, and I have gotten over it.

Mr. BUTKUS. That is probably why you have been so successful. Thank you.

Chairman ISSA. Forty years. That is all it takes?

You notice I haven't gotten over losing the Browns to Baltimore. But 40 years might do it.

With that, we now go next to—wait a second. I want to make sure I get this just right—Mr. Quigley, who was here at the start.

Mr. QUIGLEY. Thank you, Mr. Chairman.

I appreciate your having this hearing, and our panelists, to your participation. Those watching us know that the House has a long history of having hearings about performance-enhancing drugs in sports, some of them famous, some of them infamous.

But what struck me in looking at this meeting was that it used to be that Major League Baseball was behind, right? Now it is the only major sport testing for HGH. So if the MLB association and the commissioner and the teams can agree on this, it makes no sense to me that the National Football League can't as well.

I just want to go in the weeds a little bit with anybody on the panel that wants to help. The way you take HGH is in a sequence, correct? So you are on this for a while, and then you are off this for a while? I would like a little nuance here, what that means in terms of why one of these two tests is preferred, given what you mentioned earlier about the fact that there is a gap where the test only lasts for a short period of time.

Mr. BOWERS. Well, there is not a preference for one versus the other. They are complementary. So when we get them both validated, then we will use both of them. A good example was we had the biomarkers test used at the games in London this summer. And two athletes in the Paralympics in power lifting tested positive by the biomarkers test and did not test positive by the isoforms test. And the reason was they admitted to using growth hormone about 8 days before.

Now, unfortunately, since the Olympic games, one of the companies that was supplying the kits that we were using for the biomarkers test has taken it off the market. And so until we can validate another procedure for that particular test, we can't use it.

Mr. QUIGLEY. And there was—is anyone doing the biomarkers test now at all?

Mr. BOWERS. The only lab that was approved to do it was the London lab for the Olympics. To the best of my knowledge, there are no other labs that have been approved to use that test.

Mr. QUIGLEY. And again, back to what I mentioned before, and that is the sequence in which an athlete would take human growth hormone. There is a period in which they would go on, and there is a period in which they would naturally go off. How does that affect the timing of the testing?

Mr. BOWERS. Well, again, both of the tests are really best used in what we call no-advance-notice, random or out-of-competition testing. So testing on game day, for example, doesn't make a lot of sense to me. I would be doing my testing away from that, when people are training and at a time when they don't know that they are going to be tested. That makes both tests most effective.

Mr. QUIGLEY. But they take this for how long a period, and then how long are they off it, typically?

Mr. BOWERS. The answer is, it depends. But they would take a cycle that might be every day for several weeks and then stop. So any time you got them during the period of time that they were taking it, the test would probably be positive. There are some athletes who we have been—that we have interviewed that stay they take it for weight loss. Those people use it slightly differently than what I just described, so it would be a little more difficult to find them if you were going to schedule a test in advance, for example.

Mr. QUIGLEY. Again, but who advises these athletes? Who is out there that are these masterminds? How do they find the athletes or vice versa to get such—you have to admit at least some sophistication in understanding how to take this, if at all safely, safely, and then what sequence.

Mr. GIMBEL. Well, one of the things we found over the years is that there is a lot of money involved here. And there are lots of companies who are interested in getting to athletes and selling their products and teaching them how to do it. You may remember years ago, we were into this cycle with the Balco lab, where every time the government would ban a certain chemical in a steroid, they would go back and change it, because again, it is supply and demand. It was a market for the product. People were willing to pay. There is an underground. There are trainers. There are people who will teach athletes how to do things the wrong way. Because again, their goal is to play as long as they can, be as strong as they can, as fast as they can, recover from their injury. There is a lot of money at stake. So there are people that will teach them, we have found, whether it is a trainer, whether it is a coach. There are people that will teach the other side as much as we are trying to teach how to do it the right way.

Mr. QUIGLEY. Thank you.

Mr. Chairman, I also represent Wrigley Field. I actually look out over Wrigley Field from my house. And you didn't have to be a fan of the Bears or the Vikings or the Packers or whomever to appreciate what Mr. Butkus did on that field to make this game great.

And I thank all for participating.

Chairman ISSA. I thank the gentleman.

We now recognize the gentleman from South Carolina, Mr. Gowdy.

Mr. GOWDY. Thank you, Mr. Chairman.

Science, Mr. Chairman, is the reason some of us went to law school. So I am not going to be asking any questions rooted in science.

Chairman ISSA. Though the gentleman is not that kind of lawyer.

Mr. GOWDY. No, sir. I was not. And I am not any kind now.

But I do want to ask some questions concerning reliability. Because if memory serves me correctly, you can be suspended from the NFL for certain criminal offenses. And I am wondering if there are any studies on the reliability of jury verdicts that the Players Association is insisting on before you can suspend someone for suffering a criminal conviction.

Hearing no response, I think you can also be suspended, Mr. Butkus, for certain tackles or certain conduct on the field, which requires either Mr. Goodell or Mr. Tagliabue to ascertain someone's intent, whether or not they had a malicious intent to injure, before you can be suspended. And I am wondering whether or not the Players Association is insisting on some test studying the reliability of ascertaining people's malice or mental intent.

Mr. BUTKUS. That wasn't going on when I was playing. There were no rules.

Mr. GOWDY. I am not aware of any test now where they have scientifically tested Mr. Goodell's ability to ascertain people's intent when they go to tackle someone.

But here is the big issue to me. You can be suspended for trafficking in HGH. That would be a crime. So you could be suspended for that, right? What test would they use in court? If you can be suspended for the conviction, and that test is good enough for the Players Association, why can't you be—that same test be good enough in this realm? Not all at once. Is there a different test you would use if there were a prosecution for an NFL player for trafficking in HGH? And we all agree they could be suspended for suffering that conviction, right? How is the test that would be used in court to determine whether or not it was HGH any different from the test that is being proposed now?

Mr. BOWERS. Well, there is a slight difference, but I agree totally with your comments that, again, it is inconsistent, and it seems appropriate that you would do the test that you agreed to do.

Mr. GOWDY. Well, Mr. Chairman, I think that there was a clause in the CBA over the next several weeks, the two parties would develop specific arrangements to implement HGH testing with the goal of beginning testing by the first week of the 2011 regular season. Has anyone been able to determine what the intent of the Players Association was when they agreed to that language? Was there a test they had in mind when they agreed to that? Is the chairman aware? Is there any test that they would find acceptable?

Chairman ISSA. If the gentleman would yield?

Mr. GOWDY. Yes, sir.

Chairman ISSA. In the previous season, the ranking member and I had a proposed deal in which they would simply collect the samples so that when they agreed to this eventually, they would at least have a collection of essentially retroactive evidence. We had an agreement. They left. The agreement fell apart. They refused to have even a collection. So I guess I would have to tell the gen-

tleman that one of our frustrations is they wouldn't even agree to eventually have a test once they agreed to it. And that has been one of the frustrations is the ranking member and I personally met and thought we had an agreement; it then got reneged on by one side to, I think, the detriment of the players' well being.

Mr. GOWDY. Well, I will close with this, Mr. Chairman, because I just can't unlock this conundrum. You pick your favorite player. Mine would happen to be a Dallas Cowboy. But pick your favorite player, can be suspended from the NFL if they suffered a conviction for trafficking in HGH, after a court case, after due process. If they are convicted, they could be suspended. How is the test that would be used to lead to that conviction different than what is being proposed in this setting? If it is good enough for that way to be suspended, why is it not good enough for this way? Is the science somehow different in a courtroom than it is outside the courtroom?

Mr. BOWERS. Not that I am aware of, no.

Mr. GOWDY. I would welcome the opportunity to ask the Players Association that question, but I won't get it today, so I will yield back.

Chairman ISSA. I thank the gentleman. I thank him for his insightful questions.

With that, we go to the gentleman from the north of Virginia, Mr. Connolly.

Mr. CONNOLLY. Thank you, Mr. Chairman.

And thank you to our panelists for being here today.

Mr. Butkus, I want to assure you 70 is the new 40.

Mr. BUTKUS. Cool.

Mr. CONNOLLY. Just like 60 or 62 is the new 30. Better be.

And Mr. Butkus, maybe I can begin with you. You talked passionately about your awareness of the fact that, as an athlete, as a professional athlete, you are and have been a role model for a lot of young people. And you took that responsibility to heart. Among your colleagues, including those who are current players, is it your sense that most players understand that and take it seriously?

Mr. BUTKUS. I would hope so, but I can't say it is across the board. I would only say that, as far as I am concerned, football meant everything for me. And you know, it is sort of payback time. It is give back. And that is what we try to instill. We used the Butkus Award for the most outstanding in linebackers as a vehicle to play clean. Anybody that is eligible gets a letter from us, take the pledge that you will play clean. And that is all we can do.

And, you know, we reach millions of kids. And that is just one of my ways of giving back. I don't know. It has been tough, though. This is—I would pick one of the most difficult things because of what Mr. Gimbel was saying about this deal about winning.

Mr. CONNOLLY. Yeah. Because, you know, Mr. Cummings was talking about kids in his district in the Baltimore area, many of whom are low income, can't afford to ever go to an NFL game, but they are very aware of NFL players as role models. And if they are taking drugs, the rest of us can say until we are blue in the face, just say no, stay clean, don't do it, but if their role models are doing it, it kind of vitiates the whole point.

Mr. BUTKUS. I believe so.

Mr. CONNOLLY. The title of this hearing is, "HGH Testing in the NFL: Is the Science Ready?" And I am glad we are having a hearing that empowers science.

Dr. Goldberg, is the science ready?

Dr. GOLDBERG. Well, that is really up to Dr. Bowers and the validity of the test. I mean, we look at sensitivity and specificity of testing, and this is a test, the way Larry describes it, is more like testing for alcohol. It is going to be very difficult to find positive tests. But when you find a positive test, it is probably a true positive. So that is what is important.

If it is to weed out all users, because it is cycled on and off, much like anabolic steroids are, half the time when you test, you are not going to find it because—and then if you are testing only—how frequently you are testing will determine whether you are going to pick up anybody or very few people. So if an athlete feels it enhances their performance and that is the reason they are playing in the NFL or any other league, they will take that chance to use it if they think, as one athlete told me, I would rather be playing in the NFL than driving a truck in Idaho.

Mr. CONNOLLY. If I understand your testimony correctly, Dr. Goldberg, I thought you said, or maybe it was another panelist earlier, that the incidence of false positives is next to nothing?

Dr. GOLDBERG. That is what I think Larry said that.

Mr. CONNOLLY. Dr. Bowers?

Mr. BOWERS. Yeah, that is correct. And as I said, there have been—worldwide, there have been 13,000 tests done. There have been 11 positives. Eight of the eleven admitted use. The other three, you know, it is in the lawyers'——

Mr. CONNOLLY. If I can, so if I am understanding your testimony and that of Dr. Goldberg, we don't have a plethora of false positives, which would suggest the science of the testing is fairly accurate. But what we do have is an understatement of the use of HGH because of the regularity of testing, the randomness of it, the timing of it. So, as a matter of fact, those 13 positive, or whatever the number, probably significantly understate the widespread use of HGH. Is that right?

Mr. BOWERS. I would agree with that, yes.

Mr. CONNOLLY. You would agree with that. So the science isn't so much the question. And you haven't commented on that. Dr. Goldberg kind of passed that off to you, Dr. Bowers. Would you comment on the accuracy of the science? Are we ready? Is the science ready for this kind of testing in the NFL?

Mr. BOWERS. Yes. I mean, we had a question before I think about the peer review of this. I can tell you I organized a meeting in 2004. Of the 75 people that attended, 20 were growth hormone experts that had no association with sports. And based on the recommendation of that meeting in 2004, the test was implemented at the Olympics in Athens in 2004. So there definitely has been peer review. People have looked at this, discussed it, and have confidence in it.

Mr. CONNOLLY. Thank you.

Thank you, Mr. Chairman.

Chairman ISSA. I thank the gentleman.

Would you yield for a second?

Mr. CONNOLLY. Of course.

Chairman ISSA. I think the gentleman makes a great point, that this test, at best, will be a little bit like police out on the freeway with radar guns. The vast majority of people drive over the speed limit and do not encounter a policeman. But on occasions, they do. And the accuracy of the radar gun, sadly, is quite good.

Mr. CONNOLLY. And Mr. Chairman, I will also add to that, if you are charged, it is not a defense in a court of law to say, well, everyone else was doing it, too.

Chairman ISSA. Exactly. The gentleman is correct.

Dr. GOLDBERG. Mr. Issa? Right here. Over here.

Chairman ISSA. Oh, yes. Dr. Goldberg. I wasn't looking at you.

Dr. GOLDBERG. With that analogy, a very good analogy with the speed, and everyone else, as you know, will slow down when that person is caught on the side.

Chairman ISSA. Nothing slows you down more than those flashing lights for the other guy.

Dr. GOLDBERG. But then go down the road 3 more miles, and they are all speeding again.

Chairman ISSA. The gentleman is correct. Of course, no one in this audience today is suggesting that police stop looking for speeders.

And with that, we recognize the gentleman from Arizona, Dr. Gosar.

Mr. GOSAR. Thank you, Chairman.

Mr. Butkus, I would like you to look up at the monitor. We are going to look at a quote from London Fletcher, the middle linebacker for the Washington Redskins. "Hopefully, the NFL and the NFL Players Association will implement the new HGH test that has been endorsed by the international anti-doping officials."

Next slide. It shows another quote from free agent wide receiver Anthony Gonzalez. He seems to agree with London Fletcher. "It is a huge step for our league. And I know talking to other guys in the locker room, they are in favor of it, too. A lot of rules in the new CBA are safety-oriented, and this is as important, or more important, than anything else."

Let's go to the next slide. It is a quote from Atlanta Falcons tackle Tyson Clabo. And he said, "If guys start getting busted, then, obviously, there was a need. And I don't anticipate that there is going to be a large flux of guys getting caught because I don't see it really being a huge problem. But there is really only one way to find out, and that is to start testing."

So, for you, my question is, it really sounds like many of the players are in favor of it.

Mr. BUTKUS. Yeah. I haven't taken a survey, but I would believe they are.

Mr. GOSAR. And it seems to me that there is a Nike quote that really is applicable here, just do it. You know, if there is enough players, you know, you overrule your players rep, and you just do it.

Mr. BUTKUS. Well, they have got a union, and they are representing their players in what they think is right. And in this case, you have a player representative from the Falcons saying that let's move on with it, so let's get the testing done. And another one

said that there might be a surprisingly few that will come up positive. So you are right. I don't know the answer to that. Again, I would just think they would all—they all sound like they all want to play on an even playing field.

Mr. GOSAR. And it seems to me like we ought to be having their voices heard.

Mr. BUTKUS. Probably moreso than mine.

Mr. GOSAR. And I give no quarter. In fact, I am going to take it another step. I applaud you for how you look at yourself as a role model, because I think there is a counterculture. And I think it is exemplified in a comment that came from Charles Barkley in regards to his aspect as a role model versus Karl Malone. And the dialogue was very intense but so articulate. You know, I disagree with a lot of pro ball players. You know, I am around enough of them to know that it is also about me, me, me.

Mr. BUTKUS. True. And that goes along with what Mr. Gimbel has been saying, win, win, win, at any cost. I just, like I said before, football, I mean, since I was 9 years old, has been very good to me. So I am just—it is a way to pay it back. And as far as these other statements, I don't go around trying to be a hero, but I don't know what happens, but if people are going to listen to something positive that I may say or help kids with, then I got to take that obligation and do it.

I mean, believe me, I don't feel great sitting here doing this. I am a former player. But what we got to do is we got to think about the kids. And I realize that kids are looking up. I mean, to say that they are not is, geez, look at Fantasy Football. I mean, come on. What other event in the world stops—besides something tragic—than the Super Bowl. Come on.

Mr. GOSAR. I agree.

Mr. BUTKUS. You know? So I don't know, I am just doing my little part. I appreciate what you are saying.

Mr. GOSAR. And I would appreciate a lot more of the NFL players to take notice and pick up that role of leadership and personal accountability and personal responsibility to that role.

I got one more question to Dr. Tabak and Dr. Bowers. Have we seen any other studies that kids that do HGH and some of these other enhancement drugs, are they much more prone to be doing illicit other drugs?

Dr. TABAK. So, unfortunately, there are very few studies that speak to HGH, per se, amongst the young. But anecdotally, one-off case reports, there is a report of poly use, particularly with anabolic steroids.

Mr. GOSAR. I think this would be one that we would really like to follow up on because of compulsive behaviors. There is some type of tracking that is here.

Dr. Goldberg?

Dr. GOLDBERG. Yeah. There is multiple studies showing that those who take performance-enhancing drugs are polysubstance users. There is not just a case report; this is all over the world literature. So if you are going to reduce performance-enhancing drugs, you have to try and reduce alcohol and other drugs as well.

Mr. GOSAR. I just ask a point of personal privilege. I will say I was also one of those struggling Vikings fans growing up in west-

ern Wyoming. So we were really happy to see you retire. But thank you very much for the way you played and the way you hold your head very, very high. We appreciate that. Thank you.

Chairman ISSA. God, you are rough. I thought DesJarlais held a grudge.

We now go to the gentleman from Texas, Mr. Farenthold.

Mr. FARENTHOLD. Thank you, Mr. Chairman.

And Mr. Butkus, I would like to follow up on the line of questioning Dr. Gosar just completed. We heard the quotes that he brought out from various players. We have heard from this panel pretty much unanimously indicating that the use of HGH has some potential side effects. And we heard, and I think it is common sense, that we want our athletes to compete in a fair fashion, without chemically-induced advantages. So where is the resistance to this? Having been in the NFL and been looking at it from the outside for some years, why aren't both sides saying, let's just get this done, be over with it, and take this problem off the table?

Mr. BUTKUS. I don't know.

Mr. FARENTHOLD. Anybody else on the panel?

Mr. BUTKUS. I mean, I don't know why. There must be some doubt as far as the reliability. But these gentlemen have proven, or at least they got documentation that it is reliable. I have no idea with why they wouldn't go along with it. Again, I think it is the lawyers' involvement.

Mr. FARENTHOLD. Dr. Gimbel?

Mr. GIMBEL. I think as we look at the bigger picture of substances that are being used by athletes, we talked earlier about the supplements that you can buy on the Internet, that you can buy in health food stores, that may or may not contain illegal substances. And I think a lot of athletes that I have talked with, who have gotten caught through drug tests, have said, all I did was go to GNC and buy some protein powder or some muscle product. I didn't know that it had anabolic steroids or whatever broke the rule.

And I think there is some concern that this is a bigger issue. And I think some athletes may be concerned that they are going to do the right thing but also get caught doing something that might be wrong. So I think, as we look at this, as I think the panel has been talking about, that the issue of unregulated supplements is a huge issue that needs to be addressed by the FDA.

Mr. FARENTHOLD. That is probably a can of worms that we don't have time to get into today and is outside the scope of this hearing.

I do want to take another step back. And I don't want to diminish the negative impacts that these banned substances or any other substance has on our players after they retire or our youth as they are moving forward. But I would also be concerned as to what is the appropriate role of the Federal Government in here? I realize it is fun to have football greats like Mr. Butkus in to testify. It is an honor to be in the same room with somebody I admired growing up. But isn't this something that might be better worked out—is there a way to work this out without the Federal Government being involved in it? And I will entertain comments from anybody on the panel.

Mr. Gimbel?

Mr. GIMBEL. I would just like to say that several years ago, when the first steroid hearings were held, I think it opened up a dialogue and opened up to the American people about performance-enhancing drugs in Major League Baseball at the time. And I think that was such an important role that this committee did because it gave us, who work with kids, a lot of leverage, a lot of knowledge. And it also woke up a lot of professional, college, high school athletes, not only about the dangers, but the consequences. So I think there is a definite role in doing what this committee has been doing, which is dialogue and awareness and educating the public.

Mr. FARENTHOLD. Obviously, protecting our kids is absolutely critical. But I do hear from people when I am back home, you know, you are about to go off the fiscal cliff, what are you doing having a hearing on HGH? And so——

Mr. GIMBEL. Let me just finish and just add this, if the public was aware of the number of our kids who are taking some level of these performance-enhancing drugs, they would be demanding these hearings. Because if it were cocaine or heroin or anything else, they would be saying, why aren't we doing something?

Mr. FARENTHOLD. But haven't we done our part by making illegal their use? Or are we just basically up here trying to educate the public?

Mr. GIMBEL. I think that is a huge role. I think we are trying to clarify the questions and make it very clear what the role is of parents, of coaches, of the leagues, as well as the government of what we are supposed to do and what we can and can't do, what we can control and what we can't.

Mr. FARENTHOLD. I see my time has expired. I would like to thank you all for being here.

Mr. Chairman, thank you for the opportunity.

Chairman ISSA. I thank the gentleman.

Would he yield for a moment?

Mr. FARENTHOLD. I will.

Chairman ISSA. Perhaps I can answer one of your constituents' concerns before the ranking member does his closing. And that is that the one thing I get asked all the time is, can't Congress do more than one thing at a time? And so, to a great extent, yes, there are leadership working on the cliff. There are committees working on what they are doing. And I think this committee, wasn't even supposed to be in session this week, is trying to take full advantage of being here to do as many things as we can. And I might note that the gentleman has been incredibly helpful at looking at doing oversight on a lot of things that people may not have understood until we started finding out, for example, hydraulic fracturing was under attack, and so on.

So I want to thank the gentleman for multitasking in his life as well.

Mr. Gowdy, before we go to closing, did you want to do a second round for any reason?

Mr. GOWDY. No, sir, Mr. Chairman.

Chairman ISSA. Thank you.

Then I would yield to the ranking member for his closing.

Mr. CUMMINGS. Thank you very much, Mr. Chairman.

Again, I want to thank all of you for being here today.

You know, one of the things that I say to my kids, I tell them, Mr. Butkus, I tell them, try to figure out what is the enemy of your destiny. What is the enemy of your destiny? And because I believe that if they try to figure out what might block them from getting to where they have got to go, that they will begin to change those things now so they can get to where they are trying to go.

I would hate to think that the enemy of our young people's destiny is them looking up to athletes who may be doing something improper, and then they try to emulate that, and the next thing you know, they find themselves in trouble.

So a lot of people ask, why would the chairman and this committee look into these things? It is not that we want to be beating up on the league or anything like that. We do care about our children. And we have had our chance. And that is one of the things I admire about all of you all. We have had our chance. The question is, what chances are we blocking our children from having? And so your testimony has been very, very helpful.

And hopefully, as we move down the line, the players will see how incredibly ridiculous it looks for them not to—maybe they need to talk to their lawyers, let's just put it like that—and straighten this thing out. We have got to move off of this. We have got to move down the line. We are getting ready to go into a third season. And it does not look very good.

I think, too, part of responsibility is when you agree to something, carrying through with it. And if you can't carry through with it, at least show a good reason why you can't, and then make it—I mean, show that there is a way forward if you can get it done. Right now, we are not seeing that. And but your testimony has been very, very helpful because you have put on the record not only the science but the effect that it has on our young people and folks.

So thank you very much.

And thank you very much, Mr. Chairman.

Chairman ISSA. Thank you, Mr. Cummings.

And I want to again thank our witnesses. Making the record is an important part of the process. Each of you has brought an insight.

Mr. Butkus, even though you don't have a Dr. or a Ph.D. in front of or behind your name, I think your humbleness and your recognition—or our recognition that your continued dedication to a clean sport added more than all the science perhaps can add to the human side of this hearing.

For our scientists, I want to thank you for beginning the process of making it clear that a number, a contract, and a testing regime has to occur, and can occur, and certainly has occurred in most of the rest of the sports world. So again, I want to thank you for your time as we go into the holiday season.

And we stand adjourned.

[Whereupon, at 11:52 a.m., the committee was adjourned.]

Chairman Darrell Issa Hearing Preview Statement

"HGH Testing in the NFL: Is the Science Ready?"

December 11, 2012

This Committee's resources and time are normally focused on waste, fraud, and abuse in the federal bureaucracy. There is certainly no lack of challenges facing this country that the Federal government must address. So why has this hearing on the science behind HGH testing been called? The fact of the matter is that the lack of a testing regime in the NFL for Human Growth Hormone – or HGH – is a public health concern. It affects not just the health and safety of NFL players, but more importantly endangers young athletes who admire and often try to emulate them.

There is no question in my mind that the NFL and its players are best positioned to police their own league. On HGH, however, there has been a frustrating lack of progress on testing. The possibility that federal legislation could eventually be adopted to address this problem may be unlikely at this point, but the league and its players would be unwise to ignore it. For the past year and a half, the Ranking Member and I have heard from the league and the players association that they share an interest in implementing a test for HGH, which they agreed to do in August of 2011. Despite that meeting of the minds, we have played nearly two full seasons without a test in place.

In a series of meetings, the players told us that they are not comfortable with the current test for HGH. They have raised a range of concerns—that the test is unreliable, it doesn't account for the size and exertion of NFL athletes, and even that drawing blood from a player on game day would affect his performance. The Committee does not have the resources to evaluate whether those concerns are valid. What we can do is get input from the scientific community and other stakeholders to better understand whether the current test for HGH is reliable. I am hopeful that after hearing testimony from witnesses, we will be in a better position to help the league and the players overcome obstacles to implement a test without further delay.

The reality is that the actions of the NFL and its athletes matter. All across America, the passion for professional football transcends our differences. Football unites families, communities, and – as RG3 has shown us here in Washington – cities in ways that political leaders can only imagine. We all certainly agree that performance enhancing drugs are dangerous. Human Growth Hormone, when used for non-FDA approved purposes, is no exception. It has many known and potential health risks. HGH has no place in America's most popular sport. The hearing's distinguished panel of witnesses represent scientific institutes and organizations concerned about the negative effects of performance enhancing substances on the game of football and America's youth. I look forward to their testimony.

###


ENDOCRINE REVIEWS
APRIL 2012 · VOLUME 33 · NUMBER 02
2010 Impact Factor 22.469
Growth Hormone Doping in Sports: A Critical Review of Use and Detection Strategies
Gerhard P. Baumann
Cardiovascular Biology of the Incretin System
John R. Ussher and Daniel J. Drucker
New Roles of Carboxypeptidase E in Endocrine and Neural Function and Cancer
Niamh X. Cawley, William C. Wetsel, Saravana R. K. Murthy, Joshua J. Park, Karel Pacak, and Y. Peng Loh
Prolactin and Growth Hormone Aggregates in Secretory Granules: The Need to Understand the Structure of the Aggregate
Priscilla S. Dannies
Allosteric Modulators of Steroid Hormone Receptors: Structural Dynamics and Gene Regulation
Raj Kumar and Iain J. McEwan
THE ENDOCRINE SOCIETY
www.endo-society.org

REVIEW

Growth Hormone Doping in Sports: A Critical Review of Use and Detection Strategies

Gerhard P. Baumann

Partnership for Clean Competition, Colorado Springs, Colorado 80919; and Division of Endocrinology, Metabolism, and Molecular Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois 60611

GH is believed to be widely employed in sports as a performance-enhancing substance. Its use in athletic competition is banned by the World Anti-Doping Agency, and athletes are required to submit to testing for GH exposure. Detection of GH doping is challenging for several reasons including identity/similarity of exogenous to endogenous GH, short half-life, complex and fluctuating secretory dynamics of GH, and a very low urinary excretion rate. The detection test currently in use (GH isoform test) exploits the difference between recombinant GH (pure 22K-GH) and the heterogeneous nature of endogenous GH (several isoforms). Its main limitation is the short window of opportunity for detection (~12–24 h after the last GH dose). A second test to be implemented soon (the biomarker test) is based on stimulation of IGF-I and collagen III synthesis by GH. It has a longer window of opportunity (1–2 wk) but is less specific and presents a variety of technical challenges. GH doping in a larger sense also includes doping with GH secretagogues and IGF-I and its analogs. The scientific evidence for the ergogenicity of GH is weak, a fact that is not widely appreciated in athletic circles or by the general public. Also insufficiently appreciated is the risk of serious health consequences associated with high-dose, prolonged GH use. This review discusses the GH biology relevant to GH doping; the virtues and limitations of detection tests in blood, urine, and saliva; secretagogue efficacy; IGF-I doping; and information about the effectiveness of GH as a performance-enhancing agent. (*Endocrine Reviews* 33: 155–186, 2012)

I. Introduction

The use of GH as a performance-enhancing agent is believed to be widespread among both professional athletes and adolescents participating in sports (1–4). GH is classified as a prohibited substance on the World Anti-Doping Agency (WADA) Prohibited List [http://www.wada-ama.org/en/World-Anti-Doping-Program/Sports-and-Anti-Doping-Organizations/International-Standards/Prohibited-List/]. Aspects of GH that are attractive to athletes are its purported ergogenic activity, aid in recovery from injury, and "undetectablity" (Table 1). A detailed time line of the use of GH in sports is presented in Holt *et al.* (5). This review critically evaluates the scientific underpinnings of GH use in

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A

doi: 10.1210/er.2011-1035 Received August 16, 2011. Accepted December 20, 2011.
First Published Online February 24, 2012

Abbreviations: ALS, Acid-labile subunit; CS, chorionic somatomammotropin; GHBP, GH binding protein; GHR, GH receptor; GHRP, GH-releasing peptide; GHS, GH secretagogue; hGH, human GH; IGFBP, IGF-binding protein; IRMA, immunoradiometric assay; mol wt, molecular weight; MS, mass spectrometry or mass spectrometric; P-III-NP, procollagen type III amino-terminal propeptide.

TABLE 1. Rationales given for using GH as a doping agent in sports

GH is ergogenic (performance-enhancing)
GH is the master anabolic hormone
GH increases skeletal muscle mass — and hence strength and endurance
GH enhances assimilation of nutrients to build tissues
GH is lipolytic, with calories liberated from adipose tissue redirected to build muscle and to be utilized as metabolic fuel
GH accelerates recovery from sports injuries
GH causes beneficial weight loss
The use of GH, a natural substance, cannot be detected in antidoping tests

sports, with particular emphasis on strategies and methods of detection of exogenous GH administration.

II. Background Information on GH Structure, Function, and Regulation

GH is a pituitary polypeptide hormone with anabolic and growth-promoting activity. Both its structure and function are species-specific. The only GH with bioactivity in humans is human GH (hGH) or the closely related primate GH (6, 7). In contrast, hGH is biologically active in a number of lower species, a feature that has been termed "one-way species specificity." hGH also has lactogenic activity, a feature that is lacking in nonprimate GH. This review will only discuss hGH because animal GH are not pertinent in the context of doping in humans.

A. GH genes

The human genome contains five GH-related genes, located in the GH gene cluster on chromosome 17q24.2. This locus occupies approximately 47 kilobases and contains two GH genes—*GH-N* (or *GH1*) and *GH-V* (or *GH2*)—as well as the related chorionic somatomammotropin (CS) (also known as placental lactogen) genes (8). These multiple genes are believed to have arisen by gene duplication. Each of the five genes in the cluster is composed of five exons and four introns. The *GH-N* gene is expressed in pituitary somatotrope cells and, to a minor extent, in lymphocytes, whereas *GH-V* and *CS* genes are expressed in the placenta. The level of GH gene expression in lymphocytes may be sufficient to play a local paracrine/autocrine immunoregulatory role, but it is insufficient to fulfill a hormonal role at distant sites. In the absence of pituitary (or placental) GH gene expression, there is no detectable GH in blood, and the clinical features of severe GH deficiency ensue.

B. Primary GH gene products

The main product of the *GH-N* gene is a 191-amino acid, 22,129 molecular weight (mol wt), single chain, simple (unmodified) protein with two disulfide bridges (Fig. 1). It is the prototype pituitary GH and is known as 22K-GH. It is also the recombinant GH available for therapeutic use (and for doping purposes). Another GH isoform, the 20K-GH variant, is also derived from the *GH-N* gene by alternative mRNA splicing (9); it has a structure analogous to 22K-GH, except for the deletion of internal residues 32–46. It has 176 amino acids and a mol wt of 20,274. It arises from the use of an alternative splice site in exon 3 and is expressed at 5–10% of the expression level of 22K-GH. A third isoform (17.5K-GH), arising from skipping of exon 3 and lacking residues 32–71, has been proposed as an additional GH variant based on the finding of a transcript (10). This form has not been shown to be expressed in significant amounts under normal physiological conditions.

The *GH-V* gene product, GH-V, GH2 or placental GH, is a 191-amino acid, 22,321 mol wt, single chain protein with two disulfide bridges, similar in structure to 22K-GH (Fig. 1). Its sequence differs from that of 22K-GH at 13 amino acid positions. It contains a consensus sequence for N-glycosylation at position 140 and exists as both a glycosylated and a nonglycosylated form. The *GH-V* gene does not produce significant amounts of a 20K variant (11, 12). GH-V is exclusively produced by the placenta and during pregnancy progressively supplants GH-N in the maternal circulation (13, 14). It has similar somatogenic activity as GH-N but has reduced lactogenic activity (15–17).

CS is also produced by the placenta in considerable amounts. It has about 85% structural homology with GH, but has no significant somatogenic bioactivity. GH-V and CS will not be further discussed in this review because they have limited relevance for GH doping. Thus, the term "GH" will refer to hGH-N and its isoforms.

C. GH isoforms

GH is not a single protein, but consists of several molecular variants (isoforms). A detailed treatise on GH isoforms has recently been published (18); a synopsis tailored to the purposes of the current review follows (Table 2). The principal and most abundant GH form in pituitary and blood is monomeric 22K-GH. This is also the isoform produced commercially for therapeutic purposes, known as "recombinant GH." Because of its availability, it is also the form typically used for GH doping. The 20,000 mol wt variant, known as 20K-GH, is the second most abundant isoform in pituitary and plasma (5–10% of total GH) (19, 20). It has a propensity to dimerize, and its dimer is enriched compared to the 22K-GH-dimer (19, 21, 22). Recombinant 20K-GH has been produced pharmaceutically (23) but was never developed for therapeutic use. Whether

Figure 1.

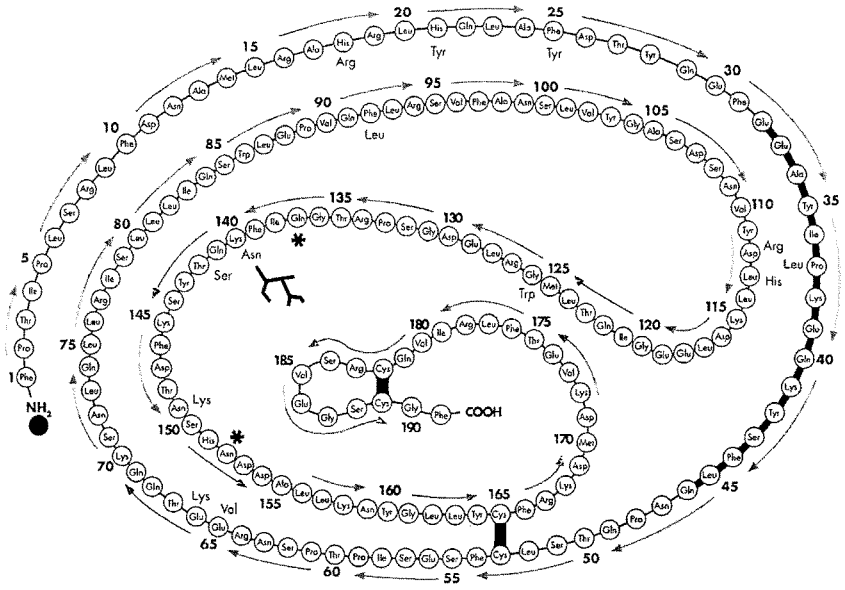


Figure 1. Primary structure of hGH and its isoforms. The main chain represents 22K-GH (GH-N). The sequence indicated by the *bold line* from residue 32 to 46 is deleted in 20K-GH. The *black dot* at the amino terminus denotes the acyl (probably acetyl) group in N-acylated GH. The *two asterisks* denote the deamidated residues in desamido-GH forms. The amino acid designations next to the main chain denote the residues that are changed in placental GH (GH-V). The *tree structure* at residue 140 indicates the glycosylation site in glycosylated GH-V. [Reproduced from G. Baumann: Growth hormone heterogeneity: genes, isohormones, variants, and binding proteins. *Endocr Rev* 12:424–449, 1991 (20), with permission. © The Endocrine Society.]

it is available for illicit use is currently unknown. Several posttranslationally modified monomeric GH forms exist; they include two deamidated forms (Asn^{137} and Asn^{152}), N_α-acylated, and glycosylated [an O-linked N-acetylhexosamine-hexose-(neuraminic acid)$_2$ glycomoiety at Thr^{60} has been proposed] 22K-GH (24–27). Proteolytically cleaved GH forms are not considered native forms (20). GH isoforms also exist as an oligomeric series of at least up to pentameric GH, with both covalent (disulfide-linked) and noncovalently associated oligomers. Homo- as well as heterooligomers composed of the described monomeric forms have been described. Oligomers are present in the pituitary, are secreted as such, and circulate in blood (21, 22, 28, 29).

D. GH structure

The tertiary structure of monomeric 22K-GH (and 20K-GH) is a four-helix, antiparallel, twisted bundle characteristic of the cytokine family of proteins (30). Crystal structures have not been obtained for the other GH isoforms, but it is likely that they retain the same overall conformation. Part of helix 1 and the loop between helices 1 and 2 with its embedded minihelix are missing in 20K-GH (30).

E. The GH receptor (GHR)

GH action is initiated by its binding to the GHR in target tissues. The GHR is a plasma membrane-resident receptor of the cytokine receptor class I superfamily (31). It is expressed ubiquitously and is particularly abundant in the liver (32, 33). The GHR primary structure differs among species, and the species specificity of GH action is dictated by high-affinity interaction of GH with its cognate GHR. GH has two receptor binding epitopes on its surface; upon binding of a GHR to site 1, a second GHR

TABLE 2. Estimated average proportions for GH isoforms in human blood 15–30 min after a secretory pulse

Monomeric GH	
22K-GH	45%
20K-GH	5%
Acidic GH (desamido-, acylated, and glycosylated GH)	5%
Dimeric GH	
22K-GH dimers	
Noncovalent dimers	14%
Disulfide dimers	6%
Total 22K-GH dimers	20%
20K-GH dimers	
Noncovalent dimers	3%
Disulfide dimers	2%
Total 20K-GH dimers	5%
Acidic GH dimers (desamido-, acylated, and glycosylated GH)	
Noncovalent dimers	1.5%
Disulfide dimers	0.5%
Total acidic GH dimers	2%
Oligomeric GH (trimer-pentamer)	
22K-GH oligomers	
Noncovalent oligomers	7%
Disulfide oligomers	3%
Total 22K-GH oligomers	10%
20K-GH oligomers	
Noncovalent oligomers	1%
Disulfide oligomers	0.5%
Total 20K-GH oligomers	2%
Acidic GH oligomers (desamido-, acylated, and glycosylated GH)	
Noncovalent oligomers	1%
Disulfide oligomers	0.5%
Total acidic GH oligomers	2%

Adapted from G. Baumann: Growth hormone heterogeneity: genes, isohormones, variants, and binding proteins. *Endocr Rev* 12:424–449, 1991 (20), with permission. © The Endocrine Society.

binds to site 2, forming a 2:1 complex between GHR and GH (34). The two GHR exist in a predimerized form; binding of GH leads to a conformational change of the dimer followed by signal transduction (35–37). The GHR signals through several intracellular phosphorylation cascades, of which the JAK2-Stat5b pathway is particularly important for its growth-promoting activity (37, 38). The other pathways include the IRS-PI3K, SHC-MAPK, PIP-Akt, Stat 1 and 3, and other signaling cascades; their discussion goes beyond the scope of this review.

hGH also interacts with the prolactin receptor (39); it is unclear whether it can fully supplant the role of prolactin in lactation. Animal GH do not bind to the prolactin receptor, although in some species (*e.g.*, cow) GH promotes milk production through the GHR. This property is the basis for the commercial use of bovine GH in the dairy industry.

F. Biological activities of GH

Table 3 lists the principal biological activities of GH. Of particular interest to the athlete are its anabolic and lipolytic activities. From these properties alone it has been assumed that GH must be an ergogenic, performance-enhancing substance.

TABLE 3. Principal biological activities of human GH

Nitrogen retention
Amino acid transport into muscle
Promotion of somatic growth
Growth plate elongation
IGF-I generation
IGFBP3 generation
ALS generation
Lipolysis
Sodium retention
Phosphorus retention
Insulin antagonism
β-Cell hyperplasia
Early insulin-like effect
Lactogenesis
Modulation of immune function

The various GH isoforms have qualitatively similar bioactivities in humans (reviewed in Ref. 18). The reduced diabetogenic activity attributed to 20K-GH based on some rodent data has not been confirmed in human subjects (40). Among the monomeric forms, their *in vivo* bioactivity appears to be similar in both qualitative and quantitative terms. Oligomeric GH forms generally have reduced bioactivity compared with GH monomers as assessed by *in vitro* assays; there is only limited information about their bioactivity *in vivo* (18).

G. Regulation of GH secretion

GH is secreted from the pituitary gland in a pulsatile fashion under dual hypothalamic control by GHRH (stimulatory) and somatostatin (inhibitory). Ghrelin, derived from the stomach and possibly the hypothalamus, plays at best a minor role in physiological GH secretion. [In contrast, ghrelin and its synthetic congeners (GH secretagogues, GHS) or GH-releasing peptides (GHRP) are potent pharmacological stimuli for GH secretion when administered *in vivo*.] GH secretory pulses occur every 2–3 h and vary greatly in amplitude (41–43) (Figs. 2 and 3). The largest pulses generally occur at night and are associated with stage IV (slow wave) sleep, typically in the early phases of the sleep cycle. The ultradian pattern of GH secretion differs between the sexes, with women having generally higher secretion rates/serum levels, more erratic secretion patterns, and higher interpeak (basal) GH secretion/serum levels compared to men (Fig. 2). This difference is attributable to an estrogen effect (44).

The GH secretion rate peaks during adolescence and declines thereafter throughout life, with an approximately 15% decline per decade (45). Obesity attenuates GH secretion; undernutrition and physical fitness enhance it

Endocrine Reviews, April 2012, 33(2):155–186

Figure 2.

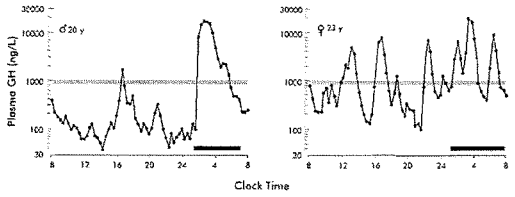


Figure 2. Diurnal profiles of plasma GH concentrations. Patterns representative for men (*left*) and women (*right*) are shown. Note the logarithmic ordinate, which serves to highlight the lower range of GH fluctuations. The *hatched bar* denotes the 1 ng/ml level commonly taken as the boundary between basal and stimulated GH levels. The *solid black bars* indicate sleep periods. Note the higher nadirs, higher peak averages, and generally "noisier" pattern characteristic of women. [Adapted from L. M. Winer *et al.*: Basal plasma growth hormone levels in man: new evidence for rhythmicity of growth hormone secretion. *J Clin Endocrinol Metab* 70:1678–1686, 1990 (41), with permission. © The Endocrine Society.]

(45–47). Acute physiological stimuli for GH release are sleep, exercise, stress, and fasting (46, 48–50). The GH response to exercise has been well-documented and reviewed in detail (51–55).

GH inhibits its own secretion through both short loop (autofeedback) (56, 57) and long loop (IGF-I-mediated) feedback (58, 59) (Fig. 4). Feedback regulation occurs both at the hypothalamic (principal site of GH autofeedback) and pituitary levels (main but not exclusive site of IGF-I feedback). Additional feedback regulation of GH secretion occurs through metabolic factors elicited by GH action (*e.g.*, free fatty acids, glucose).

With respect to GH isoform secretion, there is no evidence for differential regulation of isoforms. Rather, it appears that all isoforms are cosecreted during a secretory burst (60–63) (Fig. 3).

Figure 3.

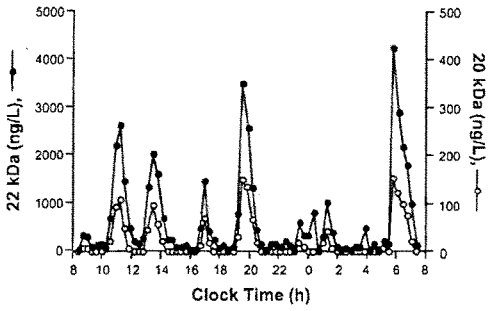


Figure 3. Cosecretion of GH isoforms. Diurnal profiles of 22K-GH and 20K-GH in serum. The temporal coincidence of 22K-GH and 20K-GH peaks is evident, indicating cosecretion of the two GH isoforms. [Reproduced from K. C. Leung *et al.*: Physiological and pharmacological regulation of 20-kDa growth hormone. *Am J Physiol Endocrinol Metab* 283:E836–E843, 2002 (62), with permission. © American Physiological Society.]

H. Metabolism and clearance

A major portion of the metabolic clearance of monomeric GH occurs in the kidney, with efficient glomerular filtration followed by extensive degradation in the proximal tubule (64–68). Only approximately 1/10,000th of glomerularly filtered GH is excreted in the final urine (69, 70). Other sites of metabolic clearance are the liver and other tissues, where GH is cleared via GHR-mediated cellular uptake and intracellular degradation. There is little quantitative information available on this process and how it is distributed among organs; the liver is thought to be an important site because the GHR is abundantly expressed in that organ.

The plasma half-life of total (free and GH-binding protein bound) GH is approximately 14–18 min (see *Section II.I* for discussion of GH-binding proteins) (67, 71). Estimates for free and bound GH are 11 and 27 min, respectively (72). The half-life of 20K-GH is somewhat longer (19–25 min) than that of 22K-GH (61, 62). It is not clear whether this property is due to its tendency for dimer formation, thereby slowing renal clearance, to its lower affinity for the GHR, or both. Similarly, the clearance of oligomeric GH forms is also slower than that of monomeric GH; with reported plasma half-lives of 19, 27, and 45 min for monomeric, dimeric, and oligomeric GH, respectively (73). The slower clearance of 20K-GH and oligomeric forms is reflected in the (compared with 22K-GH) longer half-life of "pituitary GH," which contains all these isoforms (61). Because of the differences in clearance rates, the relative proportions of GH isoforms in blood change over time, with relative accumulation of the more slowly cleared forms (61). This is the main reason for the observation that 20K-GH and oligomeric GH forms tend to be proportionately higher in blood than in the pituitary (74).

The pharmacokinetics of exogenous 22K-GH in healthy young volunteers after iv injection

Figure 4.

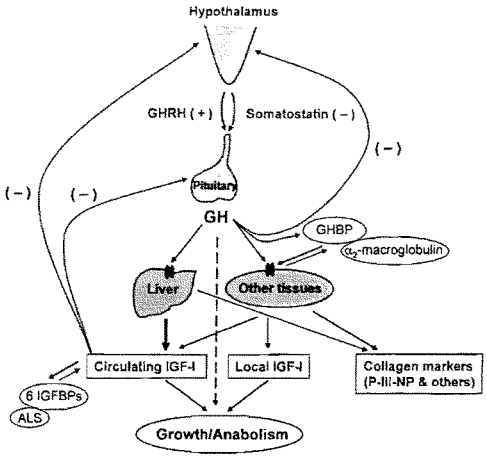


Figure 4. The GH-IGF-I axis. Schematic representation of the hypothalamic-pituitary-peripheral GH-IGF-I axis. *Minus signs* denote inhibitory action, the *plus sign* denotes stimulatory action. The *dashed line* indicates direct (non-IGF-I-mediated) GH action on tissues. Collagen markers produced by tissues in response to GH are added for the purposes of this review, although they are not strictly part of the GH-IGF axis. [Adapted from G. Baumann: Growth hormone binding proteins. In: The Endocrine System in Sports and Exercise, WJ Kraemer and AD Rogol, eds, 2005, with permission. © Wiley-Blackwell Publishing.]

show a plasma half-life of 22 min, a volume of distribution of 70 ml/kg, and a clearance rate of 135 ml/kg · h (75). After sc injection, a plasma peak is achieved at 4 h, the half-life is 3.8–4 h, the clearance rate is 179 ml/kg · h, and plasma GH stays elevated for at least 12 h (62, 75) (Fig. 5). After im injection, the values are similar to those after sc administration, except that the peak is reached earlier (at 2 h) and the half-life is 4.9 h (75). It should be noted that half-lives after sc or im administration are not true half-lives, but represent a combination of continued absorption and elimination kinetics. Absolute bioavailability is listed as 75% after sc and 63% after im injection (75). The pharmacokinetics of exogenous 20K-GH in healthy young subjects, as assessed in a single study using sc administration, showed a plasma peak time of 3.7 h and a half-life of 1.9–2.9 h (76).

Administration of either 22K-GH or 20K-GH suppresses endogenous GH secretion for at least 12 h, as evidenced by the absence of secretory pulses of 20K- or 22K-GH, respectively (62, 76) (Fig. 5).

I. GH in blood

After secretion, GH rapidly associates with two circulating GH binding proteins (GHBP) (Fig. 4). Binding to the main (high-affinity) GHBP is readily reversible and follows a dynamic equilibrium. The high-affinity GHBP is the ectodomain of the GHR, generated from the GHR by the action of the metalloproteinase TNF-α converting enzyme (see Ref. 77 for review). The low-affinity GHBP has been shown to correspond to the transformed form of α_2-macroglobulin (78). Under basal conditions (GH level <10 ng/ml), 45–55% of 22K-GH and ~25% of 20K-GH is bound to the high-affinity GHBP, and 5–7% is bound to the low-affinity GHBP. At higher GH levels (>20 ng/ml), the fraction of GH bound to the high-affinity GHBP declines due to saturation of the GHBP (79). The circulating complexes have mol wt of ~85,000 and > 150,000, respectively. GHBP protect GH from renal clearance and degradation; the complexes serve as a circulating GH pool, prolonging the bioavailability of GH. In addition, GHBP competes with GHR for GH binding and may inhibit signaling, thereby modulating GH bioactivity. The high-affinity GHBP can interfere with GH measurement in serum (see *Section II.L*).

Serum GH levels are conventionally reported as total (bound + free) GH. They fluctuate widely, reflecting the pulsatile secretion from the pituitary (Figs. 2 and 3). In the basal state (interpulse levels), GH levels range between 0.01 and 1 ng/ml. After a secretory pulse, they may range between 1 and 100 ng/ml. The boundary between a basal level and a small pulse is ill-defined and somewhat arbitrary. Pulse detection algorithms, such as cluster and deconvolution, can help define what constitutes a pulse. The highest serum GH peaks are typically seen at night (during slow-wave sleep) and generally reside in the 10–20 ng/ml range. Occasionally, peaks can be considerably higher. During the day, GH peaks are typically smaller, in the 2–10 ng/ml range. The spectrum of GH pulse amplitudes extends over at least two orders of magnitude, and peaks of widely varying height can occur at any time. Age, gender, body mass index/adiposity, physical activity, stress, time of day, and nutritional and metabolic status all influence GH secretion.

Most GH immunoassays do not fully discriminate between GH isoforms but may differ partially in their recognition of isoforms; this has implications for GH measurement by immunoassay (see *Section II.L*). Isoform-

Endocrine Reviews, April 2012, 33(2):155–186 edrv.endojournals.org 161

Figure 5.

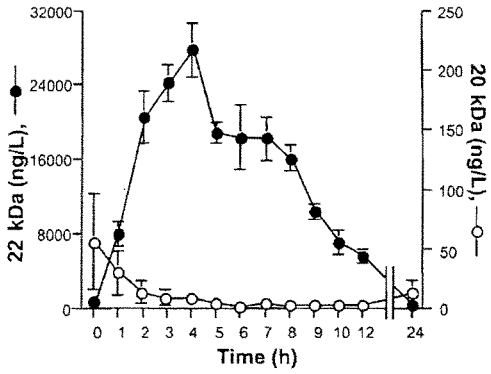


Figure 5. Response of serum 20K-GH to exogenous GH administration. The pharmacokinetic serum profile of sc injected recombinant 22K-GH is depicted in the *solid circles*. In response to the exogenous GH, endogenous 20K-GH is suppressed for a period between 12 and 24 h (*open circles*). [Reproduced from K. C. Leung *et al.*: Physiological and pharmacological regulation of 20-kDa growth hormone. *Am J Physiol Endocrinol Metab* 283:E836–E843, 2002 (62), with permission. © American Physiological Society.]

specific immunoassays have been developed for 22K-GH and 20K-GH (and placental GH). Using these assays, the proportion of 20K-GH as part of total serum GH ranges between 3 and 28%, with an average of 5–9%, and with no consistent differences between adults, children, genders, ages, or physiological states (61–63, 74, 80, 81). No specific assays exist for the other GH-N related isoforms; their proportions in serum (Table 2) are derived from physicochemical separation followed by polyvalent immunoassay (82–86).

The stability of GH in blood is high. GH is an inherently stable protein with a long shelf life when purified. Degradation within blood is minimized by the high concentration of protease inhibitors present in plasma (87). GH concentrations in serum or plasma stored at 4 C or at −20 C are not changing significantly over days to weeks (88) (G. Baumann, personal observation). Incubation of pituitary GH with human blood plasma at 37 C for up to 24 h has not revealed detectable degradation products (89). No statistically significant changes in serum immunoreactive GH concentrations were found after 24 h at room temperature, 2–7 d at 2–8 C, or 6 months at −15 C (90). Thus, GH is not subject to significant intravascular metabolism or degradation in blood plasma or serum stored *ex vivo*.

J. GH in urine

Small amounts of GH are excreted in the urine. Despite the fact that glomerular filtration is the main route of GH clearance, the uptake and degradation of filtered GH in the proximal nephron is so efficient as to leave only a minute fraction (~0.01%) to reach the final urine (69, 70). This process is mediated by the multispecific megalin-cubulin-amnionless receptor system, which leads to endocytosis of filtered proteins followed by their proteolytic digestion in lysosomes (see Ref. 91 for review). Thus, urinary GH excretion accounts for less than 0.005% of the GH secreted by the pituitary or administered exogenously (69, 70, 92, 93). Nevertheless, even these small amounts are readily measurable by modern immunoassays (94–100). In older, less sensitive assays requiring larger sample volumes, the high osmolality of urine caused interference and spuriously high readings (70, 92, 101).

With respect to urinary excretion of GH isoforms, there is only very limited information. Baumann and Abramson (70) showed evidence of the presence of monomeric 20K-GH and acidic GH forms in urine but found no evidence for dimeric or oligomeric GH. Similarly, Mauri *et al.* (102) reported only monomeric GH in urine. This would be expected based on molecular size restriction at the glomerular sieve. There are only two reports that show evidence for 20K-GH in the urine (70, 103).

The stability of GH in stored urine was evaluated by Main *et al.* (95), who showed stability at −20 C for 2 wk but a 25% loss over 7 months, whereas GH remained stable when stored at −80 C for the same period.

The amount of GH excreted in the urine is highly variable, both between subjects and within the same individual from day to day, with intraindividual coefficients of variation of 40–60% (95, 104, 105). Numerous studies in the 1990s evaluated the potential utility of 24-h urinary GH excretion as a diagnostic tool for disorders of GH secretion, such as hypopituitarism, GH deficiency, and acromegaly (94–98, 100, 104–109; only a few selected references are listed here, but a complete list is available from the author upon request). Urinary GH excretion rises after administration of exogenous GH (106, 110), but there is limited information and likely overlap with normal excretion rates. In all, over 3200 subjects have been evaluated, representing a robust database on urinary GH excretion. The results of these studies can be summarized as follows. 1) The amount of GH excreted in normal sub-

jects in a 24-h period ranges between 0.3 and 80 ng, a greater than 100-fold range, with the majority of values between 2 and 15 ng per 24 h. 2) Excreted amounts vary widely among subjects for reasons that are poorly understood. 3) On a population basis, urinary GH excretion roughly follows trends of plasma GH (*e.g.*, values are lowest in hypopituitarism, high during puberty, highest in acromegaly, *etc.*), but there is substantial overlap between these categories. 4) Among individuals, there is no correlation between 24-h integrated plasma GH levels and urinary GH excretion. 5) No correlation is found between urinary GH excretion and auxological measurements in children. 6) Day-to-day variation in excretion renders the interpretation of a single measurement unreliable. 7) The intra- and intersubject variability far exceeds that which can be attributed to analytical imprecision and disparities among assays. And 8) Individual urine GH measurements are too variable to be useful as a tool for clinical diagnosis, even in conditions at the extremes of the GH secretion spectrum (*i.e.*, hypopituitarism and acromegaly). GH excretion is also strongly impacted by renal factors, such as proteinuria of pathological or physiological origin (including exercise-induced proteinuria) (107, 108, 111). Renal insufficiency also leads to increased GH excretion (112). For all these reasons, the scientific literature on urinary GH excretion has largely fallen silent in the last decade. Two recent publications reported the use of isopropylacrylamide hydrogel particles loaded with Cibacron Blue to concentrate GH from urine before immunoassay (113, 114). The GH concentrations measured by that technique are lower (<1 pg/ml) than those by direct assay. Unfortunately, no recovery data were reported, and it appears likely that adsorptive losses may have contributed to incomplete recovery of GH from the particles. This would be expected at such low protein concentrations and would explain the lower values. No results were reported on isoforms extracted from urine. It is not clear whether concentration of GH from urine is advantageous over direct measurement using high-sensitivity assays.

K. GH in saliva

There is little information on the presence of GH in saliva. One study in normal subjects reported salivary GH levels to be 1000-fold lower than those in serum and a significant correlation between salivary and serum GH concentrations (115).

L. GH measurement

GH in biological fluids can be measured by *in vitro* bioassay, radioreceptor assay, or immunoassay. Bioassays and radioreceptor assays are not suitable for routine purposes, are highly vulnerable to interference from GHBP, and are generally used only in the research setting. Immunoassays are of either the single-site competitive type or the two-site sandwich type [radioimmunoassay (RIA), immunoradiometric assay (IRMA), enzyme immunoassay (EIA), enzyme-linked immunosorbent assay (ELISA)], and use radioactivity, colorimetry, fluorescence, or chemiluminescence as a readout. Modern immunoassays in clinical use are of the two-site immunometric design and are highly sensitive. Most antibodies recognize all GH isoforms, but a few isoform-specific assays exist for 22K-GH, 20K-GH, and placental GH. Disparities of results obtained by different assays of up to at least 100% have been reported, depending on reagents, epitope recognition among GH isoforms, assay design (equilibrium *vs.* nonequilibrium, incubation time, and temperature), and matrix effects. Important, but not exclusive, reasons for assay disparities are differential recognition of GH isoforms and interference by the high-affinity GHBP. Typically, modern monoclonal, nonequilibrium assays are more affected than older, polyclonal assays with longer incubation times. This topic has been reviewed in detail (116, 117). Efforts are under way to harmonize GH measurements in clinical chemistry laboratories as much as possible, and a recent workshop of the GH Research Society, the IGF Society, and the International Federation for Clinical Chemistry and Laboratory Medicine (IFCC) has addressed this issue (118). Although assay discrepancies present a significant problem in the clinical arena, they are less of a concern in the antidoping field because absolute levels of GH are not a major endpoint in detection of GH abuse.

Nonimmunological, mass-based measurements of GH in biological fluids [*e.g.*, mass spectrometry (MS)] are currently not used because of insufficient sensitivity of these methods at the GH levels prevailing in blood or urine. Efforts are being made to improve sensitivity with the goal to develop MS-based assays for GH in serum (119, 120).

III. Strategies for Detection of GH Abuse

The fact that exogenous GH is identical to the main form of endogenous GH (22K-GH) renders its detection challenging. Thus, conventional forensic identification methods for foreign substances are not applicable. Furthermore, the pulsatile secretion pattern of GH makes it difficult, if not impossible, to interpret a high serum GH level as evidence for GH doping. Two main strategies for detection have been developed: the GH isoform test and the biomarker test. Both are currently applicable only to blood samples.

A. The GH isoform test

The GH isoform test is a direct detection method (by itself not definitive, for reasons mentioned above) com-

bined with a biological response based on suppression of endogenous GH secretion by exogenous GH. This general strategy, first proposed by Wu *et al.* (121) and Momomura *et al.* (103), was further developed (90) and tested at the Olympic Games in 2004 (Athens), 2006 (Turin), and 2008 (Beijing); it is now in general use as a WADA-sanctioned test. In essence, the test consists of two GH immunoassays: one that is relatively specific for 22K-GH and another that is "permissive," that is it recognizes a number of pituitary isoforms in addition to 22K-GH. It is not known to what degree the various GH isoforms (except for 20K-GH; see *Section III.A*) are measured by the permissive test, but such knowledge is not critical for antidoping purposes. A dose of exogenous GH suppresses the endogenous forms, including 22K-GH, 20K-GH, and other isoforms (Fig. 5). Thus, the ratio between 22K-GH and pituitary GH increases because most of the measurable GH is of exogenous origin (90, 121). For validation purposes, WADA requires two independent assays, and thus two separate pairs of 22K-GH-specific (named "rec" for recombinant) and permissive (named "pit" for pituitary) antibodies are used in two independent assays (named A and B) (90) (Fig. 6). Using these assays, the normal rec/pit ratio has a median value of approximately 0.8 and ranges from 0.1 to 1.2. The median value of less than 1 reflects the fact that 22K-GH accounts for only 75–80% of the GH isoforms. The current rec/pit ratio cutoffs ("decision limits") used by WADA for evidence of doping is 1.81 for men and 1.46 for women (assay kit 1) and/or 1.68 for men and 1.55 for women (assay kit 2) (122). These values have been derived from the analysis of athlete samples obtained under real-world doping control conditions and are designed to yield a combined test specificity (between the two kits) of 99.99%. Of interest, none of the four assays in current use measures 20K-GH because the detection antibody used for signal generation does not recognize 20K-GH (90). Replacement of the detection antibody with one that also recognizes 20K-GH would probably be advantageous because 20K-GH is an important constituent of pituitary GH. It has been suggested that the permissive assay could/should be replaced by a specific 20K-GH assay, which would be chemically better defined and scientifically more rigorous (103, 123). Although correct, this idea would be disadvantageous if an athlete were to use a mixture of 22K-GH and 20K-GH in physiological proportions. It is unknown whether recombinant 20K-GH, which has been pharmaceutically produced but not marketed, is available on the black market. With the permissive assay, it is unlikely that an athlete could duplicate a normal pattern unless he or she were taking cadaveric GH or using a GH secretagogue. Thus, both specific assays and permissive assays have their unique advantages and disadvantages. It may be possible in the future to supplement the existing isoform test with one that specifically measures the 22K-GH/20K-GH ratio, keeping the above-mentioned relative ease of evading detection by such a test in mind. All four assays used in the GH isoform test show some cross-reactivity with GH-V (placental GH) (90), raising the question of applicability of the test in pregnant women. Interference by GH-V is negligible at levels below 10 ng/ml, which in normal pregnancy are not reached until the end of the second trimester (13, 14). Since most women in their third trimester are not likely to participate in competitive sports, and since pregnancy is usually obvious at that

Figure 6.

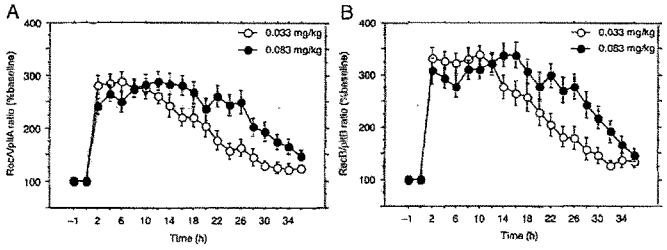


Figure 6. GH isoform test. The response of the rec/pit ratio to administration of exogenous GH (two dose levels) at time 0 in two different assays (assay A in *left panel*, assay B in *right panel*). The ratio rises to 250–350% over baseline and remains elevated for 24–36 h. The higher GH dose results in longer elevation of the ratio. For a 70-kg person, the GH doses listed correspond to 2.31 and 5.81 mg, respectively. [Reproduced from M. Bidlingmaier *et al.*: High-sensitivity chemiluminescence immunoassays for detection of growth hormone doping in sports. *Clin Chem* 55:445–453, 2009 (90), with permission. © American Association for Clinical Chemistry.]

stage, GH-V cross-reactivity in the GH isoform test is not a significant problem in practice.

The isoform test is an excellent strategy to detect GH doping, provided it is administered shortly after the last GH dose (within ~24–36 h, depending on the dose) (90), realistically probably within 12–24 h. A recent placebo-controlled study of the detection time window in young men after administration of recombinant GH (33 μg/kg, or ~2.3 mg for a 70-kg person), and using the currently employed WADA assays, procedures, and decision thresholds, showed a postinjection duration of test positivity of 14.5 ± 5.5 h (mean ± SD) (248). In the same study, repeated daily administration of the same dose of GH for 2 wk and sequential testing revealed that blood samples obtained 10 h after the preceding GH dose always tested positive, whereas samples taken 21 h after the preceding dose always tested negative. This short window of opportunity has been the Achilles heel of the isoform test, with the first positive result occurring only after more than 2 yr of general implementation encompassing more than 1500 tests (124). This experience is not indicative of presumed (and in some cases acknowledged) use of GH; it can be explained by the athletes stopping GH injections at least 1 d before an expected test. The test, therefore, is not well suited for in-competition testing. Its use in unannounced out-of-competition testing, however, should be more successful in catching GH abusers, and recently it has been used mostly in that setting. Despite that, at the time of this writing (November 2011), only eight positive findings have been recorded among over 3400 tests, one of them in an athlete possessing a therapeutic use exemption (248). One likely reason for this relatively low "yield" is the high decision threshold, designed to protect the athlete by minimizing false-positive results. As experience with the test and data for the normative range accrue, it is possible that the cutoff values for positivity can be set at a more stringent level, allowing better discrimination between users and nonusers without sacrificing the conservative nature of the test.

The strategy used for the blood isoform test would be theoretically applicable to a urine isoform test. Indeed, limited data have shown that urinary GH excretion rises after administration of exogenous GH (103, 106, 110), presumably representing the injected 22K-GH. Very little information is available about suppression of endogenous GH isoforms in urine; one publication showed no suppression or even slightly higher urinary 20K-GH levels after administration of GH, although the 20K/22K ratio was lower because of the elevated 22K-GH level (103). Reliable detection of minor isoforms in urine is a substantial challenge, given the low concentrations of total GH in urine. Additional difficulties would be those discussed in *Section II.J*, including lack of scientific background information about isoform handling by the kidney, distorted isoform profiles because of glomerular filtration cutoffs, nonspecific influences such as proteinuria, and most importantly, the same short window of opportunity that applies to blood testing.

B. The biomarker test

1. GH biomarkers and the biomarker test in blood

The GH biomarker test is an indirect test based on downstream biochemical changes resulting from GH action. Well-known effects of GH are the induction of IGF-I expression and promotion of collagen turnover in bone and connective tissues (125). Thus, IGF-I and procollagen type III amino-terminal propeptide (P-III-NP) have been selected as relatively specific GH-responsive biomarkers suitable for an antidoping test. [Other GH-dependent biomarkers considered but not ultimately selected for various reasons (discussed in *Section B.1*) were IGF-binding protein (IGFBP) 2 and IGFBP3, acid-labile subunit (ALS), and markers of bone turnover, such as procollagen type I amino-terminal propeptide (PINP) and carboxy-terminal propeptide (PICP), osteocalcin, and type I collagen carboxy-terminal cross-linked telopeptide (ICTP).] Major efforts have been made by the GH-2000/GH-2004 consortium, the Australian-Japanese consortium, and other groups to validate the biomarker test under various circumstances (age, gender and ethnicity, elite *vs.* recreational athletes *vs.* the general population, type of sport, effect of training, injury, anabolic steroid or erythropoietin use, *etc.*). A substantial database regarding these GH biomarkers and conditions has been accumulated over the past one to two decades. The history of the development of the biomarker test has been summarized by Sönksen (126) and Holt *et al.* (5).

IGF-I, a 70-amino acid peptide with three disulfide bridges and a mol wt of 7649, is an important mediator of many GH actions and exhibits mitogenic, anabolic, and insulin-like metabolic activities. It shares structural and functional features with insulin and acts through the type 1 IGF receptor (also known as IGF-1 receptor), which shares homology with the insulin receptor. IGF-I binds with high affinity to the IGF-1 receptor and with lower affinity to the insulin receptor. At physiological concentrations, most of IGF-I action is mediated through the IGF-1 receptor. GH is the principal regulator of IGF-I production in healthy individuals. IGF-I is synthesized and released into the bloodstream by the liver in response to GH; it is also produced as a paracrine/autocrine factor in many other GH-responsive tissues, with some spillover into the circulation (Fig. 4). The liver accounts for the

Endocrine Reviews, April 2012, 33(2):155–186

Figure 7.

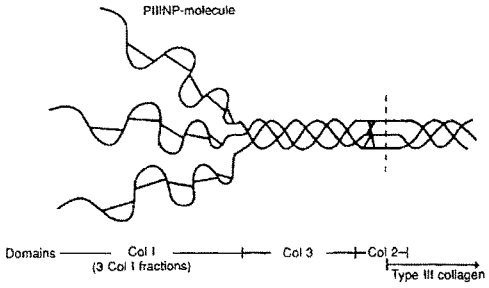


Figure 7. Structural organization of P-III-NP. The diagram represents the amino-terminal portion of the type III procollagen molecule. The triple helix of mature collagen is depicted/truncated on the *right*. The *dashed line* denotes the proteolytic cleavage site within the N-telopeptide region of procollagen that gives rise to P-III-NP. Triple helix formation of procollagen precedes P-III-NP cleavage, resulting in the latter being a homotrimer of three α1(III) linked chains, by two interchain disulfide bridges in the nonhelical Col 2 domain as well as stabilization in the triple-helical Col 3 domain. The globular Col 1 domain contains several intrachain disulfide bridges (indicated in the *graph*), the sulfate group(s), and the specific immunological epitopes. [Reproduced from K. D. Bentsen: Type III procollagen peptide: studies on the circulating peptide as a marker of fibrinogenesis with special reference to the liver. *Dan Med Bull* 40:235–246, 1993 (140), with permission. © The Danish Medical Association.]

majority (~75%) of circulating IGF-I (127). IGF-I in blood is bound to six IGFBP in ternary and binary complexes. Ternary complexes, formed with IGFBP3 and IGFBP5, also contain another GH-dependent protein, ALS, as the third component (Fig. 4). The majority of circulating IGF-I is bound in the IGFBP3/ALS/IGF-I complex. The protein-bound state of IGF-I in blood is responsible for its long circulating half-life.

P-III-NP, a protein with mol wt of approximately 40,000, is a by-product of type III collagen biosynthesis. Type III collagen is a constituent of numerous tissues, including the vasculature, skin, intestines, and other viscera; its distribution is ubiquitous as a component of blood vessels. Procollagen is secreted in soluble form into the extracellular space, where it undergoes condensation to a triple helix under the guidance of its C-terminal propeptide domain, which serves as a nucleation focus. After this, both the C-terminal and N-terminal propeptides are cleaved from procollagen by bone morphogenetic protein 1 and one or more metalloproteinases of the ADAMTS family, respectively, and released into the lymphatic system and bloodstream (see Ref. 128 for review). P-III-NP is a trimeric protein composed of three identical partial procollagen α1(III) polypeptide chains, which in humans contain 129 amino acids and have a mol wt of 13,116 each (129–132). P-III-NP consists of an amino-terminal globular region, a central triple helical region, and a carboxy-terminal telopeptide region; these domains are named Col 1, Col 3, and Col 2, respectively (133, 134) (Fig. 7). The trimer is stabilized by two interchain disulfide bridges near the carboxy-terminus and by a collagen-like triple helix formation in the central Col 3 domain (135). P-III-NP is a very acidic protein (pI- ~3) due to sulfation in the Col 1 domain; the precise residue(s) carrying sulfate has not been identified (130). A consensus sequence for N-linked glycosylation exists near the carboxy-terminus, but no glycosylated P-III-NP has been described. The globular Col 1 domain appears to be the principal epitope recognized by polyclonal antisera generated against P-III-NP (130). Human and bovine P-III-NP have 95% sequence identity (131), and human, bovine and porcine P-III-NP show complete cross-reactivity in polyclonal immunoassays (130, 136). The principal immunoreactive region resides in the Col 1 domain; this is a conformational epitope because the intact P-III-NP trimer is much more immunoreactive than the monomeric peptide (130, 137, 138). Monoclonal antibodies have been developed, but it has been difficult to define the exact epitopes recognized because of the complexities inherent in P-III-NP and its isoforms and degradation products (for review, see Ref. 139).

P-III-NP circulating in blood is heterogeneous and consists of at least four immunoreactive forms of different molecular size (see Refs. 134 and 140 for review) (Fig. 8). Intact P-III-NP is a minority component designated Peak III on gel filtration chromatography. Peak II, with molecular size about twice that of P-III-NP, is thought to be a P-III-NP dimer [*i.e.*, a hexamer of monomeric partial procollagen α1(III) chains]. Peak I is of high mol wt and remains largely uncharacterized. It may represent P-III-NP aggregates, P-III-NP bound to plasma proteins, or incompletely cleaved P-III-NP still attached to the rest of the collagen molecule (also known as pN-collagen type III). Peak IV has a smaller molecular size than P-III-NP and is assumed to be the Col 1 fragment and/or degradation product(s) of P-III-NP, or a species unrelated to procollagen III. To date, none of these interpretations of the nature of P-III-NP size variants has been corroborated by direct chemical analysis. Of importance, depending on the immunoassay, these different molecular species are recognized to different degrees. The two commercial assays cur-

Figure 8.

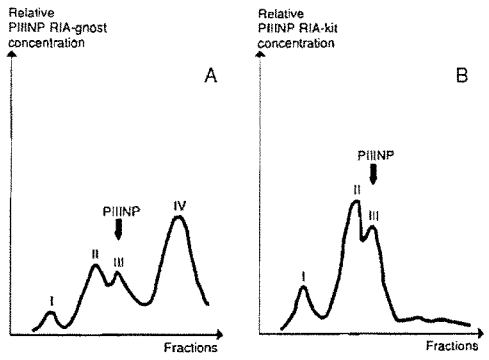


Figure 8. P-III-NP immunoreactivity in serum. Gel filtration profiles of serum P-III-NP immunoreactivity, as measured by two immunoassays. Four peaks of different molecular size are seen; the elution position of intact P-III-NP is indicated. A, Profile obtained with the CIS RIA-gnost assay. B, Profile obtained with an early version of the Orion UniQ assay. The different components are recognized to different degrees by the two assays. The precise molecular nature of the four peaks has not been determined. [Reproduced from K. D. Bentsen: Type III procollagen peptide: studies on the circulating peptide as a marker of fibrinogenesis with special reference to the liver. *Dan Med Bull* 40:235–246, 1993 (140), with permission. © The Danish Medical Association.]

rently in use (see *Section III.B.4*) are reportedly not sensitive to Col 1/peak IV material.

The blood levels of both IGF-I and P-III-NP increase in response to GH and disappear with reported half-lives of 90 and 700 h, respectively (141). These values are probably overestimates of true plasma half-lives, which are 14–18 h for IGF-I in man (142) and ~60 min for P-III-NP in the pig (143) (no human data on plasma P-III-NP half-life are available). The discrepancies may be explained by continued production of the biomarkers for some time after cessation of GH dosing and, in the case of P-III-NP, generation of high mol wt immunoreactive degradation products with long half-lives (143). In any case, serum immunoreactive IGF-I and P-III-NP remain elevated for about 4 d and 2–8 wk, respectively, depending on the GH dose (144–146) (Fig. 9). Unlike the pulsatile pattern of GH in blood, their serum levels remain relatively constant throughout the day and between days (147). Thus, although less specific than a direct test for GH, biomarkers have the practical advantage of a longer window of opportunity for detection. The biomarker test is also potentially applicable to the detection of IGF-I abuse, and studies to assess this possibility are in progress (see *Section V*).

Two concerns exist with respect to the biomarker test: 1) lack of specificity and vulnerability to factors not related to GH or IGF-I; and 2) limitations of available assays. In addition, test interpretations are complicated by age- and sex-dependent variation.

With respect to specificity of IGF-I, few if any conditions elevate IGF-I as consistently as GH. One possibility is obesity, which can result in mildly increased serum IGF-I, but most studies show no correlation between body mass index and serum IGF-I. Furthermore, obesity is not likely to be a major confounder in most sports, with the possible exception of Sumo wrestling. Neither exercise nor injury significantly affects IGF-I levels, although in some subjects exercise resulted in a mild and transient (<30 min) increase in serum IGF-I that may represent hemoconcentration (148, 149). Sports injuries have been shown to have either no effect or only a minimal effect on IGF-I (150, 151). Even after major injury (tibia fracture), the transient IGF-I response is much lower than that obtained with even a modest GH dose (15 μg/kg · d; ~1 mg/d) (151). Testosterone administration does not alter IGF-I levels or the response of IGF-I to GH (152). Similarly, erythropoietin has no effect on IGF-I levels (153). Thus, serum IGF-I is a very good biomarker for GH action; its only drawback is the relatively short duration of elevation (a few days).

The specificity of P-III-NP is not as narrow as that of IGF-I. Its plasma levels have been evaluated in the context of exercise and injury. Exercise increased P-III-NP levels in some studies but not others, and when present, the rise was much smaller than what is seen after GH administration (reviewed in Ref. 149). After an injury, collagen turnover is expected to be increased as part of the healing process, and indeed P-III-NP levels rise after sports injuries. After a soft tissue injury, they peak at 2 wk and are back to baseline after 7 wk; after a bony injury, they peak at 6 wk and return to baseline after 12 wk (150). However, the rise is relatively minor compared to that which occurs after GH administration (150). Similarly, other markers of collagen and bone turnover (small fragment of C-terminal cross-linked telopeptide of type I collagen (CTX) and osteocalcin) after tibial fracture show elevations that are substantially lower than those seen with GH treatment (151). Erythropoietin has no effect on P-III-NP levels (153), but testosterone administration mildly increases P-III-NP and enhances its response to GH (152). However, this effect appears insufficient to adversely affect the dis-

Endocrine Reviews, April 2012, 33(2):155–186 edrv.endojournals.org 167

Figure 9.

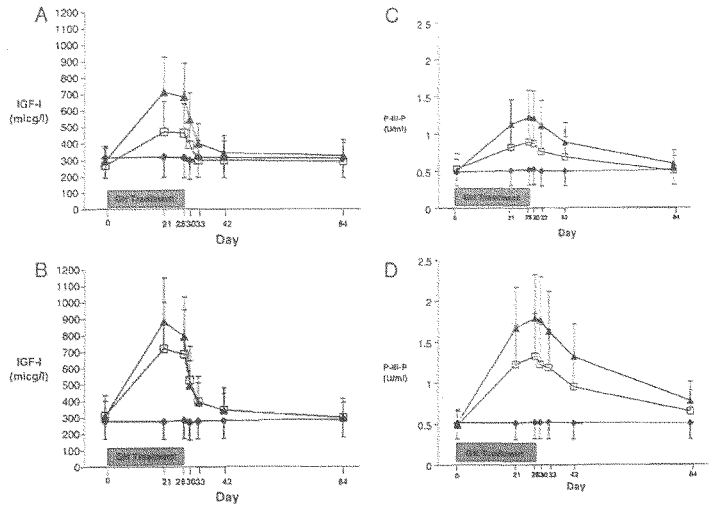


Figure 9. The biomarker test. Time course of changes in serum IGF-I (A and B) and P-III-NP (C and D) during and after cessation of GH treatment. A and C, Women; B and D, men. The period of GH treatment (28 d) is indicated by the *cross-hatched bar*. *Diamonds*, placebo; *squares*, low-dose GH (33 μg/kg · d; ~2.3 μg/d); *triangles*, high-dose GH (66 μg/kg · d; ~4.6 μg/d). Note the more exuberant responses for both biomarkers in men. [Reproduced from J. K. Powrie *et al.*: Detection of growth hormone abuse in sport. *Growth Horm IGF Res* 17:220–226, 2007 (146), with permission. © Elsevier B.V.]

criminant function (see below) used to distinguish GH abusers from nonusers (5).

Because both IGF-I and P-III-NP levels change as a function of age, with a peak in adolescence and a gradual, lifelong decline thereafter (paralleling the age-dependent changes in GH secretion), values must be interpreted against an age-appropriate normative range. Similarly, gender and possibly ethnicity affect these biomarkers, which requires interpretation against appropriate normative ranges. IGF-I levels tend to be higher in women, whereas collagen markers, including P-III-NP, are higher in men. Extensive study of these parameters in elite athletes, both immediately after a competitive event and at random times (representing out-of-competition conditions) have shown that age and gender are the major confounders, whereas ethnicity and sport type have only a minor influence (149, 154–156).

The dynamics of IGF-I and P-III-NP during and after GH treatment can be summarized as follows (152): IGF-I rises rapidly to near peak levels within 2 wk after starting GH, with P-III-NP following more slowly to near peak levels within 4–6 wk. After cessation of GH treatment, IGF-I falls most rapidly to reach baseline after 7 d, whereas P-III-NP declines more slowly toward near-baseline after 4 wk and fully to baseline by 6 wk. Thus, IGF-I is more useful as a detection tool in the early phases of both initiation and cessation of GH use, whereas P-III-NP is most useful for the later time points after cessation.

The combined values of IGF-I and P-III-NP have been used to devise a discriminant formula that separates GH users from nonusers and thus can be used as a practical GH doping detection test (146). The discriminant functions are different for men and women, they take age into account, and they are based on biomarker values obtained in specific commercial immunoassays (see *Section III.B.4* for comments on the latter). Using these formulae, a positive doping test score has been proposed at a threshold that is predicted to yield a false-positive reading in no more than 1 in 10,000 tests, *i.e.*, at a Z value of at least 3.72 (146, 157). Because of the above-mentioned dynamics, the test relies increasingly on P-III-NP as time elapses after stopping GH use, and P-III-NP is therefore given more weight.

For the biomarker test as currently designed, a window of opportunity of several days following cessation of GH exists. In normal volunteers given doses of approximately 2–4 mg of GH daily, the test remained positive following cessation of GH in 69–79% after 2 d, in 53–64% after 5 d, and in 20% after 14 d (146). The duration of this window of opportunity is dose-dependent, varies among individuals, and tends to be longer in men. A realistic estimate in practice may be 1 wk, although a window of up to 14 d has been suggested (5).

Intraindividual fluctuations in biomarkers over time have been examined, and coefficients of variation ranging from 14 to 20% for IGF-I and 7 to 18% for P-III-NP have been found (147, 158). This degree of variability did not interfere with the performance of the discriminant function (147). Both IGF-I and P-III-NP show the most rapid changes during adolescence under the influence of pubertal up-regulation of GH secretion. A study in adolescent elite athletes has confirmed that the discriminant function remains valid as a determinant of GH abuse even in this most demanding circumstance (159), but particular caution is probably advisable for the interpretation of results in adolescents.

GH biomarkers other than IGF-I and P-III-NP have also been investigated for their suitability for a detection test; they include several members of the IGF system and various markers of collagen and bone turnover. Most have been less extensively studied than IGF-I and P-III-NP, and some were not further pursued because they were judged to be less well-suited for a detection test than those two biomarkers. Among members of the IGF system, IGFBP3, IGFBP2, and ALS were shown to be less responsive to GH treatment than IGF-I (144, 152, 160). Among collagen and bone markers, osteocalcin, procollagen type I amino-terminal propeptide (PINP), carboxy-terminal propeptide (PICP), and type I collagen carboxy-terminal cross-linked telopeptide (ICTP) were found to respond less vigorously to GH and return to baseline more quickly after GH cessation than P-III-NP (141, 145, 160–162). Other considerations include the inherent variability of a biomarker within or between subjects, or as a function of gender and ethnicity, which from the standpoint of a detection test should be kept to a minimum (158, 163). The aggregate of all these observations led to the selection of IGF-I and P-III-NP as the currently most suitable biomarker pair for development of a GH doping detection test.

2. Biomarkers in urine

Biomarker testing is currently only applicable to blood; its potential use as a urine test faces significant obstacles. There is little information on how the kidney handles IGF-I or P-III-NP. Based on insulin excretion data (164), it can be assumed that (free) IGF-I is filtered at the glomerulus and extensively taken up and degraded in the proximal tubule, akin to the fate of GH described in *Section II.J*. A similar renal degradation process has been shown for P-III-NP (165). There is evidence that IGF-I is directly produced by the kidney and excreted in the urine (166, 167). Some studies have examined urinary IGF-I in clinical and antidoping contexts, whereas there is very little information on urinary P-III-NP. Tönshoff *et al.* (168) reported urinary IGF-I concentrations of 0.08 ± 0.07 ng/ml, which did not change after 3 d of GH treatment. Gill *et al.* (98) showed widely varying excretion rates (0–1350 ng/24 h) in normal adults and a similar range of values (0–950 ng/24 h) in matched patients with severe organic GH deficiency. Similarly, no difference in IGF-I excretion rates was shown between GH-deficient and GH-sufficient children and adolescents (169). Attempts to use urinary IGF-I as a diagnostic tool for IGF deficiency or excess states were abandoned when it was realized that urinary IGF-I does not correlate with serum IGF-I and does not reflect underlying GH secretion status (98). De Palo *et al.* (170, 171) compared IGF-I excretion in sedentary individuals and trained cyclists before and after strenuous exercise. They found a wide interindividual range of IGF-I excretion (0–350 ng/liter) and a 240% increase in excretion after exercise. A highly significant correlation existed between urinary total protein and IGF-I, but no correlation was found between plasma IGF-I and urinary IGF-I. A weak correlation was shown between urinary GH and urinary IGF-I excretion, but this was mostly dependent on a few outlier values. The urinary IGF-I/urinary GH molar ratio showed major differences between sedentary subjects, cyclists before exercise, and cyclists after exercise (means of 190, 15, and 577, respectively). The high variability of these findings may be explained by inherent variability of IGF-I (and GH) excretion, exercise-induced proteinuria (including IGF-I and GH), and renal production of IGF-I not reflective of plasma IGF-I. Pichini *et al.* (172) compared urinary IGF-I values in sedentary individuals and recreational and elite athletes and also found wide ranges and overlaps among the three groups, without consistent changes in response to training and competition. Uemasu *et al.* (173) examined the effect of exogenous GH administration on urinary IGF-I excretion and found that despite the expected increase in serum GH and IGF-I, urinary IGF-I output actually decreased significantly. Taken together, the available literature on urinary IGF-I can be summarized as follows. 1) Urinary IGF-I excretion is highly variable, ranging from undetectable to 1000 ng/24 h with an approximate mean of 130–450 ng/24 h, depending on the study. 2) Urinary IGF-I excretion does not reflect serum IGF-I or GH secretion rate in clinical studies.

Endocrine Reviews, April 2012, 33(2):155–186 edrv.endojournals.org 169

3) Exercise increases urinary IGF-I, an effect that can be at least partially attributed to exercise-induced proteinuria. And 4) The administration of GH does not raise urinary IGF-I excretion. Thus, the biology of IGF-I in urine does not appear to be an index of GH status and is unlikely to be useful for detection of illicit GH use. Furthermore, because IGFBPs are also present in urine (98, 169, 172, 174), the use of urine does not avoid the problem of IGFBP interference in IGF-I measurements (see *Section III.B.4*), thereby not conferring an analytical advantage over the use of blood.

With respect to urinary P-III-NP, one publication listed a daily excretion of P-III-NP immunoreactivity of 30–110 μg, but indicated that this represented the Col 1 fragment rather than the intact peptide (175). Another recent publication reports a range of 2–110 ng/mmol creatinine (corresponding to an excretion rate of roughly 20–1430 ng/24 h) in subjects with normal renal function (176). The vast majority of this activity is kidney-derived, rather than blood-derived, and urinary P-III-NP is increased in patients with renal disease resulting in fibrosis (176). The scientific background information on urinary P-III-NP and its relation to GH is insufficient to permit contemplation of a detection test for GH abuse based on urine P-III-NP at this time. The nature of the limited data available raises doubts about the feasibility of a robust urine test.

Urinary excretion of other, small collagen biomarkers [N- and C-terminal cross-linked telopeptides of type I collagen (NTX and CTX), pyridinoline, deoxypyridinoline, and hydroxyproline] is known to be highly variable and subject to diurnal fluctuation, which necessitates 24-h urine collections (177). Because of these characteristics, their measurement has proven to be of limited diagnostic value in the assessment of clinical bone disorders. Although these urinary biomarkers have not been examined in an antidoping context, the experience in the clinic does not support their suitability for a reliable GH detection test.

3. Biomarkers in saliva

Saliva has also been considered as a biological fluid for IGF-I measurement. Limited data show that salivary IGF-I concentration is 40- to 200-fold lower than serum IGF-I, and that its source is at least in part derived from local synthesis in the salivary gland (178–181). Early suggestions of using saliva as a diagnostic tool to assess GH deficiency or excess states have not been adopted because salivary GH did not reliably identify such conditions (180). Antonelli *et al.* (182, 183) examined salivary IGF-I in athletes and found that they had lower levels than control subjects, and that after exercise IGF-I levels rose in saliva, but not in blood. No reports have yet appeared on the response of salivary IGF-I to exogenous GH. Taken together, the published data suggest that salivary IGF-I may bear a rough relationship to serum IGF-I and GH, but that its biology is poorly understood and its correlation with GH status is insufficient to yield a robust detection tool for GH abuse.

4. Analytical considerations and challenges

a. IGF-I measurement. Currently the measurement of IGF-I in blood is conducted by immunoassay. Its assay presents significant challenges, primarily because of interference by IGFBPs. The "gold standard" for IGF-I measurement in serum is acidification, which dissociates the complexes, followed by removal of binding proteins by acid gel filtration on a sizing column. This technique is laborious and not amenable to routine, high throughput use. Alternative methods are acid-ethanol precipitation, extraction of IGF-I on C_{18} Sep-Pak cartridges, dissociation of complexes with acid followed by blocking of rebinding with excess IGF-II, and conducting the assay in commercial "dissociation buffers." The latter likely contain IGF-II. None of these methods are successful in completely removing IGFBP interference. As a result, major disparities in results exist among assays. This issue has been recently reviewed in detail (118, 184).

An additional problem with IGF-I measurement lies with the international reference standard, against which assays are calibrated. The World Health Organization international reference reagent 87/518 is not pure and therefore has an artificially high weight assignment. In addition, its stocks are depleted, and a new, pure international reference reagent (02/254) has been adopted. Assays calibrated against the new standard will yield lower results, thereby rendering comparisons with earlier studies difficult. Efforts to harmonize IGF-I assay results are being undertaken after a recent workshop jointly sponsored by the GH Research Society, the IGF Society, and the IFCC (118), but the effect of residual IGFBP in assayed samples will remain a thorny problem.

The two IGF-I assays used for the GH-2004 project were the DSL-5600 IRMA and the Immunotech A15728 IRMA; their technical aspects have been reported in detail (185). To minimize IGFBP interference, the DSL assay uses acid-ethanol precipitation, whereas the Immunotech assay uses acidification and excess IGF-II to prevent rebinding of IGF-I. There is good correlation between the two assays, but there is a systematic bias in favor of the DSL assay, which yields values that are about 20% higher than those obtained by the Immunotech assay (185). The DSL assay is no longer available and has been replaced by the Siemens Immulite assay system, which does not use extraction. No back-to-back comparison between the Immunotech and Immulite assays has been published.

Preanalytical considerations are not of major concern because IGF-I is a stable peptide, and no special precautions are necessary during transport and storage of serum (118, 186).

Mass-based measurements of IGF-I are being developed and are beginning to approach the necessary sensitivity for measuring IGF-I concentrations in serum (187–190) and urine (191). Measurement by MS would alleviate some of the problems with immunoassays, although the issue of removal of (or accounting for) IGFBP would still be a challenge for accurate quantitation.

b. P-III-NP measurement. Serum P-III-NP is currently also measured by immunoassay. Unlike for IGF-I, where a number of commercial and in-house assays are widely employed, there are only two commercial assays in general use: the Orion UniQ RIA and the CIS Biointernational RIA-gnost IRMA. No international reference standard exists for P-III-NP, and there is no information given by the manufacturers regarding the exact nature or source of their standards (natural or recombinant, monomeric or trimeric, human, bovine, or porcine, *etc.*).

Knowledge about the specificity of either assay with respect to the different immunoreactive forms of circulating P-III-NP is limited. The Orion UniQ assay is described as measuring intact P-III-NP and its higher mol wt forms, but not smaller degradation products found in blood (assay kit instructional pamphlet). The CIS RIA-gnost assay is reported to measure P-III-NP Col 1–3 (intact P-III-NP), but not the Col 1 fragment (assay kit brochure and Ref. 139). These descriptions do not take into account the complexity of immunoreactive P-III-NP species in serum, nor do they identify the epitopes recognized. An early version of the RIA-gnost assay recognized peak IV material (Fig. 8A), which is thought to at least partially consist of the Col 1 fragment, suggesting that the assay reagents or conditions have changed over time.

The two assays are not directly comparable because they express results in different units (nanograms per milliliter and units per milliliter, respectively), but they show a good correlation (185, 192), suggesting that they measure a comparable substance(s). Moreover, when the conversion factor of 8 (provided in the RIA-gnost brochure) is used to convert units per milliliter to nanograms per milliliter, values for the normative ranges in the two assays are comparable. It is unclear why the RIA-gnost manufacturer does not use this conversion factor in expression of results. Technical details of the two commercial assays are summarized by Abellan *et al.* (192) and Cowan and Bartlett (185). The absence of a universal standard for P-III-NP is a major shortcoming that should be addressed by the antidoping and clinical chemistry communities.

The stability of P-III-NP during storage and transportation has been evaluated and found to be acceptable when serum was stored frozen or kept at 4 C for up to at least 5 d (186, 192). Two to three freeze-thaw cycles did not significantly affect assay results (192).

As with IGF-I and all other analytes, a mass-based measurement technique would be highly desirable. Currently there are no reports on attempts to develop MS analysis of P-III-NP in serum. Although its mol wt (~40,000) may act as a deterrent to such efforts, it should be realized that P-III-NP is a homotrimer of a protein that has a mol wt of only about 13,000. The molecular heterogeneity of circulating P-III-NP may be elucidated by MS. However, its low concentration in blood (subnanomolar) still presents a challenge for current MS technology.

c. Reagent availability. From the antidoping perspective, an additional significant problem with the vagaries of immunoassays is that the original reference values used to derive the discriminant functions are no longer representative for values obtained with the newer assays. For example, the Nichols IGF-I assay employed for accumulating the original large GH-2000 database is no longer available, and several subsequent efforts at securing a stable reagent supply were unsuccessful (see Ref. 5 for review). Similarly, the DSL IGF-I assay used for the GH-2004 project is no longer available. Adjustments in the form of correction factors can be made to allow comparison of newer values with historical results, and this has been successfully applied in clinical chemistry, including for IGF-I and P-III-NP (156, 157, 193, 194). Nevertheless, such correction maneuvers are not optimal because they do not represent primary data, and the need for assays that perform in a robust manner over long time periods is evident. History has shown that commercial immunoassays are probably not able to fulfill this requirement. Hence, the need for future assays that do not depend on biologics or commercial suppliers of unique reagents.

d. Implementation. The WADA code requires that a positive test result be confirmed by a second, independent method. Ideally, the two methods should be based on different analytical principles, but currently both IGF-I and P-III-NP measurements are limited to immunoassay measurement. In the case of immunoassays, the WADA code stipulates that the assay used for confirmation needs to recognize a different epitope(s) on the analyte than the original assay. Alternatively, a purification/separation method can be used before immunoassay to eliminate potential cross-reactivity. Precise epitope maps are not available for either IGF-I or P-III-NP, but indirect evidence suggests that the diverse antibodies used in the assays recognize different

Endocrine Reviews, April 2012, 33(2):155–186 edrv.endojournals.org 171

aspects of the analytes. In addition, one of the IGF-I assays used incorporates a purification step. [It should be noted that for the GH isoform test described in *Section III.A*, the epitopes recognized by the four assays employed are well characterized (90).] These criteria may be sufficient to satisfy WADA requirements. Nevertheless, for the purpose of independent confirmatory testing, it would be highly desirable to have available mass spectroscopy-based methods that are unquestionably independent and distinct from immunologically based methods.

The biomarker test is poised for general implementation as a WADA-sanctioned test in the near future. It will serve as an important complementary test to the already implemented GH isoform test, providing independent confirmation and a longer window of opportunity. Because of the latter characteristic, it may be suitable for both in-competition and out-of-competition testing. It is important to note that thus far neither the isoform test nor the biomarker test has been scrutinized under legal challenge.

C. Novel approaches

Research is continuing to identify additional indicators for GH use that may be useful for antidoping purposes. In particular, genomic and proteomic approaches are being explored in an attempt to identify a "signature" that would be indicative of exogenous GH use. Mitchell *et al.* (195) examined transcriptome changes in peripheral blood leukocytes obtained from recreational athletes treated with GH (2 mg/d) for 8 wk. They identified induction or repression of several genes in GH-treated subjects, but the magnitude of transcript changes was small and within the variability range seen among different untreated subjects. None of the genes significantly up-regulated (*IGF2*, *MED18*, *PDK4*) or down-regulated (*AREG*, *ARG1*, *CYYR1*) are classical GH-responsive genes, and disparate responses have been found for some of them (*PDK4* and *AREG*) in different tissues or physiological states. The authors concluded that transcriptome analysis in leukocytes is unlikely to yield a viable antidoping test.

Proteomic approaches to detection of GH use have been employed using serum and peripheral blood leukocytes and either protein chip adsorption or two-dimensional electrophoresis followed by mass spectroscopy (196–200). These efforts have identified changes in unexpected proteins, such as free hemoglobin A1 chain, β-hemoglobin, transthyretin, apolipoprotein A_1, and fragments of albumin and Ig in serum, and calgranulins and DAMP (damage-associated molecular pattern) proinflammatory molecules in leukocytes. Some of the serum proteins are acute-phase reactants, and all proteins mentioned show considerable variability. Their physiological significance and potential biological link to GH remains to be established. It is evident from these preliminary data that a considerable amount of work will be required before proteomic approaches will become a realistic tool for antidoping purposes. It is currently not clear whether anonymous/comprehensive or GH-targeted proteomic or genomic inquiries will be more productive in yielding a GH-specific signature. It is also not clear whether the identification of many GH-responsive endpoints is superior to one or a few well-chosen endpoints, or whether it simply increases analytical noise.

Reports on new GH-responsive biochemical markers, such as mannan-binding lectin (201), will continue to appear in the literature. The specificity and sensitivity of such novel markers will have to be rigorously demonstrated before they are considered as an antidoping strategy. The experience with IGF-I and P-III-NP, two well-established GH biomarkers, suggests that development of a robust biomarker test is a time-consuming process.

IV. Secretagogues

GH secretagogues are peptides or nonpeptidic agents that act to release GH from the pituitary. There is evidence that they are being used by athletes as an indirect method for GH doping. Secretagogues include GHRH and its analogs, ghrelin analogs [known as GH-releasing peptides (GHRP) or GHS (GH secretagogues in a narrower sense), and amino acids (*e.g.*, arginine or ornithine). GHRH acts through the GHRH receptor; GHRP/GHS acts through the ghrelin receptor, also known as the GHS receptor 1a; both receptors are coupled to G proteins and signal primarily though $G_s\alpha$ and $G_{q/11}$ pathways, respectively. Arginine and ornithine have to be given in high doses (*e.g.*, 30 g iv); they are thought to stimulate GH secretion through suppression of somatostatin. General features of secretagogues are that their effect is short-lived and they provide a relatively weak boost in GH exposure compared with what can be achieved by direct GH administration. GH secretagogues are attractive to athletes who want to avoid detection because the GH released is endogenous and therefore not detectable by the GH isoform test.

A. GHRH and its analogs

GHRH is a 44- or 40-amino acid linear peptide secreted by the hypothalamus; it stimulates pituitary somatotroph proliferation and GH production (both synthesis and release). Its fully bioactive shorter version, GHRH(1–29) (sermorelin), was marketed in the 1980s to treat idiopathic GH deficiency in children and also for diagnostic purposes in pituitary disease. It was found to be largely ineffective as a growth promoter, and its use as a thera-

peutic agent was abandoned. It is no longer available on the U.S. market. It is unclear whether it exists on the black market for doping purposes. Bioactive GHRH has a very short half-life (~7 min) in blood, being rapidly degraded by dipeptidyl-aminopeptidase IV (202). Intravenous GHRH administration elicits a spike in plasma GH that peaks (at ~10–25 ng/ml) at 15–30 min and returns to baseline after 120 min. Studies conducted with GHRH in the elderly in an effort to reverse the somatopause have yielded varying degrees of mild elevation of serum IGF-I and changes in body composition, but little improvement in physical performance (203, 204). Based on its short duration, need for repeated administration, and limited efficacy in GH deficiency or GH insufficiency in the elderly, it is unlikely that GHRH provides significant GH doping "benefits" to the athlete.

There is currently no detection test for GHRH abuse. Its low dosing, short half-life, and structural similarity with endogenous GHRH (which is produced not only in the hypothalamus, but primarily in gut and other extraneural tissues) would present a substantial challenge to development of a detection test.

Newer, long-acting analogs of GHRH, such as tesamorelin and CJC-1295 have been developed; the former is approved by the Food and Drug Administration for treatment of HIV-associated lipodystrophy; the latter has undergone clinical trials. Strategies to increase half-life include amino acid substitutions and other modifications targeting the dipeptidyl-aminopeptidase IV cleavage site at position 2 and incorporating a linker with a reactive group that allows covalent linkage to albumin *in vivo* after injection. The plasma half-life of tesamorelin is ~30 min (205); and that of CJC-1295 is 6–8 d (206). Despite the relatively short half-life of tesamorelin, once a day administration results in enhanced GH pulsatility over 24 h and a mean IGF-I increase of 108–122% (205, 207). Treatment of HIV-associated lipodystrophy with tesamorelin resulted in an 18% loss of visceral fat, suggesting a GH-induced lipolytic effect (207). Administration of a single dose of CJC-1295 resulted in an elevation of plasma GH trough, but not peak levels, and an ~40% increase in IGF-I levels 1 wk later (208). Thus, it appears that these long-acting GHRH analogs have a moderate enhancing effect on GH secretion and its downstream biomarkers. There is evidence that these drugs have entered the black market (209).

Currently there is no published method to detect use of these GHRH analogs, but because they differ structurally from native GHRH, unequivocal detection methods should be feasible if sufficient sensitivity can be achieved.

B. Ghrelin mimetics

Ghrelin is an orexigenic peptide produced by the stomach. It is a 28-amino acid, linear peptide that exists both as a 3-octanoylated form and as a nonacylated form. The octanoylated form is bioactive; the biological role of the nonacylated form is currently a matter of debate. In the presence of an intact hypothalamo-pituitary system (*i.e.*, GHRH functionality), ghrelin is a potent secretagogue for GH *in vivo*. GHRH signaling is crucial for this pronounced ghrelin effect on GH release (210). Despite its efficacy as a pharmacological agent, the role of ghrelin in the physiological regulation of GH secretion is minor at best. Its main physiological role appears to lie in the area of appetite regulation. Discovery of ghrelin analogs (GHRP, GHS) as well as the ghrelin receptor preceded the identification of ghrelin by many years.

GHRPs are non-native hexapeptides originally derived from enkephalin, including GHRP-6, GHRP-2 (pralmorelin), and hexarelin; other GHS are modified peptides such as tabimorelin, and nonpeptide compounds such as MK-677, L-692,429, SM-130,686, and TZP-101. A considerable number of studies have evaluated the short-term and long-term effects of ghrelin mimetics on the GH-IGF axis. A typical GH response to an iv bolus of ghrelin or GHRP yields a peak serum GH of 70–110 ng/ml at 15–30 min, with return to baseline at 120–180 min. Long-term therapy has been attempted for idiopathic GH deficiency or short stature, frailty in the elderly, osteoporosis, and amyotrophic lateral sclerosis. A few representative studies will be cited. For example, a 2-yr study in children with idiopathic GH deficiency or short stature with intranasal GHRP-2 three times a day produced a modest gain in growth velocity but no change in serum IGF-I (211). Oral GHRP-2 in a similar study resulted in an approximate 2-fold increase in GH secretion, a modest increase in growth velocity, and again no change in serum IGF-I (212). Addition of GHRH to the GHRP regimen did not improve outcome (212). Tabimorelin treatment for 7 d in young, healthy male subjects yielded a 50% increase of serum IGF-I and an attenuation of the GH response over time (213). A 2-yr, randomized, double-blind trial of daily MK-677 treatment in elderly subjects showed a 1.8-fold increase in GH secretion and a 1.5-fold increase in serum IGF-I, an increase in both lean body mass/water and fat mass, little effect on bone mineral density, a smaller decline in muscle strength than in controls, and no effect on physical function and quality of life (214). A 1-yr trial of capromorelin in elderly subjects increased IGF-I by 60%, and some performance measures (stair climb and tandem walk) increased, whereas several others did not (215). The effect was considered insufficient to warrant continuation

Endocrine Reviews, April 2012, 33(2):155–186 edrv.endojournals.org 173

of the trial or further development of the drug. The topic of ghrelin mimetic and GHRH therapy was reviewed by Hersch and Merriam (216).

Taken together, these and several other studies indicate that ghrelin mimetics have a moderate effect on GH secretion and IGF-I levels, but they have insufficient impact on growth or physical performance to be considered marketable at this time. The same side effects as those noted with GH treatment were observed, but at a lesser frequency and severity. This observation is congruent with the pharmacological concept that less effect is accompanied by fewer side effects. An undesirable and GH-unrelated side effect of all ghrelin mimetics is increased cortisol production and increased appetite/adipose weight gain—both intrinsic features of the ghrelin system.

Given the relatively mild effect of ghrelin mimetics on overall GH secretion and the uncertainty about the ergogenicity of even large GH doses (see *Section VI*), it appears unlikely that athletes would derive significant performance-enhancing benefits from abusing ghrelin mimetics or GHRH analogs.

There is evidence that ghrelin mimetics are being offered on the black market for doping purposes (217, 218). Methods to identify these non-native substances in urine have been developed (219–222).

C. Amino acids

Large iv doses of certain amino acids (arginine, ornithine, lysine) have GH-releasing activity and are in use diagnostically as a GH stimulation test (especially arginine, 30 g rapidly iv). Even at these large doses they are relatively weak stimuli unless given together with GHRH. These uses of amino acids have been extrapolated to mean that oral arginine supplements are GH stimulators, and the Internet is replete with arginine advertisements. There is no reason to believe that typical oral doses of arginine elicit significant GH release. This can be verified during a protein meal and has indeed been directly shown (223). Testing for abuse of amino acids is not currently feasible, but may also not be necessary in view of their limited efficacy.

V. IGF-I as a Doping Agent

Since many actions of GH are mediated through IGF-I, it is not surprising that IGF-I is also being abused for the purposes of performance enhancement. IGF-I appears on the WADA list of banned substances. IGF-I is commercially available for medical indications, such as genetic GH resistance and primary IGF-I deficiency. A preparation combining IGF-I with IGFBP3 is not marketed the United States, but clinical trials for certain neurological diseases (amyotrophic lateral sclerosis) are ongoing. The Internet is replete with advertisements for IGF-I and its more potent analogs—des(1–3)IGF-I, R^3-IGF-I, Long-R^3-IGF-I, and mechano-growth factor (IGF-IEc or a peptide derived from the E-domain of pro-IGF-I). The former three analogs have low affinity for IGFBPs due to modification of the amino terminus (deletion of residues 1–3, substitution of glutamic acid in position 3 with arginine, and a 13-amino acid amino-terminal extension in addition to the Glu^3-Arg modification, respectively). The latter is derived from an *IGF1* gene splice variant that includes a carboxy-terminal sequence encoded by a 3′-exon (exon *5*) that is excluded from liver IGF-I transcripts. The physiological importance of IGF-IEc is controversial, and the existence of mechano-growth factor as a native peptide is not established (see Ref. 224 for review). IGF-I analogs have been discovered in supplement products sold on the black market (217). There is also evidence that even IGF-I products strictly intended for *in vitro* use have entered the supply stream available to athletes (225).

IGF-I is a mitogenic, anabolic, and metabolically active peptide generated in response to GH in most tissues, with the liver the predominant source. The bioactivity spectra of GH and IGF-I are overlapping but not identical. One prominent example where GH and IGF actions diverge is lipolysis: GH has a direct lipolytic activity, whereas IGF-I does not. The treatment of patients with GH resistance with IGF-I does not completely mimic the treatment of GH deficiency with GH, and the phenotypic features differ (226). Thus, it cannot be presumed that IGF-I abuse in sports has the identical effect as GH abuse. IGF-I does have anabolic action in numerous tissues, including muscle, and is an important mediator of GH action in muscle. This anabolic action cannot, however, be interpreted as necessarily indicating that IGF-I enhances athletic performance in healthy individuals (see *Section VI*). In contrast to GH, there is relatively little information on the possible performance-enhancing action of IGF-I in normal human subjects.

Currently, there is no established detection method for IGF-I abuse. Studies evaluating the biomarker approach outlined above for detection of IGF-I abuse are ongoing (227, 228).

VI. GH as an Ergogenic Substance

GH appears as the ideal ergogenic agent: it is the prototype master anabolic hormone, promoting nitrogen accretion, protein synthesis in numerous tissues including muscle, and physical growth. In addition, it has lipolytic activity,

causing adipose tissue to shrink and divert liberated calories toward carbohydrate fuel generation and protein synthesis. GH undeniably exhibits all these activities, which have been documented in numerous *in vitro* and *in vivo* studies. Based on these facts, the sports, body-building, and antiaging communities believe that GH must be beneficial for building musculature and therefore physical performance. This apparently reasonable assumption is, however, still a matter of debate as far as athletic performance is concerned, due to the difficulty in demonstrating ergogenicity of GH in scientific studies (229).

A fundamental principle in endocrinology states that the effect of a hormone is most evident when the hormone is replaced in an individual who is deficient in that hormone. Accordingly, the ergogenic effect of GH should be most obvious in GH-deficient patients when treated with GH. The scientific literature on this point is mixed: some studies show increased stamina, few show increased strength, and some show little effect on parameters related to physical performance. The complexity of GH status (deficiency or excess) on muscle morphology, metabolism, and function has been reviewed in detail by Woodhouse *et al.* (230). From that review, it appears that both a deficiency and an excess of GH are deleterious to muscle health. Assessment of physical function in GH deficiency and its response to GH replacement has been the subject of numerous studies, with less than consistent conclusions. The very fact that this is still a subject of investigation after two decades of study attests to the difficulty of settling this issue. A detailed discussion of the many studies addressing the ergogenic effects (or lack thereof) of GH replacement therapy in hypopituitarism is beyond the scope of this review. A recent meta-analysis of 11 randomized, double-blind, placebo-controlled studies concluded that GH replacement improved the exercise performance of GH-deficient patients (231). Another meta-analysis of muscle strength outcome in eight randomized, double-blind, placebo-controlled studies (some are the same as those included above) concluded that there was no improvement in muscle strength after 6–8 months of GH replacement (232). The authors point out that longer duration (years) of therapy might have resulted in increased strength. A recent study of cardiovascular function in patients given physiological replacement doses of GH (mean, 0.64 mg/d) found no improvement in exercise performance, in contrast to earlier studies using higher GH doses (233). Taken together, the studies in GH deficiency suggest that there probably is an overall improvement in physical function with GH replacement, but this is variable, complex in nature, less than compelling, and not universally accepted. Thus, even in the "ideal" setting of GH deficiency, it is difficult to unequivocally demonstrate an ergogenic effect of GH.

The question then arises whether ergogenicity can be shown in normal (*i.e.*, GH-replete) subjects, which includes both untrained individuals and athletes. Based on the above-mentioned endocrine/biological concept, it would be predicted that this may be more difficult. A number of studies examining the effect of GH on athletic performance have been conducted. A systematic literature review by Liu *et al.* (234) summarized the results of 27 randomized, controlled trials involving 303 young, lean, physically fit subjects receiving GH at an average dose of ~2.5 mg/d—a 5- to 10-fold excess over the physiological GH production rate. While there were the expected changes in body composition (increased lean body mass and marginally lower fat mass), there were no differences in strength or exercise capacity between those taking GH and those who did not. The authors point out the limitations of the studies in terms of duration and dose of GH, which may be less than what is typically used by athletes. Nevertheless, the typical side effects associated with GH administration (edema, arthralgias, carpal tunnel syndrome, sweating) were observed in 15–44% of the participants. A list of typical adverse effects seen with GH administration is given in Table 4.

There are relatively few controlled studies of GH effects in trained athletes. The Mitchell report (Ref. 4, pages 9–10) relates the impression of athletes that GH did not have a positive effect on their performance. Deyssig *et al.* (235) showed in a double-blind, placebo-controlled trial

TABLE 4. Adverse effects of GH administration

Sodium and fluid retention
Soft tissue swelling
Paresthesias
Nerve entrapment, carpal tunnel syndrome
Joint stiffness
Hypertension
Peripheral edema
Arthralgias
Myalgias
Insulin resistance
Carbohydrate intolerance
Diabetes mellitus
Gynecomastia
Acromegalic changes expected with prolonged, high-dose GH
Acral enlargement
Bone remodeling
Arthritis
Bone spurs
Frontal bossing
Dental malocclusion
Spinal stenosis
Disfigurement
Cardiovascular changes
Cardiac dysfunction

Adverse effects are dose-dependent, treatment duration-dependent, and age-dependent. Susceptibility varies among individuals. Older people are more prone to side effects even at low doses.

that GH [30 μg/kg · d (or ~2–2.5 mg/d) for 6 wk] had no effect on muscle strength. Lange *et al.* (236) showed that acute GH administration (2.5 mg 4 h before exercise) did not increase bicycling performance measured as speed or VO_2 but had a deleterious effect in two cyclists. Meinhardt *et al.* (237), in a double-blind, placebo-controlled study of recreational athletes, showed that GH (2 mg/d for 8 wk) had no effect on muscle strength (dead lift), power (jump height), or endurance (VO_2max) but did improve sprint capacity by 5.5% in men but not women (by 2.5%; not significant). Testosterone coadministration in men enhanced the effect of GH. Adverse effects typical for GH administration were seen in a significant number of the treated subjects. This isolated improvement in anaerobic muscle performance during sprinting is somewhat unexpected, especially because other anaerobic muscle functions were not affected. The authors state that athletic significance of this finding is uncertain, but they also speculate that the improvement might translate into a 0.4-sec advantage in a 100-m sprint.

In view of the overall scientific literature, the evidence for GH as an ergogenic substance in healthy humans is weak. Yet athletes continue GH abuse in the belief that it improves their performance. Numerous reasons can be given why the scientific literature does not reflect GH use in the sports arena: GH doses are too low; duration of treatment is not long enough; GH in conjunction with anabolic steroids, insulin, and other doping agents may have greater ergogenicity than when given alone; GH in combination with exercise is particularly potent; athletes react to GH in a different manner than nonathletes, *etc.* While all of these arguments have some validity and should not be readily dismissed, perhaps the most pertinent are those regarding dose and duration. Dosages and injection patterns among athletes are difficult to assess because of the lack of documentation and prevailing secrecy. Ehrnborg *et al.* (2) mention doses of 3–8 mg three to four times a week but state that the mean daily dose is mostly ~1.3 mg. Saugy *et al.* (238) estimate that, based on underground information, athletes inject 3–8 mg three to four times a week. The reliability of such underground information is uncertain because athletes themselves (or their trainers) may not know in detail what or how much is being administered. Nature has provided for an excellent model of the effects of high-dose, long-duration GH exposure: the patient with acromegaly. Acromegaly is caused by excess production of GH, usually by a benign pituitary tumor. It is a disease with insidious onset; the delay between onset and diagnosis is estimated as at least 7–10 yr (239). Acromegaly has a high morbidity and carries a 1.5- to 3-fold increase in mortality, with a direct relationship between GH levels and risk of premature death (240); it adversely affects many tissues and functions critical to physical performance (joints, heart and skeletal muscle, connective tissue, nerve entrapment, hypertension, metabolic derangements, diabetes mellitus, *etc.*) (241). Physical performance is clearly impaired in established acromegaly due to numerous physical and metabolic reasons. Therefore, high doses of GH over a long time are not performance enhancing. It could be argued that there may be an early phase of acromegaly, before the establishment of physical and metabolic derangements, when the high prevailing GH levels are ergogenic. This would be akin to the athlete abusing GH. However, with the exception of one spectacular case self-report (242), there is no evidence that patients with acromegaly experience such a phase of enhanced physical functioning. Rather, the disease progresses in silence for years before disfigurement leads to the diagnosis. Of interest, the patient in the cited case report was still growing at age 22, with a height increase of 6 inches (15.2 cm) over the preceding 4 yr. Given his pituitary tumor, this phenomenon is best explained by hypogonadism, calling into question the contribution of high endogenous testosterone levels to the postulated ergogenic effect high GH levels. Despite this report, the general lesson taught by acromegaly does not support the notion that high-dose GH is more ergogenic than low-dose GH.

Another reason sometimes given for the use of GH by athletes is the belief that GH accelerates recovery from injury. There is only limited information about this issue in the scientific literature. Involvement of GH in healing may be postulated based on the fact that collagen turnover increases after GH administration (see *Section III.B.1*). However, it is unknown whether after an injury GH plays a role in this response or whether local factors operating at the injury site are responsible. Furthermore, it is unknown whether supraphysiological GH concentrations confer any advantage over the normal physiological response of the GH-IGF system. One recent study examined collagen synthesis in patellar tendon and quadriceps muscle in response to 14 d of high-dose GH treatment (33–50 μg/kg · d, ~2–4 mg/d) in noninjured young male volunteers; GH treatment increased collagen protein synthesis 1.3-fold over placebo (significant) in tendon and 5.8-fold (not significant) in muscle (243). Another study examined the effect of three doses of GH (15, 30, and 60 μg/kg · d, ~1, 2, and 4 mg/d) on tibial fracture healing (244). At the highest dose, GH accelerated fracture healing by 29% in patients with closed fractures, but had no significant effect on the healing of open fractures. The two lower doses of GH had no discernible effect on fracture healing (244). These findings need to be corroborated and expanded before firm conclusions can be drawn about the effect of GH

on recovery from injury. Furthermore, the response of different types of injury and tissues to GH treatment, as well as the doses required need to be investigated before the significance of GH for recovery from athletic injuries becomes clear. It is of interest that promising early trials of GH therapy for burns (245, 246) have not been widely accepted as a therapeutic modality. The currently available evidence is insufficient to warrant the use of GH to promote healing of sports injuries.

A third reason for GH misuse is the belief by athletes that the lipolytic activity of GH results in weight loss, which they believe to be beneficial to athletic performance. However, GH administration does not typically result in a net weight change because the loss of fat is compensated for by a gain in lean body mass [of which a substantial part (50–80%) represents retained fluid]. This is true in the GH-deficient patient on GH replacement therapy as well as in normal subjects, including athletes, taking GH (237, 247).

The conviction in athletic circles that GH is a performance-enhancing substance appears to run deep, despite assertions to the contrary cited in the Mitchell report (4). An athlete's personal sense of what makes him or her perform better should not be easily dismissed. Neither should the powers of a placebo effect, hearsay, peer/coach pressure, and advertising be underestimated. It should also be remembered in this context that an ergogenic effect of androgens was questioned by the scientific community for years before their performance-enhancing potency was proven. In the final analysis, even with the best scientific evidence it will be impossible to prove a negative, namely that GH does not have an ergogenic effect. Nevertheless, given what is known, the burden of proof lies with those who advocate GH use in the belief that it enhances physical performance in healthy humans. Education of athletes, trainers and other sports personnel about the facts known regarding GH effects on performance should be undertaken by sports organizations as part of their antidoping strategy. This education should also include information about the short-term and long-term side effects of high-dose GH use. Given the dearth of scientific evidence for ergogenicity and the potential serious adverse effects on health, it seems ill-advised to use GH for uncertain performance enhancement in healthy individuals.

VII. Summary and Conclusions

GH is reported to be widely abused by athletes in many types of sport. The attractiveness of GH lies in its anabolic and lipolytic activities, combined with an aura of "undetectability." GH abuse extends beyond professional sports and is also present among adolescents engaged in sports in schools. This widespread use presents a public health problem because GH use is accompanied by adverse effects, and long-term use can lead to serious morbidity.

Because GH is secreted in a pulsatile manner and therefore fluctuates widely in blood, a high serum GH cannot be interpreted as evidence for exogenous GH administration.

GH used for doping purposes is said to be like a natural substance and therefore not detectable. However, pituitary GH consists of a number of molecular variants (isoforms), whereas recombinant GH corresponds to only one (the most prevalent) isoform, 22K-GH. This difference forms the basis of a detection test, where the ratio between 22K-GH and pituitary GH (a mixture of isoforms) is used as the endpoint. The isoform detection test performs well, but has a limited window of opportunity (12–24 h after the last GH injection). It has been a WADA-sanctioned and generally implemented test for over 2 yr; positive results have been few, presumably because of the short window of detection opportunity. The isoform test can be circumvented by using cadaveric GH (with attendant risk of acquiring Creutzfeld-Jakob disease) or using GH secretagogues (resulting in only mild GH stimulation).

A second detection test for GH abuse, the biomarker test, is based on measurement of biochemical effects of GH administration. Serum levels of IGF-I and P-III-NP rise after GH administration and remain elevated for several days to weeks after a GH dose. They are not completely specific for GH, but extensive validation studies have resulted in a discriminant formula that allows distinction of GH-induced elevation from most if not all nonspecific stimuli. The biomarker test has a window of opportunity of several days—realistically probably 5–7 d. It is scheduled to be implemented by WADA in time for the London 2012 Olympiad.

The immunoassays currently used for IGF-I and P-III-NP are somewhat problematic because of the lack of consistency over time and notorious interference by IGFBPs (IGF-I), and insufficient standardization due to absence of an international reference standard (P-III-NP). The development of mass-based identification and quantification methods that do not depend on antibodies or poorly defined/impure reference standards is highly recommended as MS-based technology becomes feasible.

Detection of doping substances (such as anabolic steroids) in urine has been a time-honored and successful tradition in sports. This methodology is not easily applicable to polypeptides such as GH, IGF-I, or P-III-NP. The reasons are multiple and include extremely low levels of residual peptide in urine, renal factors impinging on excretion, lack of evidence that urinary peptide concentra-

Endocrine Reviews, April 2012, 33(2):155–186

tion reflects plasma concentration or overall production/dose, and insufficient scientific background information on how peptide excretion is regulated. The fact that for the polypeptides under consideration here, quantitative differences rather than qualitative differences (such as *e.g.*, a foreign substance or an abnormal glycosylation pattern) are determined presents an additional challenge to urine testing. For all these reasons, it is probably unwise to pursue the elusive goal of a urine test for detection of GH abuse. It is likely more productive to expend efforts to convince athletes that blood testing is necessary for these substances and to develop ultrasensitive methods that permit minimization of the required blood volume. The former should not be as difficult as is assumed because blood testing is already well-accepted in the blood doping field.

Saliva is under consideration as an ideal biological fluid that would allow noninvasive testing for doping substances. However, obstacles similar to those mentioned for urine would have to be overcome. The limited data available about salivary GH and IGF-I do not appear encouraging.

GH secretagogues of the GHRH and particularly GHRP/GHS variety are likely being used as doping agents in an effort to boost endogenous GH production, while at the same time evading detection by the GH isoform test. The boost in GH levels is far smaller than what can be achieved with direct GH administration, and the ergogenic effect (if any) would be significantly less. Amino acids (arginine, ornithine, lysine) are ineffective in boosting GH secretion unless they are given as large iv bolus doses. Urine tests are being developed for GHRP/GHS and possibly GHRH analogs; this is feasible because these compounds are structurally different from their endogenous counterparts.

Doping with IGF-I is the newest form of "GH doping;" there is forensic evidence that IGF-I and its congeners are being used. To date, no test to detect IGF-I abuse is available, but the above-mentioned GH biomarker test (see *Section III.B.1*) and variations thereof are being studied as a detection strategy. Obviously, the GH isoform test would not be applicable, nor would urinary IGF-I testing be suitable for the reasons outlined above.

The question regarding the ergogenicity of GH has been asked for many years. The notion that GH is a performance-enhancing substance is based on its known anabolic action, amplified by its lipolytic action. Countless studies have documented the effect of GH on muscle mass, muscle architecture, metabolism, and function *in vitro*, and there is no doubt about the anabolic effects of GH, especially in the context of GH deficiency. The picture is less clear in GH sufficiency. Furthermore, the link between muscle mass, muscle function, and physical performance *in vivo* is less than straightforward. Accumulating scientific evidence in normal humans (including athletes) has for the most part failed to demonstrate a significant ergogenic effect of GH in supraphysiological doses, although perhaps in lower doses than those speculated to be used by athletes. The best model of high-dose, long-term GH "administration," acromegaly, also fails to support an ergogenic effect. There is anecdotal evidence [from the Mitchell report (4)] that athletes recognize that GH does not enhance their performance. Given this overall evidence, the burden of proof that GH is ergogenic lies with those advocating its use. Sports organizations should educate athletes and trainers about these facts in an effort to combat GH doping, an expensive, probably poorly effective, medically hazardous form of unfair behavior.

Acknowledgments

The author thanks his colleagues on the Partnership for Clean Competition (PCC) Scientific Advisory Board, Drs. Larry Bowers, Bryan Finkle, Gary Green, Alvin Matsumoto, Michael Sawka, Lawrence Silverman, and John Yates for many helpful discussions and a critical review of the manuscript.

Address all correspondence and requests for reprints to: G. Baumann, M.D., Northwestern University Feinberg Medical School, Division of Endocrinology, Metabolism and Molecular Medicine, 303 East Chicago Avenue, Tarry Building Room 15-703, Chicago, Illinois 60611. E-mail: gbaumann@northwestern.edu.

This work was supported by a grant from PCC.

Disclosure Summary: The author is a member of the Scientific Advisory Board of the Partnership for Clean Competition.

References

1. Rickert VI, Pawlak-Morello C, Sheppard V, Jay MS 1992 Human growth hormone: a new substance of abuse among adolescents? Clin Pediatr (Phila) 31:723–726
2. Ehrnborg C, Bengtsson BA, Rosén T 2000 Growth hormone abuse. Baillieres Best Pract Res Clin Endocrinol Metab 14:71–77
3. Buzzini SR 2007 Abuse of growth hormone among young athletes. Pediatr Clin North Am 54:823–843, xiii
4. Mitchell G 2007 Report to the commissioner of baseball of an independent investigation into the illegal use of steroids and other performance enhancing substances by players in major league baseball. http://files.mlb.com/mitchrpt.pdf
5. Holt RI, Erotokritou-Mulligan I, Sönksen PH 2009 The history of doping and growth hormone abuse in sport. Growth Horm IGF Res 19:320–326
6. Beck JC, McGarry EE, Dyrenfurth I, Venning EH 1957 Metabolic effects of human and monkey growth hormone in man. Science 125:884–885
7. Raben MS 1958 Treatment of a pituitary dwarf with human growth hormone. J Clin Endocrinol Metab 18:901–903

8. Chen EY, Liao YC, Smith DH, Barrera-Saldaña HA, Gelinas RE, Seeburg PH 1989 The human growth hormone locus: nucleotide sequence, biology, and evolution. Genomics 4:479–497
9. DeNoto FM, Moore DD, Goodman HM 1981 Human growth hormone DNA sequence and mRNA structure: possible alternative splicing. Nucleic Acids Res 9:3719–3730
10. Lecomte CM, Renard A, Martial JA 1987 A new natural hGH variant—17.5 kd—produced by alternative splicing. An additional consensus sequence which might play a role in branchpoint selection. Nucleic Acids Res 15:6331–6348
11. Cooke NE, Ray J, Watson MA, Estes PA, Kuo BA, Liebhaber SA 1988 Human growth hormone gene and the highly homologous growth hormone variant gene display different splicing patterns. J Clin Invest 82:270–275
12. Palmetshofer A, Zechner D, Luger TA, Barta A 1995 Splicing variants of the human growth hormone mRNA: detection in pituitary, mononuclear cells and dermal fibroblasts. Mol Cell Endocrinol 113:225–234
13. Chellakooty M, Vangsgaard K, Larsen T, Scheike T, Falck-Larsen J, Legarth J, Andersson AM, Main KM, Skakkebaek NE, Juul A 2004 A longitudinal study of intrauterine growth and the placental growth hormone (GH)-insulin-like growth factor I axis in maternal circulation: association between placental GH and fetal growth. J Clin Endocrinol Metab 89:384–391
14. Wu Z, Bidlingmaier M, Friess SC, Kirk SE, Buchinger P, Schiessl B, Strasburger CJ 2003 A new nonisotopic, highly sensitive assay for the measurement of human placental growth hormone: development and clinical implications. J Clin Endocrinol Metab 88:804–811
15. MacLeod JN, Worsley I, Ray J, Friesen HG, Liebhaber SA, Cooke NE 1991 Human growth hormone-variant is a biologically active somatogen and lactogen. Endocrinology 128:1298–1302
16. Baumann G, Dávila N, Shaw MA, Ray J, Liebhaber SA, Cooke NE 1991 Binding of human growth hormone (GH)-variant (placental GH) to GH-binding proteins in human plasma. J Clin Endocrinol Metab 73:1175–1179
17. Igout A, Frankenne F, L'Hermite-Balériaux M, Martin A, Hennen G 1995 Somatogenic and lactogenic activity of the recombinant 22 kDa isoform of human placental growth hormone. Growth Regul 5:60–65
18. Baumann GP 2009 Growth hormone isoforms. Growth Horm IGF Res 19:333–340
19. Lewis UJ, Dunn JT, Bonewald LF, Seavey BK, Vanderlaan WP 1978 A naturally occurring structural variant of human growth hormone. J Biol Chem 253:2679–2687
20. Baumann G 1991 Growth hormone heterogeneity: genes, isohormones, variants, and binding proteins. Endocr Rev 12:424–449
21. Chapman GE, Rogers KM, Brittain T, Bradshaw RA, Bates OJ, Turner C, Cary PD, Crane-Robinson C 1981 The 20,000 molecular weight variant of human growth hormone. Preparation and some physical and chemical properties. J Biol Chem 256:2395–2401
22. Stolar MW, Amburn K, Baumann G 1984 Plasma "big" and "big-big" growth hormone (GH) in man: an oligomeric series composed of structurally diverse GH monomers. J Clin Endocrinol Metab 59:212–218
23. Uchida H, Naito N, Asada N, Wada M, Ikeda M, Kobayashi H, Asanagi M, Mori K, Fujita Y, Konda K, Kusuhara N, Kamioka T, Nakashima K, Honjo M 1997 Secretion of authentic 20-kDa human growth hormone (20K hGH) in *Escherichia coli* and properties of the purified product. J Biotechnol 55:101–112
24. Lewis UJ, Singh RN, Bonewald LF, Lewis LJ, Vanderlaan WP 1979 Human growth hormone: additional members of the complex. Endocrinology 104:1256–1265
25. Lewis UJ, Singh RN, Bonewald LF, Seavey BK 1981 Altered proteolytic cleavage of human growth hormone as a result of deamidation. J Biol Chem 256:11645–11650
26. Haro LS, Lewis UJ, Garcia M, Bustamante J, Martinez AO, Ling NC 1996 Glycosylated human growth hormone (hGH): a novel 24 kDa hGH-N variant. Biochem Biophys Res Commun 228:549–556
27. Kohler M, Thomas A, Püschel K, Schänzer W, Thevis M 2009 Identification of human pituitary growth hormone variants by mass spectrometry. J Proteome Res 8:1071–1076
28. Lewis UJ, Peterson SM, Bonewald LF, Seavey BK, Vanderlaan WP 1977 An interchain disulfide dimer of human growth hormone. J Biol Chem 252:3697–3702
29. Brostedt P, Roos P 1989 Isolation of dimeric forms of human pituitary growth hormone. Prep Biochem 19:217–229
30. Ultsch MH, Somers W, Kossiakoff AA, de Vos AM 1994 The crystal structure of affinity-matured human growth hormone at 2 A resolution. J Mol Biol 236:286–299
31. Brooks AJ, Waters MJ 2010 The growth hormone receptor: mechanism of activation and clinical implications. Nat Rev Endocrinol 6:515–525
32. Mercado M, DáVila N, McLeod JF, Baumann G 1994 Distribution of growth hormone receptor messenger ribonucleic acid containing and lacking exon 3 in human tissues. J Clin Endocrinol Metab 78:731–735
33. Mertani HC, Delehaye-Zervas MC, Martini JF, Postel-Vinay MC, Morel G 1995 Localization of growth hormone receptor messenger RNA in human tissues. Endocrine 3:135–142
34. de Vos AM, Ultsch M, Kossiakoff AA 1992 Human growth hormone and extracellular domain of its receptor: crystal structure of the complex. Science 255:306–312
35. Ross RJ, Leung KC, Maamra M, Bennett W, Doyle N, Waters MJ, Ho KK 2001 Binding and functional studies with the growth hormone receptor antagonist, B2036-PEG (pegvisomant), reveal effects of pegylation and evidence that it binds to a receptor dimer. J Clin Endocrinol Metab 86:1716–1723
36. Gent J, van Kerkhof P, Roza M, Bu G, Strous GJ 2002 Ligand-independent growth hormone receptor dimerization occurs in the endoplasmic reticulum and is required for ubiquitin system-dependent endocytosis. Proc Natl Acad Sci USA 99:9858–9863
37. Brooks AJ, Wooh JW, Tunny KA, Waters MJ 2008 Growth hormone receptor; mechanism of action. Int J Biochem Cell Biol 40:1984–1989
38. Lanning NJ, Carter-Su C 2006 Recent advances in growth hormone signaling. Rev Endocr Metab Disord 7:225–235
39. Cunningham BC, Bass S, Fuh G, Wells JA 1990 Zinc me-

Endocrine Reviews, April 2012, 33(2):155–186 edrv.endojournals.org 179

diation of the binding of human growth hormone to the human prolactin receptor. Science 250:1709–1712
40. Hayakawa M, Shimazaki Y, Tsushima T, Kato Y, Takano K, Chihara K, Shimatsu A, Irie M 2004 Metabolic effects of 20-kilodalton human growth hormone (20K-hGH) for adults with growth hormone deficiency: results of an exploratory uncontrolled multicenter clinical trial of 20K-hGH. J Clin Endocrinol Metab 89:1562–1571
41. Winer LM, Shaw MA, Baumann G 1990 Basal plasma growth hormone levels in man: new evidence for rhythmicity of growth hormone secretion. J Clin Endocrinol Metab 70:1678–1686
42. Hartman ML, Faria AC, Vance ML, Johnson ML, Thorner MO, Veldhuis JD 1991 Temporal structure of in vivo growth hormone secretory events in humans. Am J Physiol 260:E101–E110
43. Maheshwari HG, Pezzoli SS, Rahim A, Shalet SM, Thorner MO, Baumann G 2002 Pulsatile growth hormone secretion persists in genetic growth hormone-releasing hormone resistance. Am J Physiol Endocrinol Metab 282:E943–E951
44. Ho KY, Evans WS, Blizzard RM, Veldhuis JD, Merriam GR, Samojlik E, Furlanetto R, Rogol AD, Kaiser DL, Thorner MO 1987 Effects of sex and age on the 24-hour profile of growth hormone secretion in man: importance of endogenous estradiol concentrations. J Clin Endocrinol Metab 64:51–58
45. Iranmanesh A, Lizarralde G, Veldhuis JD 1991 Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men. J Clin Endocrinol Metab 73:1081–1088
46. Ho KY, Veldhuis JD, Johnson ML, Furlanetto R, Evans WS, Alberti KG, Thorner MO 1988 Fasting enhances growth hormone secretion and amplifies the complex rhythms of growth hormone secretion in man. J Clin Invest 81:968–975
47. Weltman A, Weltman JY, Hartman ML, Abbott RD, Rogol AD, Evans WS, Veldhuis JD 1994 Relationship between age, percentage body fat, fitness, and 24-hour growth hormone release in healthy young adults: effects of gender. J Clin Endocrinol Metab 78:543–548
48. Van Cauter E 2000 Slow wave sleep and release of growth hormone. JAMA 284:2717–2718
49. Pritzlaff CJ, Wideman L, Weltman JY, Abbott RD, Gutgesell ME, Hartman ML, Veldhuis JD, Weltman A 1999 Impact of acute exercise intensity on pulsatile growth hormone release in men. J Appl Physiol 87:498–504
50. Vigas M, Malatinský J, Németh S, Jurcovicová J 1977 α-Adrenergic control of growth hormone release during surgical stress in man. Metabolism 26:399–402
51. Vanhelder WP, Goode RC, Radomski MW 1984 Effect of anaerobic and aerobic exercise of equal duration and work expenditure on plasma growth hormone levels. Eur J Appl Physiol Occup Physiol 52:255–257
52. Felsing NE, Brasel JA, Cooper DM 1992 Effect of low and high intensity exercise on circulating growth hormone in men. J Clin Endocrinol Metab 75:157–162
53. Weltman A, Weltman JY, Schurrer R, Evans WS, Veldhuis JD, Rogol AD 1992 Endurance training amplifies the pulsatile release of growth hormone: effects of training intensity. J Appl Physiol 72:2188–2196
54. Godfrey RJ, Madgwick Z, Whyte GP 2003 The exercise-induced growth hormone response in athletes. Sports Med 33:599–613
55. Kraemer WJ, Dunn-Lewis C, Comstock BA, Thomas GA, Clark JE, Nindl BC 2010 Growth hormone, exercise, and athletic performance: a continued evolution of complexity. Curr Sports Med Rep 9:242–252
56. Rosenthal SM, Hulse JA, Kaplan SL, Grumbach MM 1986 Exogenous growth hormone inhibits growth hormone-releasing factor-induced growth hormone secretion in normal men. J Clin Invest 77:176–180
57. Ross RJ, Borges F, Grossman A, Smith R, Ngahfoong L, Rees LH, Savage MO, Besser GM 1987 Growth hormone pretreatment in man blocks the response to growth hormone-releasing hormone; evidence for a direct effect of growth hormone. Clin Endocrinol (Oxf) 26:117–123
58. Hartman ML, Clayton PE, Johnson ML, Celniker A, Perlman AJ, Alberti KG, Thorner MO 1993 A low dose euglycemic infusion of recombinant human insulin-like growth factor I rapidly suppresses fasting-enhanced pulsatile growth hormone secretion in humans. J Clin Invest 91:2453–2462
59. Bermann M, Jaffe CA, Tsai W, DeMott-Friberg R, Barkan AL 1994 Negative feedback regulation of pulsatile growth hormone secretion by insulin-like growth factor I. Involvement of hypothalamic somatostatin. J Clin Invest 94:138–145
60. Baumann G, Stolar MW 1986 Molecular forms of human growth hormone secreted *in vivo*: nonspecificity of secretory stimuli. J Clin Endocrinol Metab 62:789–790
61. Wallace JD, Cuneo RC, Bidlingmaier M, Lundberg PA, Carlsson L, Boguszewski CL, Hay J, Healy ML, Napoli R, Dall R, Rosén T, Strasburger CJ 2001 The response of molecular isoforms of growth hormone to acute exercise in trained adult males. J Clin Endocrinol Metab 86:200–206
62. Leung KC, Howe C, Gui LY, Trout G, Veldhuis JD, Ho KK 2002 Physiological and pharmacological regulation of 20-kDa growth hormone. Am J Physiol Endocrinol Metab 283:E836–E843
63. Wu Z, Devany E, Balarini G, Junnila R, Bidlingmaier M, Strasburger CJ 2010 Specific monoclonal antibodies and ultrasensitive immunoassays for 20K and 22K human growth hormone. Growth Horm IGF Res 20:239–244
64. Johnson V, Maack T 1977 Renal extraction, filtration, absorption, and catabolism of growth hormone. Am J Physiol 233:F185–F196
65. Kau ST, Maack T 1986 Mechanism of tubular uptake on human growth hormone in perfused rat kidneys. J Pharmacol Exp Ther 236:596–601
66. Rabkin R, Gottheiner TI, Fang VS 1981 Removal and excretion of immunoreactive rat growth hormone by the isolated kidney. Am J Physiol 240:F282–F287
67. García-Mayor RV, Pérez AJ, Gandara A, Andrade A, Mallo F, Casanueva FF 1993 Metabolic clearance rate of biosynthetic growth hormone after endogenous growth hormone suppression with a somatostatin analogue in chronic renal failure patients and control subjects. Clin Endocrinol (Oxf) 39:337–343
68. Haffner D, Schaefer F, Girard J, Ritz E, Mehls O 1994

Metabolic clearance of recombinant human growth hormone in health and chronic renal failure. J Clin Invest 93: 1163–1171
69. Hanssen KF 1972 Immunoreactive growth hormone in human urine. Acta Endocrinol (Copenh) 71:665–676
70. Baumann G, Abramson EC 1983 Urinary growth hormone in man: evidence for multiple molecular forms. J Clin Endocrinol Metab 56:305–311
71. Faria AC, Veldhuis JD, Thorner MO, Vance ML 1989 Half-time of endogenous growth hormone (GH) disappearance in normal man after stimulation of GH secretion by GH-releasing hormone and suppression with somatostatin. J Clin Endocrinol Metab 68:535–541
72. Veldhuis JD, Johnson ML, Faunt LM, Mercado M, Baumann G 1993 Influence of the high-affinity growth hormone (GH)-binding protein on plasma profiles of free and bound GH and on the apparent half-life of GH. Modeling analysis and clinical applications. J Clin Invest 91:629–641
73. Hendricks CM, Eastman RC, Takeda S, Asakawa K, Gorden P 1985 Plasma clearance of intravenously administered pituitary human growth hormone: gel filtration studies of heterogeneous components. J Clin Endocrinol Metab 60:864–867
74. Murakami Y, Mori T, Koshimura K, Kurosaki M, Takenobu A, Hashimoto Y, Kato Y 2000 Twenty-kilodalton human growth hormone (20K hGH) secretion from growth hormone-secreting pituitary adenoma cells in vitro. Endocr J 47:563–568
75. Product insert 2010 Humatrope. Indianapolis, IN: Eli Lilly & Co.
76. Hashimoto Y, Kamioka T, Hosaka M, Mabuchi K, Mizuchi A, Shimazaki Y, Tsunoo M, Tanaka T 2000 Exogenous 20K growth hormone (GH) suppresses endogenous 22K GH secretion in normal men. J Clin Endocrinol Metab 85:601–606
77. Baumann G, Frank SJ 2002 Metalloproteinases and the modulation of growth hormone signalling. J Endocrinol 174:361–368
78. Kratzsch J, Selisko T, Birkenmeier G 1995 Identification of transformed α2-macroglobulin as a growth hormone-binding protein in human blood. J Clin Endocrinol Metab 80:585–590
79. Baumann G, Amburn K, Shaw MA 1988 The circulating growth hormone (GH)-binding protein complex: a major constituent of plasma GH in man. Endocrinology 122: 976–984
80. Ishikawa M, Yokoya S, Tachibana K, Hasegawa Y, Yasuda T, Tokuhiro E, Hashimoto Y, Tanaka T 1999 Serum levels of 20-kilodalton human growth hormone (GH) are parallel those of 22-kilodalton human GH in normal and short children. J Clin Endocrinol Metab 84:98–104
81. Tsushima T, Katoh Y, Miyachi Y, Chihara K, Teramoto A, Irie M, Hashimoto Y 1999 Serum concentration of 20K human growth hormone (20K hGH) measured by a specific enzyme-linked immunosorbent assay. Study Group of 20K hGH. J Clin Endocrinol Metab 84:317–322
82. Baumann G, MacCart JG 1982 Growth hormone production by human pituitary glands in organ culture: evidence for predominant secretion of the single-chain 22,000 molecular weight form (isohormone B). J Clin Endocrinol Metab 55:611–618
83. Baumann G, MacCart JG, Amburn K 1983 The molecular nature of circulating growth hormone in normal and acromegalic man: evidence for a principal and minor monomeric forms. J Clin Endocrinol Metab 56:946–952
84. Stolar MW, Baumann G, Vance ML, Thorner MO 1984 Circulating growth hormone forms after stimulation of pituitary secretion with growth hormone-releasing factor in man. J Clin Endocrinol Metab 59:235–239
85. Baumann G, Stolar MW, Amburn K 1985 Molecular forms of circulating growth hormone during spontaneous secretory episodes and in the basal state. J Clin Endocrinol Metab 60:1216–1220
86. Stolar MW, Baumann G 1986 Big growth hormone forms in human plasma: immunochemical evidence for their pituitary origin. Metabolism 35:75–77
87. Norman PS 1958 Studies of the plasmin system. II. Inhibition of plasmin by serum or plasma. J Exp Med 108: 53–68
88. Derr RL, Cameron SJ, Golden SH 2006 Pre-analytic considerations for the proper assessment of hormones of the hypothalamic-pituitary axis in epidemiological research. Eur J Epidemiol 21:217–226
89. Baumann G 1976 Failure of endogenous plasmin to convert human growth hormone to its "activated" isohormones. J Clin Endocrinol Metab 43:222–225
90. Bidlingmaier M, Suhr J, Ernst A, Wu Z, Keller A, Strasburger CJ, Bergmann A 2009 High-sensitivity chemiluminescence immunoassays for detection of growth hormone doping in sports. Clin Chem 55:445–453
91. Christensen EI, Verroust PJ, Nielsen R 2009 Receptor-mediated endocytosis in renal proximal tubule. Pflugers Arch 458:1039–1048
92. Bala RM, Beck JC 1971 Human growth hormone in urine. J Clin Endocrinol Metab 33:799–806
93. Owens D, Srivastava MC, Tompkins CV, Nabarro JD, Sönksen PH 1973 Studies on the metabolic clearance rate, apparent distribution space and plasma half-disappearance time of unlabelled human growth hormone in normal subjects and in patients with liver disease, renal disease, thyroid disease and diabetes mellitus. Eur J Clin Invest 3:284–294
94. Main K, Philips M, Jørgensen M, Skakkebaek NE 1991 Urinary growth hormone excretion in 657 healthy children and adults: normal values, inter- and intraindividual variations. Horm Res 36:174–182
95. Main KM, Jarden M, Angelo L, Dinesen B, Hertel NT, Juul A, Müller J, Skakkebaek NE 1994 The impact of gender and puberty on reference values for urinary growth hormone excretion: a study of 3 morning urine samples in 517 healthy children and adults. J Clin Endocrinol Metab 79: 865–871
96. Pirazzoli P, Mandini M, Zucchini S, Gualandi S, Vignutelli L, Capelli M, Cacciari E 1996 Urinary growth hormone estimation in diagnosing severe growth hormone deficiency. Arch Dis Child 75:228–231
97. Georges P, Liefooghe J, Ponchaux D, Forzy G, Di Nicola L, Chaussain JL 1997 Urinary growth hormone excretion: results of a multicenter study in France. Horm Res 47: 30–37

98. Gill MS, Toogood AA, O'Neill PA, Thorner MO, Shalet SM, Clayton PE 1998 Urinary growth hormone (GH), insulin-like growth factor I (IGF-I), and IGF-binding protein-3 measurements in the diagnosis of adult GH deficiency. J Clin Endocrinol Metab 83:2562–2565
99. Cappellin E, Gatti R, De Palo EF 1999 Influence of gender in growth hormone status in adults: role of urinary growth hormone. Clin Chem 45:443–444
100. Bona G, Petri A, Rapa A, Conti A, Sartorio A 1999 The impact of gender, puberty and body mass on reference values for urinary growth hormone (GH) excretion in normally growing non-obese and obese children. Clin Endocrinol (Oxf) 50:775–781
101. Girard J, Greenwood FC 1968 The absence of intact growth hormone in urine as judged by radioimmunoassay. J Endocrinol 40:493–503
102. Mauri M, Picó AM, Alfayate R, Dominguez JR, Cámara R, Miralles C 1993 Usefulness of urinary growth hormone (GH) measurement for evaluating endogenous GH secretion in acromegaly. Horm Res 39:13–18
103. Momomura S, Hashimoto Y, Shimazaki Y, Irie M 2000 Detection of exogenous growth hormone (GH) administration by monitoring ratio of 20 kDa- and 22 kDa-GH in serum and urine. Endocr J 47:97–101
104. Winer LM, Shaw MA, Baumann G 1989 Urinary growth hormone excretion rates in normal and acromegalic man: a critical appraisal of its potential clinical utility. J Endocrinol Invest 12:461–467
105. Léger J, Reverchon C, Porquet D, Noël M, Czernichow P 1995 The wide variation in urinary excretion of human growth hormone in normal growing and growth hormone-deficient children limits its clinical usefulness. Horm Res 44:57–63
106. Skinner AM, Clayton PE, Addison GM, Price DA 1995 Nocturnal urinary growth hormone excretion in growth hormone-deficient children on and off growth hormone treatment. Horm Res 44:147–151
107. Turner G, Coates P, Warren S, Woodhead JS, Peters JR 1997 Proximal tubular reabsorption of growth hormone and sodium/fluid in normo- and microalbuminuric insulin-dependent diabetes mellitus. Acta Diabetol 34:27–32
108. Flanagan DE, Taylor MG, Parfitt V, Mardell R, Wood PJ, Leatherdale BA 1997 Urinary growth hormone following exercise to assess growth hormone production in adults. Clin Endocrinol (Oxf) 46:425–429
109. Fall CH, Clark PM, Hindmarsh PC, Clayton PE, Shiell AW, Law CM 2000 Urinary GH and IGF-I excretion in nine year-old children: relation to sex, current size and size at birth. Clin Endocrinol (Oxf) 53:69–76
110. Saugy M, Cardis C, Schweizer C, Veuthey JL, Rivier L 1996 Detection of human growth hormone doping in urine: out of competition tests are necessary. J Chromatogr B Biomed Appl 687:201–211
111. Turner G, Coates P, Porter S, Peters JR, Woodhead JS 1993 Urinary growth hormone measurements as a marker of renal tubular function in diabetes mellitus. Clin Chim Acta 220:19–30
112. Hattori N, Kato Y, Murakami Y, Hashida S, Ishikawa E, Mohri Z, Imura H 1988 Urinary growth hormone levels measured by ultrasensitive enzyme immunoassay in patients with renal insufficiency. J Clin Endocrinol Metab 66:727–732
113. Fredolini C, Meani F, Reeder KA, Rucker S, Patanarut A, Botterell PJ, Bishop B, Longo C, Espina V, Petricoin 3rd EF, Liotta LA, Luchini A 2008 Concentration and preservation of very low abundance biomarkers in urine, such as human growth hormone (hGH), by Cibacron Blue F3G-A loaded hydrogel particles. Nano Res 1:502–518
114. Fredolini C, Tamburro D, Gambara G, Lepene BS, Espina V, Petricoin 3rd EF, Liotta LA, Luchini A 2009 Nanoparticle technology: amplifying the effective sensitivity of biomarker detection to create a urine test for hGH. Drug Test Anal 1:447–454
115. Rantonen PJ, Penttilä I, Meurman JH, Savolainen K, Närvänen S, Helenius T 2000 Growth hormone and cortisol in serum and saliva. Acta Odontol Scand 58:299–303
116. Popii V, Baumann G 2004 Laboratory measurement of growth hormone. Clin Chim Acta 350:1–16
117. Bidlingmaier M, Freda PU 2010 Measurement of human growth hormone by immunoassays: current status, unsolved problems and clinical consequences. Growth Horm IGF Res 20:19–25
118. Clemmons DR 2011 Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. Clin Chem 57:555–559
119. Thevis M, Bredehöft M, Kohler M, Schänzer W 2010 Mass spectrometry-based analysis of IGF-1 and hGH. Handb Exp Pharmacol 195:201–207
120. Arsene CG, Henrion A, Diekmann N, Manolopoulou J, Bidlingmaier M 2010 Quantification of growth hormone in serum by isotope dilution mass spectrometry. Anal Biochem 401:228–235
121. Wu Z, Bidlingmaier M, Dall R, Strasburger CJ 1999 Detection of doping with human growth hormone. Lancet 353:895
122. 2010 World Anti-Doping Agency Guidelines: hGH isoform differential immunoassays for anti-doping analyses, version 1.0, June 2010. http://www.wada-ama.org/Documents/Science_Medicine/Anti-Doping-Labs-Guidelines/WADA_SCGuidelines_hGH%20Differential%20Immunoassays_EN_June10.pdf
123. Irie M, Ueki M, Kishikawa Y, Nishii M, Kawahara T 2009 20K-GH and its use in detecting GH abuse. Growth Horm IGF Res 19:352–356
124. Travis J 2010 Pharmacology. Growth hormone test finally nabs first doper. Science 327:1185
125. Kassem M, Brixen K, Blum WF, Mosekilde L, Eriksen EF 1994 Normal osteoclastic and osteoblastic responses to exogenous growth hormone in patients with postmenopausal spinal osteoporosis. J Bone Miner Res 9:1365–1370
126. Sönksen P 2009 The International Olympic Committee (IOC) and GH-2000. Growth Horm IGF Res 19:341–345
127. Sjögren K, Liu JL, Blad K, Skrtic S, Vidal O, Wallenius V, LeRoith D, Törnell J, Isaksson OG, Jansson JO, Ohlsson C 1999 Liver-derived insulin-like growth factor I (IGF-I) is the principal source of IGF-I in blood but is not required for postnatal body growth in mice. Proc Natl Acad Sci USA 96:7088–7092
128. Greenspan SL 2005 Biosynthetic processing of collagen molecules. Top Curr Chem 247:149–183
129. Brandt A, Glanville RW, Hörlein D, Bruckner P, Timpl R,

Fietzek PP, Kühn K 1984 Complete amino acid sequence of the N-terminal extension of calf skin type III procollagen. Biochem J 219:625–634
130. Niemelä O, Risteli L, Parkkinen J, Risteli J 1985 Purification and characterization of the N-terminal propeptide of human type III procollagen. Biochem J 232:145–150
131. Ala-Kokko L, Kontusaari S, Baldwin CT, Kuivaniemi H, Prockop DJ 1989 Structure of cDNA clones coding for the entire prepro α1 (III) chain of human type III procollagen. Differences in protein structure from type I procollagen and conservation of codon preferences. Biochem J 260: 509–516
132. Bulleid NJ, Wilson R, Lees JF 1996 Type-III procollagen assembly in semi-intact cells: chain association, nucleation and triple-helix folding do not require formation of interchain disulphide bonds but triple-helix nucleation does require hydroxylation. Biochem J 317:195–202
133. Nowack H, Olsen BR, Timpl R 1976 Characterization of the amino-terminal segment in type III procollagen. Eur J Biochem 70:205–216
134. Jensen LT 1997 The aminoterminal propeptide of type III procollagen. Studies on physiology and pathophysiology. Dan Med Bull 44:70–78
135. Kühn K, Wiestner M, Krieg T, Müller PK 1982 Structure and function of the amino terminal propeptide of type I and III collagen. Connect Tissue Res 10:43–50
136. Jensen LT, Risteli J, Nielsen MD, Henriksen JH, Olesen HP, Risteli L, Lorenzen I 1992 Purification of porcine aminoterminal propeptide of type III procollagen from lymph and use for lymphatic clearance studies in pigs. Matrix 12:73–79
137. Rohde H, Bruckner P, Timpl R 1983 Immunochemical properties of the aminopropeptide of procollagen type III. Eur J Biochem 135:197–202
138. Risteli J, Niemi S, Trivedi P, Mäentausta O, Mowat AP, Risteli L 1988 Rapid equilibrium radioimmunoassay for the amino-terminal propeptide of human type III procollagen. Clin Chem 34:715–718
139. Burchardt ER, Kroll W, Gehrmann M, Schröder W 2009 Monoclonal antibody and assay for detecting PIIINP. U.S. Patent no. 7,541,149 B1
140. Bentsen KD 1993 Type III procollagen peptide: studies on the circulating peptide as a marker of fibrinogenesis with special reference to the liver. Dan Med Bull 40:235–246
141. Wallace JD, Cuneo RC, Lundberg PA, Rosén T, Jørgensen JO, Longobardi S, Keay N, Sacca L, Christiansen JS, Bengtsson BA, Sönksen PH 2000 Responses of markers of bone and collagen turnover to exercise, growth hormone (GH) administration, and GH withdrawal in trained adult males. J Clin Endocrinol Metab 85:124–133
142. Guler HP, Zapf J, Schmid C, Froesch ER 1989 Insulin-like growth factors I and II in healthy man. Estimations of half-lives and production rates. Acta Endocrinol (Copenh) 121: 753–758
143. Jensen LT, Henriksen JH, Risteli J, Olesen HP, Nielsen MD, Lorenzen I 1993 Fate of circulating amino-terminal propeptide of type III procollagen in conscious pigs. Am J Physiol 265:R139–R145
144. Dall R, Longobardi S, Ehrnborg C, Keay N, Rosén T, Jørgensen JO, Cuneo RC, Boroujerdi MA, Cittadini A, Napoli R, Christiansen JS, Bengtsson BA, Sacca L, Baxter RC, Basset EE, Sönksen PH 2000 The effect of four weeks of supraphysiological growth hormone administration on the insulin-like growth factor axis in women and men. GH-2000 Study Group. J Clin Endocrinol Metab 85:4193–4200
145. Longobardi S, Keay N, Ehrnborg C, Cittadini A, Rosén T, Dall R, Boroujerdi MA, Bassett EE, Healy ML, Pentecost C, Wallace JD, Powrie J, Jørgensen JO, Saccà L 2000 Growth hormone (GH) effects on bone and collagen turnover in healthy adults and its potential as a marker of GH abuse in sports: a double blind, placebo-controlled study. The GH-2000 Study Group. J Clin Endocrinol Metab 85: 1505–1512
146. Powrie JK, Bassett EE, Rosen T, Jørgensen JO, Napoli R, Sacca L, Christiansen JS, Bengtsson BA, Sönksen PH 2007 Detection of growth hormone abuse in sport. Growth Horm IGF Res 17:220–226
147. Erotokritou-Mulligan I, Eryl Bassett E, Cowan DA, Bartlett C, Milward P, Sartorio A, Sönksen PH, Holt RI 2010 The use of growth hormone (GH)-dependent markers in the detection of GH abuse in sport: physiological intra-individual variation of IGF-I, type 3 pro-collagen (P-III-P) and the GH-2000 detection score. Clin Endocrinol (Oxf) 72:520–526
148. Wallace JD, Cuneo RC, Baxter R, Orskov H, Keay N, Pentecost C, Dall R, Rosén T, Jørgensen JO, Cittadini A, Longobardi S, Sacca L, Christiansen JS, Bengtsson BA, Sönksen PH 1999 Responses of the growth hormone (GH) and insulin-like growth factor axis to exercise, GH administration, and GH withdrawal in trained adult males: a potential test for GH abuse in sport. J Clin Endocrinol Metab 84:3591–3601
149. Abellan R, Ventura R, Pichini S, Di Giovannandrea R, Bellver M, Olive R, Pacifici R, Pascual JA, Zuccaro P, Segura J 2006 Effect of physical fitness and endurance exercise on indirect biomarkers of recombinant growth hormone misuse: insulin-like growth factor I and procollagen type III peptide. Int J Sports Med 27:976–983
150. Erotokritou-Mulligan I, Bassett EE, Bartlett C, Cowan D, McHugh C, Seah R, Curtis B, Wells V, Harrison K, Sönksen PH, Holt RI 2008 The effect of sports injury on insulin-like growth factor-I and type 3 procollagen: implications for detection of growth hormone abuse in athletes. J Clin Endocrinol Metab 93:2760–2763
151. Krusenstjerna-Hafstrøm T, Rasmussen MH, Raschke M, Govender S, Madsen J, Christiansen JS 2011 Biochemical markers of bone turnover in tibia fracture patients randomly assigned to growth hormone (GH) or placebo injections: implications for detection of GH abuse. Growth Horm IGF Res 21:331–335
152. Nelson AE, Meinhardt U, Hansen JL, Walker IH, Stone G, Howe CJ, Leung KC, Seibel MJ, Baxter RC, Handelsman DJ, Kazlauskas R, Ho KK 2008 Pharmacodynamics of growth hormone abuse biomarkers and the influence of gender and testosterone: a randomized double-blind placebo-controlled study in young recreational athletes. J Clin Endocrinol Metab 93:2213–2222
153. Nelson AE, Howe CJ, Nguyen TV, Seibel MJ, Baxter RC, Handelsman DJ, Kazlauskas R, Ho KK 2005 Erythropoietin administration does not influence the GH–IGF axis or

Endocrine Reviews, April 2012, 33(2):155–186 edrv.endojournals.org 183

makers of bone turnover in recreational athletes. Clin Endocrinol (Oxf) 63:305–309
154. Healy ML, Dall R, Gibney J, Bassett E, Ehrnborg C, Pentecost C, Rosen T, Cittadini A, Baxter RC, Sönksen PH 2005 Toward the development of a test for growth hormone (GH) abuse: a study of extreme physiological ranges of GH-dependent markers in 813 elite athletes in the post-competition setting. J Clin Endocrinol Metab 90:641–649
155. Nelson AE, Ho KK 2009 Demographic factors influencing the GH system: implications for the detection of GH doping in sport. Growth Horm IGF Res 19:327–332
156. Erotokritou-Mulligan I, Bassett EE, Cowan DA, Bartlett C, McHugh C, Sönksen PH, Holt RI 2009 Influence of ethnicity on IGF-I and procollagen III peptide (P-III-P) in elite athletes and its effect on the ability to detect GH abuse. Clin Endocrinol (Oxf) 70:161–168
157. Erotokritou-Mulligan I, Bassett EE, Kniess A, Sönksen PH, Holt RI 2007 Validation of the growth hormone (GH)-dependent marker method of detecting GH abuse in sport through the use of independent data sets. Growth Horm IGF Res 17:416–423
158. Nguyen TV, Nelson AE, Howe CJ, Seibel MJ, Baxter RC, Handelsman DJ, Kazlauskas R, Ho KK 2008 Within-subject variability and analytic imprecision of insulin-like growth factor axis and collagen markers: implications for clinical diagnosis and doping tests. Clin Chem 54:1268–1276
159. Guha N, Erotokritou-Mulligan I, Burford C, Strobridge G, Brigg J, Drake T, Bassett EE, Cowan D, Bartlett C, Sönksen PH, Holt RI 2010 Serum insulin-like growth factor-I and pro-collagen type III N-terminal peptide in adolescent elite athletes: implications for the detection of growth hormone abuse in sport. J Clin Endocrinol Metab 95:2969–2976
160. Kniess A, Ziegler E, Kratzsch J, Thieme D, Müller RK 2003 Potential parameters for the detection of hGH doping. Anal Bioanal Chem 376:696–700
161. Sartorio A, Agosti F, Marazzi N, Maffiuletti NA, Cella SG, Rigamonti AE, Guidetti L, Di Luigi L, Muller EE 2004 Combined evaluation of resting IGF-I, N-terminal propeptide of type III procollagen (PIIINP) and C-terminal cross-linked telopeptide of type I collagen (ICTP) levels might be useful for detecting inappropriate GH administration in athletes: a preliminary report. Clin Endocrinol (Oxf) 61:487–493
162. Di Luigi L, Rigamonti AE, Agosti F, Mencarelli M, Sgrò P, Marazzi N, Cella SG, Müller EE, Sartorio A 2009 Combined evaluation of resting IGF1, N-terminal propeptide of type III procollagen and C-terminal cross-linked telopeptide of type I collagen levels might be useful for detecting inappropriate GH administration in female athletes. Eur J Endocrinol 160:753–758
163. Nelson AE, Howe CJ, Nguyen TV, Leung KC, Trout GJ, Seibel MJ, Baxter RC, Handelsman DJ, Kazlauskas R, Ho KK 2006 Influence of demographic factors and sport type on growth hormone-responsive markers in elite athletes. J Clin Endocrinol Metab 91:4424–4432
164. Maack T 1975 Renal handling of low molecular weight proteins. Am J Med 58:57–64
165. Jensen LT, Blaehr H, Andersen CB, Risteli J, Lorenzen I 1992 Metabolism of the aminoterminal propeptide of type III procollagen in cultures of human proximal tubular cells. Scand J Clin Lab Invest 52:1–8
166. Aron DC, Rosenzweig JL, Abboud HE 1989 Synthesis and binding of insulin-like growth factor I by human glomerular mesangial cells. J Clin Endocrinol Metab 68:585–591
167. Aron DC, Saadi HF, Nye CN, Douglas JG 1991 Secretion of insulin-like growth factor I and its binding proteins by collecting duct cells. Kidney Int 39:27–32
168. Tönshoff B, Blum WF, Vickers M, Kurilenko S, Mehls O, Ritz E 1995 Quantification of urinary insulin-like growth factors (IGFs) and IGF binding protein 3 in healthy volunteers before and after stimulation with recombinant human growth hormone. Eur J Endocrinol 132:433–437
169. Gill MS, Whatmore AJ, Tillman V, White A, Addison GM, Price DA, Clayton PE 1997 Urinary IGF and IGF binding protein-3 in children with disordered growth. The North West Paediatric Endocrine Group. Clin Endocrinol (Oxf) 46:483–492
170. De Palo EF, Gatti R, Lancerin F, Cappellin E, Soldà G, De Palo CB, Spinella P 2002 Urinary insulin-like growth factor I in athletes, before and after physical exercise, and in sedentary subjects. Clin Chim Acta 322:51–57
171. De Palo EF, Gatti R, Lancerin F, Cappellin E, De Palo CB, Spinella P 2005 Urinary insulin-like growth factor-I measurement in an actual sport competition, an additional approach in laboratory antidoping tests. Clin Chim Acta 351:73–78
172. Pichini S, Ventura R, Palmi I, di Carlo S, Bacosi A, Langohr K, Abellan R, Pascual JA, Pacifici R, Segura J, Zuccaro P 2010 Effect of physical fitness and endurance exercise on indirect biomarkers of growth hormone and insulin misuse: immunoassay-based measurement in urine samples. J Pharm Biomed Anal 53:1003–1010
173. Uemasu J, Fujihara M, Kawasaki H 1996 Effects of low dose of recombinant human growth hormone on renal excretion of insulin-like growth factor-I (IGF-I) in humans: an inverse relation between serum and urinary IGF-I level. Clin Nephrol 46:1–5
174. Gargosky SE, Hasegawa T, Tapanainen P, MacGillivray M, Hasegawa Y, Rosenfeld RG 1993 Urinary insulin-like growth factors (IGF) and IGF-binding proteins in normal subjects, growth hormone deficiency, and renal disease. J Clin Endocrinol Metab 76:1631–1637
175. Rohde H, Langer I, Krieg T, Timpl R 1983 Serum and urine analysis of the aminoterminal procollagen peptide type III by radioimmunoassay with antibody Fab fragments. Coll Relat Res 3:371–379
176. Ghoul BE, Squalli T, Servais A, Elie C, Meas-Yedid V, Trivint C, Vanmassenhove J, Grünfeld JP, Olivo-Marin JC, Thervet E, Noël LH, Prié D, Fakhouri F 2010 Urinary procollagen III aminoterminal propeptide (PIIINP): a fibrotest for the nephrologist. Clin J Am Soc Nephrol 5:205–210
177. Civitelli R, Armamento-Villareal R, Napoli N 2009 Bone turnover markers: understanding their value in clinical trials and clinical practice. Osteoporos Int 20:843–851
178. Costigan DC, Guyda HJ, Posner BI 1988 Free insulin-like growth factor I (IGF-I) and IGF-II in human saliva. J Clin Endocrinol Metab 66:1014–1018
179. Ryan J, Mantle T, Costigan DC 1992 A normal population study of human salivary insulin-like growth factor 1 (IGF

1) concentrations from birth through puberty. J Clin Endocrinol Metab 74:774–778
180. Halimi S, Tepavceviæ D, Suchanek D, Giljeviæ Z, Palvsiæ V, Korsiæ M 1994 Measurement of salivary insulin-like growth factor-I in acromegaly: comparison with serum insulin-like growth factor-I and growth hormone concentrations. Eur J Clin Chem Clin Biochem 32:705–707
181. Ryan J, Mantle T, McQuaid S, Costigan DC 1992 Salivary insulin-like growth factor-I originates from local synthesis. J Endocrinol 135:85–90
182. Antonelli G, Cappellin E, Gatti R, Chiappin S, Spinella P, De Palo EF 2007 Measurement of free IGF-I saliva levels: perspectives in the detection of GH/IGF axis in athletes. Clin Biochem 40:545–550
183. Antonelli G, Gatti R, Prearo M, De Palo EF 2009 Salivary free insulin-like growth factor-I levels: effects of an acute physical exercise in athletes. J Endocrinol Invest 32:1–5
184. Frystyk J, Freda P, Clemmons DR 2010 The current status of IGF-I assays—a 2009 update. Growth Horm IGF Res 20:8–18
185. Cowan DA, Bartlett C 2009 Laboratory issues in the implementation of the marker method. Growth Horm IGF Res 19:357–360
186. Holt RI, Erotokritou-Mulligan I, Ridley SA, McHugh CM, Bassett EE, Cowan DA, Bartlett C, Sönksen PH 2009 A determination of the pre-analytical storage conditions for insulin like growth factor-I and type III procollagen peptide. Growth Horm IGF Res 19:43–50
187. Kirsch S, Widart J, Louette J, Focant JF, De Pauw E 2007 Development of an absolute quantification method targeting growth hormone biomarkers using liquid chromatography coupled to isotope dilution mass spectrometry. J Chromatogr A 1153:300–306
188. Bredehöft M, Schänzer W, Thevis M 2008 Quantification of human insulin-like growth factor-1 and qualitative detection of its analogues in plasma using liquid chromatography/electrospray ionisation tandem mass spectrometry. Rapid Commun Mass Spectrom 22:477–485
189. Kay RG, Barton C, Velloso CP, Brown PR, Bartlett C, Blazevich AJ, Godfrey RJ, Goldspink G, Rees R, Ball GR, Cowan DA, Harridge SD, Roberts J, Teale P, Creaser CS 2009 High-throughput ultra-high-performance liquid chromatography/tandem mass spectrometry quantitation of insulin-like growth factor-I and leucine-rich α-2-glycoprotein in serum as biomarkers of recombinant human growth hormone administration. Rapid Commun Mass Spectrom 23:3173–3182
190. Barton C, Kay RG, Gentzer W, Vitzthum F, Pleasance S 2010 Development of high-throughput chemical extraction techniques and quantitative HPLC-MS/MS (SRM) assays for clinically relevant plasma proteins. J Proteome Res 9:333–340
191. Thomas A, Kohler M, Schänzer W, Delahaut P, Thevis M 2011 Determination of IGF-1 and IGF-2, their degradation products and synthetic analogues in urine by LC-MS/MS. Analyst 136:1003–1012
192. Abellan R, Ventura R, Pichini S, Pascual JA, Pacifici R, Di Carlo S, Bacosi A, Segura J, Zuccaro P 2005 Evaluation of immunoassays for the measurement of insulin-like growth factor-I and procollagen type III peptide, indirect biomarkers of recombinant human growth hormone misuse in sport. Clin Chem Lab Med 43:75–85
193. Holt RI, Bassett EE, Erotokritou-Mulligan I, McHugh C, Cowan D, Bartlett C, Sönksen PH 2009 Moving one step closer to catching the GH cheats: the GH-2004 experience. Growth Horm IGF Res 19:346–351
194. Bassett EE, Erotokritou-Mulligan I 2009 Statistical issues in implementing the marker method. Growth Horm IGF Res 19:361–365
195. Mitchell CJ, Nelson AE, Cowley MJ, Kaplan W, Stone G, Sutton SK, Lau A, Lee CM, Ho KK 2009 Detection of growth hormone doping by gene expression profiling of peripheral blood. J Clin Endocrinol Metab 94:4703–4709
196. Chung L, Clifford D, Buckley M, Baxter RC 2006 Novel biomarkers of human growth hormone action from serum proteomic profiling using protein chip mass spectrometry. J Clin Endocrinol Metab 91:671–677
197. Chung L, Nelson AE, Ho KK, Baxter RC 2009 Proteomic profiling of growth hormone-responsive proteins in human peripheral blood leukocytes. J Clin Endocrinol Metab 94:3038–3043
198. Chung L, Baxter RC 2009 Detection of growth hormone responsive proteins using SELDI-TOF mass spectrometry. Growth Horm IGF Res 19:383–387
199. Sackmann-Sala L, Ding J, Frohman LA, Kopchick JJ 2009 Activation of the GH/IGF-1 axis by CJC-1295, a long-acting GHRH analog, results in serum protein profile changes in normal adult subjects. Growth Horm IGF Res 19:471–477
200. Ding J, Okada S, Jørgensen JO, Kopchick JJ 2011 Novel serum protein biomarkers indicative of growth hormone doping in healthy human subjects. Proteomics 11:3565–3571
201. Such-Sanmartín G, Bosch J, Segura J, Gutiérrez-Gallego R 2011 Growth hormone abuse and biological passport: is mannan-binding lectin a complementary candidate? Clin J Sport Med 21:441–443
202. Frohman LA, Downs TR, Williams TC, Heimer EP, Pan YC, Felix AM 1986 Rapid enzymatic degradation of growth hormone-releasing hormone by plasma in vitro and in vivo to a biologically inactive product cleaved at the NH2 terminus. J Clin Invest 78:906–913
203. Corpas E, Harman SM, Piñeyro MA, Roberson R, Blackman MR 1993 Continuous subcutaneous infusions of growth hormone (GH) releasing hormone 1–44 for 14 days increase GH and insulin-like growth factor-I levels in old men. J Clin Endocrinol Metab 76:134–138
204. Veldhuis JD, Patrie JT, Frick K, Weltman JY, Weltman A 2004 Sustained growth hormone (GH) and insulin-like growth factor I responses to prolonged high-dose twice-daily GH-releasing hormone stimulation in middle-aged and older men. J Clin Endocrinol Metab 89:6325–6330
205. Stanley TL, Chen CY, Branch KL, Makimura H, Grinspoon SK 2011 Effects of a growth hormone-releasing hormone analog on endogenous GH pulsatility and insulin sensitivity in healthy men. J Clin Endocrinol Metab 96:150–158
206. Teichman SL, Neale A, Lawrence B, Gagnon C, Castaigne JP, Frohman LA 2006 Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by

CJC-1295, a long-acting analog of GH-releasing hormone, in healthy adults. J Clin Endocrinol Metab 91:799–805
207. Falutz J, Mamputu JC, Potvin D, Moyle G, Soulban G, Loughrey H, Marsolais C, Turner R, Grinspoon S 2010 Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. J Clin Endocrinol Metab 95:4291–4304
208. Ionescu M, Frohman LA 2006 Pulsatile secretion of growth hormone (GH) persists during continuous stimulation by CJC-1295, a long-acting GH-releasing hormone analog. J Clin Endocrinol Metab 91:4792–4797
209. Henninge J, Pepaj M, Hullstein I, Hemmersbach P 2010 Identification of CJC-1295, a growth-hormone-releasing peptide, in an unknown pharmaceutical preparation. Drug Test Anal 2:647–650
210. Maheshwari HG, Rahim A, Shafet SM, Baumann G 1999 Selective lack of growth hormone (GH) response to the GH-releasing peptide hexarelin in patients with GH-releasing hormone receptor deficiency. J Clin Endocrinol Metab 84:956–959
211. Pihoker C, Badger TM, Reynolds GA, Bowers CY 1997 Treatment effects of intranasal growth hormone releasing peptide-2 in children with short stature. J Endocrinol 155: 79–86
212. Mericq V, Cassorla F, Salazar T, Avila A, Iñiguez G, Bowers CY, Merriam GR 1998 Effects of eight months treatment with graded doses of a growth hormone (GH)-releasing peptide in GH-deficient children. J Clin Endocrinol Metab 83: 2355–2360
213. Zdravkovic M, Christiansen T, Eliot L, Agersoe H, Thomsen MS, Falch JF, Søgaard B, Ynddal L, Ilondo MM 2001 The pharmacokinetics, pharmacodynamics, safety and tolerability following 7 days daily oral treatment with NN703 in healthy male subjects. Growth Horm IGF Res 11:41–48
214. Nass R, Pezzoli SS, Oliveri MC, Patrie JT, Harrell Jr FE, Clasey JL, Heymsfield SB, Bach MA, Vance ML, Thorner MO 2008 Effects of an oral ghrelin mimetic on body composition and clinical outcomes in healthy older adults: a randomized trial. Ann Intern Med 149:601–611
215. White HK, Petrie CD, Landschulz W, MacLean D, Taylor A, Lyles K, Wei JY, Hoffman AR, Salvatori R, Ettinger MP, Morey MC, Blackman MR, Merriam GR 2009 Effects of an oral growth hormone secretagogue in older adults. J Clin Endocrinol Metab 94:1198–1206
216. Hersch EC, Merriam GR 2008 Growth hormone (GH)-releasing hormone and GH secretagogues in normal aging: Fountain of Youth or Pool of Tantalus? Clin Interv Aging 3:121–129
217. Kohler M, Thomas A, Geyer H, Petrou M, Schänzer W, Thevis M 2010 Confiscated black market products and nutritional supplements with non-approved ingredients analyzed in the Cologne Doping Control Laboratory 2009. Drug Test Anal 2:533–537
218. Thomas A, Kohler M, Mester J, Geyer H, Schänzer W, Petrou M, Thevis M 2010 Identification of the growth-hormone-releasing peptide-2 (GHRP-2) in a nutritional supplement. Drug Test Anal 2:144–148
219. Thevis M, Wilkens F, Geyer H, Schänzer W 2006 Determination of therapeutics with growth-hormone secretagogue activity in human urine for doping control purposes. Rapid Commun Mass Spectrom 20:3393–3402
220. Okano M, Sato M, Ikekita A, Kageyama S 2010 Determination of growth hormone secretagogue pralmorelin (GHRP-2) and its metabolite in human urine by liquid chromatography/electrospray ionization tandem mass spectrometry. Rapid Commun Mass Spectrom 24:2046–2056
221. Okano M, Nishitani Y, Sato M, Ikekita A, Kageyama S 2010 Influence of intravenous administration of growth hormone releasing peptide-2 (GHRP-2) on detection of growth hormone doping: growth hormone isoform profiles in Japanese male subjects. Drug Test Anal 2:548–556
222. Thomas A, Höppner S, Geyer H, Schänzer W, Petrou M, Kwiatkowska D, Pokrywka A, Thevis M 2011 Determination of growth hormone releasing peptides (GHRP) and their major metabolites in human urine for doping controls by means of liquid chromatography mass spectrometry. Anal Bioanal Chem 401:507–516
223. Corpas E, Blackman MR, Roberson R, Scholfield D, Harman SM 1993 Oral arginine-lysine does not increase growth hormone or insulin-like growth factor-I in old men. J Gerontol 48:M128–M133
224. Matheny Jr RW, Nindl BC, Adamo ML 2010 Minireview: mechano-growth factor: a putative product of IGF-I gene expression involved in tissue repair and regeneration. Endocrinology 151:865–875
225. Kohler M, Thomas A, Walpurgis K, Terlouw K, Schänzer W, Thevis M 2010 Detection of His-tagged Long-R(3)-IGF-I in a black market product. Growth Horm IGF Res 20:386–390
226. Chernausek SD, Backeljauw PF, Frane J, Kuntze J, Underwood LE 2007 Long-term treatment with recombinant insulin-like growth factor (IGF)-I in children with severe IGF-I deficiency due to growth hormone insensitivity. J Clin Endocrinol Metab 92:902–910
227. Guha N, Dashwood A, Thomas NJ, Skingle AJ, Sönksen PH, Holt RI 2009 IGF-I abuse in sport. Curr Drug Abuse Rev 2:263–272
228. Erotokritou-Mulligan I, Holt RI 2010 Insulin-like growth factor I and insulin and their abuse in sport. Endocrinol Metab Clin North Am 39:33–43, viii
229. Birznicce V, Nelson AE, Ho KK 2011 Growth hormone and physical performance. Trends Endocrinol Metab 22: 171–178
230. Woodhouse LJ, Mukherjee A, Shalet SM, Ezzat S 2006 The influence of growth hormone status on physical impairments, functional limitations, and health-related quality of life in adults. Endocr Rev 27:287–317
231. Widdowson WM, Gibney J 2008 The effect of growth hormone replacement on exercise capacity in patients with GH deficiency: a meta-analysis. J Clin Endocrinol Metab 93: 4413–4417
232. Widdowson WM, Gibney J 2010 The effect of growth hormone (GH) replacement on muscle strength in patients with GH-deficiency: a meta-analysis. Clin Endocrinol (Oxf) 72:787–792
233. Newman CB, Frisch KA, Rosenzweig B, Roubenoff R, Rey M, Kidder T, Kong Y, Pursnani A, Sedlis SP, Schwartzbard A, Kleinberg DL 2011 Moderate doses of

hGH (0.64 mg/d) improve lipids but not cardiovascular function in GH-deficient adults with normal baseline cardiac function. J Clin Endocrinol Metab 96:122–132
234. Liu H, Bravata DM, Olkin I, Friedlander A, Liu V, Roberts B, Bendavid E, Saynina O, Salpeter SR, Garber AM, Hoffman AR 2008 Systematic review: the effects of growth hormone on athletic performance. Ann Intern Med 148: 747–758
235. Deyssig R, Frisch H, Blum WF, Waldhör T 1993 Effect of growth hormone treatment on hormonal parameters, body composition and strength in athletes. Acta Endocrinol (Copenh) 128:313–318
236. Lange KH, Larsson B, Flyvbjerg A, Dall R, Bennekou M, Rasmussen MH, Ørskov H, Kjaer M 2002 Acute growth hormone administration causes exaggerated increases in plasma lactate and glycerol during moderate to high intensity bicycling in trained young men. J Clin Endocrinol Metab 87:4966–4975
237. Meinhardt U, Nelson AE, Hansen JL, Birzniece V, Clifford D, Leung KC, Graham K, Ho KK 2010 The effects of growth hormone on body composition and physical performance in recreational athletes: a randomized trial. Ann Intern Med 152:568–577
238. Saugy M, Robinson N, Saudan C, Baume N, Avois L, Mangin P 2006 Human growth hormone doping in sport. Br J Sports Med 40(Suppl 1):i35–i39
239. Holdaway IM, Rajasoorya C 1999 Epidemiology of acromegaly. Pituitary 2:29–41
240. Holdaway IM 2007 Excess mortality in acromegaly. Horm Res 68(Suppl 5):166–172
241. Melmed S 2006 Medical progress: acromegaly. N Engl J Med 355:2558–2573
242. Sharp RJ 2009 Land of the giants. Growth Horm IGF Res 19:291–293
243. Doessing S, Heinemeier KM, Holm L, Mackey AL, Schjerling P, Rennie M, Smith K, Reitelseder S, Kappelgaard AM, Rasmussen MH, Flyvbjerg A, Kjaer M 2010 Growth hormone stimulates the collagen synthesis in human tendon and skeletal muscle without affecting myofibrillar protein synthesis. J Physiol 588:341–351
244. Raschke M, Rasmussen MH, Govender S, Segal D, Suntum M, Christiansen JS 2007 Effects of growth hormone in patients with tibial fracture: a randomised, double-blind, placebo-controlled clinical trial. Eur J Endocrinol 156: 341–351
245. Wilmore DW, Moylan Jr JA, Bristow BF, Mason Jr AD, Pruitt Jr BA 1974 Anabolic effects of human growth hormone and high caloric feedings following thermal injury. Surg Gynecol Obstet 138:875–884
246. Ramirez RJ, Wolf SE, Herndon DN 1998 Is there a role for growth hormone in the clinical management of burn injuries? Growth Horm IGF Res 8(Suppl B):99–105
247. Salomon F, Cuneo RC, Hesp R, Sönksen PH 1989 The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med 321:1797–1803
248. Jing J, Yang S, Zhou X, Zhang L, Xu Y, Xie M, Wu M Detection of doping with rhGH-Detection time with WADA approved kits. Program of the 10th Annual USADA Symposium on Anti-Doping Science, London, UK, 2011 p 8–10

ONE HUNDRED TWELFTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM
2157 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6143

MAJORITY (202) 225-5074
FACSIMILE (202) 225-3974
MINORITY (202) 225-5051
http://oversight.house.gov

Opening Statement
Rep. Elijah E. Cummings, Ranking Member

Hearing on "HGH Testing in the NFL: Is the Science Ready?"

December 12, 2012

Thank you, Mr. Chairman. And thanks to all of our witnesses for being here.

Today's hearing is not only about the NFL, and it is not only about Human Growth Hormone (HGH). This hearing is also about millions of young people throughout this country in high school and college who look up to professional athletes, and the lengths to which these young people go to emulate their role models.

Let me tell you about some of the young people in my district in Baltimore, many of whom come from very challenging backgrounds, and from very difficult home situations. They have dreams about making it as lawyers, engineers, teachers, maybe even as a Congressman like me. I have seen their smiling faces at graduation ceremonies. They are dedicated, they are smart, and they have amazing potential.

Some of these young people dream about becoming ball players, and succeeding beyond their wildest expectations. When I meet these young people, I share the same advice my parents gave me—that there are no short cuts in life. If they want to become a successful entrepreneur, a best-selling author, or a Pro-Bowl linebacker for the Baltimore Ravens, they have to put in the work to reach their goals.

But when they see their role models in pro sports using illegal drugs to try to get an edge, and when they see the professional leagues looking the other way, refusing to test, and going easy on abusers, they start thinking they need to use these substances just to compete. They start thinking they are expected to use these substances. This is what we need to change.

HGH is a dangerous drug with both short-term and long-term risks. Let me read just a few of the negative health effects of HGH: "hypertension … diabetes … arthritis … bone spurs … spinal stenosis … disfigurement … and cardiac dysfunction." These come directly from a scientific journal article published in April of this year. Mr. Chairman, I ask that this study be placed into the hearing record.

There is no serious dispute in the scientific community that the test to detect HGH abuse is effective. This test—which has been in place for the past decade—is actually designed to be conservative in order to avoid false positives. As one of our witnesses will testify today, you are more likely to get struck by lightning than to get a false positive in an HGH test.

There is also no dispute that on August 4, 2011, more than a year ago, the NFL Players Association entered into a contract to begin testing NFL players for HGH "by the first week of the 2011 regular season." As we all know, that season passed without any HGH testing. And now, the 2012 season will also pass without HGH testing.

Despite their commitment, lawyers for the Players Association now say they do not trust the HGH test. Although it has been used for years on Olympic athletes, Major League Baseball players, and a host of other athletes, they argue that NFL players are somehow different. They claim their bodies are not the same as wrestlers, runners, weightlifters, and thousands of other athletes who are tested regularly. They say they need much more time to study this issue before doing what they agreed to do.

To me, it seems obvious that the Players Association is simply running out the clock. Although they agreed to HGH testing, they are now trying to back out of the contract. Well, today we will have the opportunity to hear directly from medical experts, and we will examine the claims of the Players Association under the bright light of science.

Let me address one point that has been raised, which is why Congress is getting involved in this issue. In my opinion, this dispute should be resolved by the NFL and the Players Association. They have a contract, and they should honor it. But when they refuse to do so, that sends exactly the wrong message to the kids we have sworn to protect. And that is when it becomes our business.

Finally, on a personal level, I have worked on this issue for most of my life in public service. I helped with the formation of a group in Baltimore in 2007 called "Powered by ME!" that has reached more than 30,000 young athletes, coaches, and parents, warning them about the dangers of these substances. The group's director, Mike Gimbel, has spearheaded efforts to prevent young athletes from being brainwashed by the mantra of "winning at all costs." I am very thankful he is testifying here today.

Mr. Chairman, thank you again for calling today's hearing, and I look forward to the testimony of all of our witnesses.

Contact: Ashley Etienne, Communications Director, (202) 226-5181.

chaffetz 12/12/12

BASIC
RESEARCH

5742 West Harold Gatty Drive
Salt Lake City, UT 84116
phone (801) 517-7000
fax (801) 517-7001
website www.BasicResearch.org

December 5, 2012

Congressman Jason Chaffetz
1032 Longworth HOB
Washington, DC 20515

Re: The House Oversight and Government Reform Committee Hearing, December 12, 2012, at 10:00 a.m., on "HGH Testing in the NFL: Is the Science Ready?"

Dear Congressman Jason Chaffetz:

It has come to my attention that the House Oversight and Government Reform Committee will be convening on December 12, 2012, at 10:00 a.m. to examine science necessary for NFL hGH testing in the hearing, "HGH Testing in the NFL: Is the Science Ready?"

We are concerned about two issues. First, we believe the Committee is blurring the distinction between natural increases in endogenous growth hormone (hGH) levels and the doping of athletes using synthetic injections of recombinant human growth hormone (rhGH). Second, we wish to ensure that the testing methods designed to detect illegal doping with injectable, synthetic recombinant human growth hormone do not produce a false positive for an endogenous increase of natural growth hormone secreted by the pituitary.

These concerns arise because at Basic Research, LLC, we have secured the rights to distribute an innovative new natural health product for pituitary support, which offers results that are distinctly different from those secured by the synthetic recombinant human growth hormone used in doping.

We have taken earnest initiatives to collaborate with multiple academic and research institutions for the ongoing research of natural products for human health in the form of unrestricted grants and funding. It is important to us that research in the dietary supplement category have scientific rigor and be met with integrity by the scientific community.

A recent collaboration with Pennington Biomedical Research Center at Louisiana State University has led to an innovative natural product called "SeroVital." This specialized amino acid blend was shown to significantly increase natural, endogenous hGH to more youthful, healthy levels. Indeed, research shows that adequate, natural hGH levels are a health benefit to the general population. An analogy would be the benefit of adequate iodine levels for healthy thyroid function.

BASIC
RESEARCH

5742 West Harold Gatty Drive
Salt Lake City, UT 84116
phone (801) 517-7000
fax (801) 517-7001
website www.BasicResearch.org

The randomized, cross-over, double-blind clinical trial recruited men and women of a wide age range. In the study, blood samples were drawn after an overnight fast for a period of 120 minutes after consumption of either the proprietary amino acid SeroVital blend or placebo. At the end of the study, the samples were tested for serum hGH levels, and the results showed that SeroVital led to a 682% mean increase in serum hGH levels at 120 minutes (p=0.01 vs. placebo).

This natural support of pituitary function is in contrast to the artificially produced recombinant human growth hormone (rhGH), as discussed above, used for illegal doping via injection by athletes. We agree strongly that doping with injections of rhGH by athletes is dangerous and leads to an unnatural physical advantage in competition. Thus, to properly relay this information to the public, we urge that further designations to the banned recombinant human growth hormone (rhGH) injections by government and athletic agencies be distinguished clearly from natural, endogenous hGH, of which adequate levels play an important role in human health.

Further, we would like to stress the necessity that any testing methods used for the detection of illegal doping with rhGH injections not elicit a false positive resultant from natural increases in endogenous hGH levels. It is our understanding that all methodologies currently under consideration already account for this difference, but we feel it's important to ensure that this issue is addressed by the Committee.

We would greatly appreciate it if you would address the following considerations to the expert panel that will be appearing before the Committee:

> Will you be distinguishing between banned recombinant human growth hormone (rhGH) injections and the generalized term hGH?
>
> We are of the understanding that the current testing methods which will be put into place will only cause a positive test result when banned, synthetic rhGH from injections is detected, NOT when endogenous, natural growth hormone levels have been increased through the use of a pituitary-nourishing dietary supplement. How will you ensure that any future testing methods that may be used will continue to detect only banned, synthetic rhGH injections rather than endogenous hGH levels that have been raised naturally?

Thank you so much for taking the time to raise these concerns with the Committee.

Sincerely,

Dennis W. Gay, CEO

UNITED STATES
OLYMPIC COMMITTEE
1 Olympic Plaza
Colorado Springs, CO
80909

December 11, 2012

The Honorable Darrell E. Issa
Chairman
Committee on Oversight & Government Reform
U.S. House of Representatives
Washington, DC 20515

The Honorable Elijah E. Cummings
Ranking Member
Committee on Oversight & Government Reform
U.S. House of Representatives
Washington, DC 20515

Dear Chairman Issa and Ranking Member Cummings:

I want to thank you and the Committee for scheduling a hearing on December 12, 2012 to examine the science behind the testing used to detect and deter the illicit use of human growth hormone (HGH). We hope the hearing will provide an important forum to gather facts and testimony about how best to keep young athletes away from this potentially dangerous performance enhancing substance.

The U.S. Olympic Committee is an organization chartered by the U.S. Congress through the Ted Stevens Olympic and Amateur Sports Act and, and as such, the USOC is responsible for the oversight of 46 sport national governing bodies that comprise Olympic and Paralympic sport. We help train, enter, fund, and transport the U.S. teams to the Olympic, Paralympic, Pan American and Parapan American Games, while serving as a steward of the Olympic Movement throughout the country.

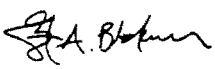
The USOC was involved in reforms over a decade ago that created the US Anti-doping Agency (USADA). While USADA is the entity responsible for undertaking anti-doping testing and adjudication in the United States, that testing is undertaken following protocols and policies developed and approved by both the USOC and USADA. All doping protocols and policies must conform to the World Anti-Doping Code (Code) and meet the global standards of the World Anti-Doping Agency (WADA). WADA periodically updates its Code and standards and only incorporates new forms of testing that have been rigorously evaluated using globally accepted science. WADA accredited laboratories presently use testing to identify the improper usage of hGH, which is a prohibited substance on the WADA Prohibited List. Given the stringent review process, the USOC has the utmost confidence in the WADA approved testing methods to detect hGH. Our athletes are subject to the Code, including the testing and enforcement for hGH, and the USOC firmly believes that the current global anti-doping establishment and its enforcement measures are critical to ensuring clean and healthy sports competition in the United States.

Your Committee's efforts help bring attention to the damaging and long-term health hazards that performance enhancing drugs, such as hGH, can have on athletes, particularly our youth. There are numerous health-related risks associated with the use of hGH, including the potential for thyroid problems, diabetes, possible harm to reproductive health, muscle and joint disorders, and even cancer. There are also other safety issues that can arise when hGH is used or obtained in an illegal manner,

including the risk of obtaining contaminated or adulterated products and other risks associated with needle injections.

Human growth hormone testing sets the right example for all athletes, professional and amateur. Millions of sports fans and followers – especially our youth – understand that there are no shortcuts to greatness and that doping is a very risky and dangerous detour.

Sincerely,



Scott A. Blackmun
Chief Executive Officer

Statement of Congressman Gerald E. Connolly (VA-11)
Committee on Oversight and Government Reform
HGH Testing in the NFL: Is the Science Ready?
December 12, 2012

Chairman Issa and Ranking Member Cummings, thank you for holding today's hearing to examine the scientific validity of testing for the use of synthetic Human Growth Hormone (HGH) in the National Football League (NFL).

Since synthetic HGH was developed in 1985, the Food and Drug Administration (FDA) and Congress have recognized the dangers associated with abuse of this drug, only approving its use by prescription for specific medical purposes, such as adolescents suffering from kidney problems, or individuals with a natural growth hormone deficiency. In a decisive step to protect public health, Congress made it clear that illicit use of synthetic HGH, which includes efforts to enhance athletic performance and slow or reverse aging, is illegal.

Although the scientific literature is inconclusive with regard to whether synthetic HGH actually boosts athletic performance, the evidence is clear that HGH abuse is a threat to public health. Adults who abuse synthetic HGH may experience high cholesterol, edema, joint and muscle pain, carpal tunnel syndrome, and an increased risk of developing diabetes.

Adolescents and teenagers who illegally use synthetic HGH may develop dangerously high levels of HGH, resulting in musculoskeletal, cardiovascular, and endocrine disorders; elevated leukemia risks; and bone disfigurement and stunted growth. Worst of all, it is precisely this cohort that is most vulnerable to experiencing negative health impacts that may be the most tempted to emulate professional athletes they admire, and abuse synthetic HGH as a performance enhancing drug (PED).

In 2004, for the first time, Olympic athletes were subjected to HGH testing, in the form of an isoform test that measures the ratio of growth hormone in the body. However, as many observers have noted, this isoform test has significant limitations, since it must be administered within a day or two of injecting synthetic HGH, prior to the body reverting to a normal isoform ratio. Lending credence to this view that the isoform test may be easily gamed is the fact that no Olympians tested positive for HGH in 2004, and only eight athletes worldwide have tested positive for HGH abuse using the isoform test.

However, technology appears to be catching up, and the biomarker test, a new type of test that does not measure isoforms of growth hormone but rather looks for unnatural increases in two "biomarkers" that occur after injection, may be administered over a longer period of time, specifically a week as opposed to a few days. Following twelve years of research to ensure the biomarker test was valid, the World Anti-Doping Agency (WADA) implemented this more advanced form of testing in the 2012 Olympics.

Unfortunately, our Nation's leading professional sports leagues appear to be lagging behind the Olympics with respect to HGH testing. Major League Baseball (MLB) is the only major American professional sports league that currently tests for HGH use, while the National Hockey League has no agreement in place for HGH testing at all. The National Basketball Association (NBA) and NFL have

(OVER)

each included HGH provisions in their respective collective bargaining agreements (CBA) with the NBA and NFL players unions, yet neither has reached an agreement on the implementation of the HGH testing process.

In the case of the NFL, the league owners and the NFL Players Association (NFLPA) signed a CBA on August 4, 2011, that committed both parties to "discuss and develop the specific arrangements relating to the safe and secure collection of samples, transportation and testing of samples, the scope of review of the medical science, and the arbitrator review policy, with the goal of beginning testing by the first week of the 2011 regular season." Yet, despite this commitment, as the Committee meets today on December 12, 2012, there is still no HGH testing in the NFL.

NFLPA claims that WADA's HGH testing protocols are not applicable to athletes with the physical profiles of NFL players is not only wholly without scientific merit, but also raises questions as to whether the Players Association was even negotiating in good faith over the 2011 CBA. Surely the NFLPA was aware of the existing HGH testing protocols by August 4, 2011. It is puzzling why they would sign a document committing to develop HGH testing protocols over a time period of "several weeks" if they did not even accept the science behind existing tests. Further, if there were truly a great risk of false positives with either the isoform or biomarker HGH tests, a cynic might note that it would be very odd for the NFL – whose owners have absolutely no economic incentive to unnecessarily keep its star players off the field – to go forth with an invalid test that would result in a large number of false positives.

Given the supposed "uncertainty" over the WADA tests when applied to athletes of the NFL physical profile, it is very peculiar that representatives of prominent NBA athletes who were members of the 2012 U.S. Olympic Basketball team, such as Tyson Chandler, Anthony Davis, and Kevin Love, who each are listed at 7-1, 6-10, and 6-10, and 240 lbs, 220 lbs, and 260 lbs, would permit their clients to be subject to the biomarker HGH test administered by WADA at the 2012 Olympics, if it is indeed not applicable to athletes of a certain height and weight. The NFLPA's assertion that WADA must conduct a population study solely consisting of NFL players to establish HGH cutoff ratios appears to be a case of foot-dragging, particularly in light of the willingness of NBA and MLB players to submit to HGH testing, and the scientific community's judgment that such a test would be neither necessary nor scientifically valid due to the small sample size.

While I recognize that observers may question whether holding a hearing on HGH testing in the NFL is a valuable use of this Committee's time – in fact, I would include myself in that group of skeptics – having reviewed the witnesses statements and hearing materials, I have concluded that it is indeed unfortunate the Committee had to hold this hearing, but the blame lies squarely with the NFLPA.

I want to thank the witnesses for participating in today's hearing, and would urge the NFLPA to finally fulfill the commitment it made in signing the August 2011 CBA to implement rigorous HGH testing. If football is to become our new national pastime, a title that some commentators have suggested the NFL is on track to achieve, it would do well do emulate our current national pastime and take the necessary steps to uphold the integrity of the game.

-END-

TAYLOR HOOTON FOUNDATION

December 17, 2012

The Honorable Darrell E. Issa
Chairman
Committee on Oversight & Gov't Reform
2347 Rayburn H.O.B.
Washington, D.C. 20515

The Honorable Elijah E. Cummings
Ranking Member
Committee on Oversight & Gov't Reform
2235 Rayburn H.O.B.
Washington, D.C. 20515

Dear Chairman Issa and Ranking Member Cummings:

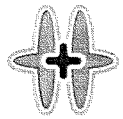
I commend the House Committee on Oversight and Government Reform for holding a hearing on December 12th regarding human growth hormone (hGH) testing in the National Football League. The indefinite delay of hGH testing in the nation's most popular professional sports league sends a dangerous and perverse message to millions of young people that the use of hGH and other performance-enhancing drugs is acceptable, if not condoned.

The Taylor Hooton Foundation is the leading non-profit organization that raises awareness among youth and adults about the real dangers of anabolic steroids, hGH, unregulated dietary supplements, and other appearance and performance-enhancing drugs (APEDs). Our vision to eliminate youth APEDs use has led to the creation of our "Hoot's Chalk Talk" education programs, which we have delivered to about a half million kids and their adult influencers across the US, Canada, and beyond. My family and I established the foundation in 2004 in memory of my son, Taylor E. Hooton, who took his own life at 17-years old as a result of abusing anabolic steroids.

When I testified before Congress in 2005 about the influence of professional athletes on our nation's children, this is part of what I said:

> ***"I believe the poor example being set by professional athletes is a major catalyst fueling the high usage of steroids amongst our kids. Our kids look up to these guys. They want to do the things the pros do to be successful."***

That statement remains as true today as it was then. Young people idolize and imitate the pros. Their actions send loud and clear messages to our youth, messages that can overpower those of parents and other adults who are striving to keep kids away from drugs.



Protecting young people from the serious health risks of hGH use -- such as diabetes, cardiomyopathy, renal failure and cancer -- is an important public health and public policy matter. I hope that the Committee's inquiry will help lead to the implementation of hGH testing in the NFL, sooner rather than later. Doing so will send the right message to young people about keeping away from performance enhancing drugs – and will help us all to avoid what could be a deadly mistake.

Warm regards,

Donald M. Hooton
President

Preserving the integrity of competition. Inspiring true sport. Protecting the rights of athletes.

Via Electronic Mail & U.S. Mail

October 12, 2011

Roger Goodell, Commissioner
NATIONAL FOOTBALL LEAGUE
345 Park Avenue
New York, New York 10154

DeMaurice Smith, Executive Director
NFL PLAYERS ASSOCIATION
1133 20th St, NW
Washington DC 20036

Re: *Human Growth Hormone*

Dear Commissioner Goodell and Executive Director Smith:

I hope this letter finds you well.

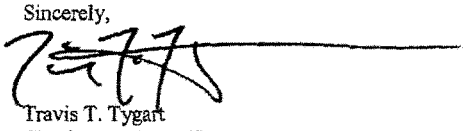
As you may be aware, the United States Anti-Doping Agency ("USADA") recently held its 10th Annual USADA Symposium on Anti-Doping Science in conjunction with U.K. Anti-Doping. This multi-day scientific symposium on "Detection of Growth Factors" brought together top scientific, laboratory, and medical experts from around the world, to discuss the implementation in sport of the isoform test for the detection of human growth hormone and to discuss the continuing abuse of human growth hormone and the severe health risks borne by athletes who abuse this powerful drug.

During the Symposium, it was reported in the international press that the implementation of the isoform test for human growth hormone in the National Football League has been delayed. The attendees at the USADA Symposium were uniformly troubled by the reports and the continuing delay in implementing the isoform test for human growth hormone. This delay is troubling because the scientific validity, reliability and accuracy of the isoform test is universally accepted and attendees at the Symposium recognize that the test is currently the best way to detect and deter the use of this dangerous, performance enhancing drug.

In an effort to assist you to move forward on behalf of clean athletes and for the integrity of football, I have enclosed two separate letters, one from those in attendance at the Symposium and another from an additional group of experts who resoundingly support the scientific validity of the isoform test for human growth hormone and endorse its use in all sport including by the National Football League. I trust that you will receive these letters as confirmation of the overwhelming support for this test by the experts in the scientific community.

Please do not hesitate to contact me if I can do anything to assist you in the effort to protect the rights of clean athletes and the integrity of sport.

Sincerely,



Travis T. Tygart
Chief Executive Officer

Enclosures

Preserving the integrity of competition. Inspiring true sport. Protecting the rights of athletes.

VIA HAND DELIVERY & REGULAR U.S. MAIL

October 3, 2011

Roger Goodell, Commissioner
NATIONAL FOOTBALL LEAGUE
345 Park Avenue
New York, New York 10154

DeMaurice Smith, Executive Director
NFL PLAYERS ASSOCIATION
1133 20th St, NW
Washington DC 20036

Re: ***Human Growth Hormone***

Dear Commissioner Goodell and Executive Director Smith:

We write as scientists, physicians, toxicologists, administrators and other experts who have observed with increasing concern the public conversation regarding human growth hormone (hGH) testing in the National Football League. Inaccurate and misleading information about the science of hGH testing has permeated the public debate.

We are all familiar with the current hGH testing method, known as the isoforms test, and have examined the relevant data in our professional work. Simply stated, the current hGH test is safe, scientifically reliable and appropriate for use in professional sports leagues. There is no scientific question about its validity.

Any suggestion in the press that its accuracy is a matter of debate is incorrect. Such comments do a disservice to the public understanding of this issue and may have negative health consequences for those who are misled and choose to experiment with hGH as a result.

We are also disturbed by the recent suggestion that hGH has been shown to "heal injury or speed recovery" and is appropriately used for those purposes. Such statements are incorrect and dangerous. Its use in the context of treating acute muscle, bone, tendon or ligament injuries to normal and otherwise healthy male athletes is against the law and ill advised.

USADA

Preserving the integrity of competition. Inspiring true sport. Protecting the rights of athletes.

Even more, the scientific literature does not support the effectiveness of hGH as an ergogenic aid in normal males. The literature does, however, demonstrate that hGH can cause serious medical problems including diabetes, abnormal bone growth, increased risk of cancer, and hypertension. There is also the risk associated with introducing contamination or contaminated products and serious risks associated with botched injections.

Concluding, we appreciate your desire to be well-educated on the matter of hGH testing prior to incorporating it into the NFL anti-doping program. We hope that this letter will serve to reassure you that from a scientific standpoint, the NFL and its players should be fully confident that the hGH test currently in use is accurate and reliable, and that it will effectively deter players from using hGH to the benefit of those who compete with integrity.

We appreciate your attention to this letter.

Name	Title	Organization
Brendan Buckley MD	Chairman	Anti Doping Committee Irish Sports Council
Olivier de Hon	Manager Scientific Affairs	Anti-Doping Authority the Netherlands
[illegible]	Director	Doping Control Center, KCIST
[illegible] MD	Chair Emeritus	Canadian Centre for Ethics in Sport
Wendy Hamblin PhD	Chair DCRC	USA Test for Drug-free Sport
JORDI SEGURA	Chair DCRB FINA	IMIM Hospital del Mar
MITCHELL SAFF	PROFESSOR	WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

USADA

Preserving the integrity of competition. Inspiring true sport. Protecting the rights of athletes.

Even more, the scientific literature does not support the effectiveness of hGH as an ergogenic aid in normal males. The literature does, however, demonstrate that hGH can cause serious medical problems including diabetes, abnormal bone growth, increased risk of cancer, and hypertension. There is also the risk associated with introducing contamination or contaminated products and serious risks associated with botched injections.

Concluding, we appreciate your desire to be well-educated on the matter of hGH testing prior to incorporating it into the NFL anti-doping program. We hope that this letter will serve to reassure you that from a scientific standpoint, the NFL and its players should be fully confident that the hGH test currently in use is accurate and reliable, and that it will effectively deter players from using hGH to the benefit of those who compete with integrity.

We appreciate your attention to this letter.

Name	Title	Organization
DANIEL EICHNER	LAB DIRECTOR	SMRTL
MATTHEW FEDORUK PHD.	MANAGER ANTI-DOPING OPERATIONS	CANADIAN CENTRE FOR ETHICS IN SPORT
FRANCISCO ROCHA DE ABREU NETO	DIRECTOR	RIO DE JANEIRO ANTI-DOPING CONTROL LAB
SHIKA JAIN	Lab Director	National Dope Testing Lab., India
Larry J. Bowers	Chief Science Officer	USADA
CHRISTIAN BARNETT	Certifying Analyst	Drug Control Centre King's College Lond

USADA

Preserving the integrity of competition. Inspiring true sport. Protecting the rights of athletes.

Even more, the scientific literature does not support the effectiveness of hGH as an ergogenic aid in normal males. The literature does, however, demonstrate that hGH can cause serious medical problems including diabetes, abnormal bone growth, increased risk of cancer, and hypertension. There is also the risk associated with introducing contamination or contaminated products and serious risks associated with botched injections.

Concluding, we appreciate your desire to be well-educated on the matter of hGH testing prior to incorporating it into the NFL anti-doping program. We hope that this letter will serve to reassure you that from a scientific standpoint, the NFL and its players should be fully confident that the hGH test currently in use is accurate and reliable, and that it will effectively deter players from using hGH to the benefit of those who compete with integrity.

We appreciate your attention to this letter.

Name	Title	Organization
RICHARD HOLT	PROFESSOR IN DIABETES + ENDOCRINOLOGY	UNIVERSITY OF SOUTHAMPTON, UK
MADS RAVNE	DIRECTOR - TESTING DIVISION	ANTI-DOPING NORWAY
COSTAS GEORGAKOPOULOS	ATHENS DOPING CONTROL LABORATORY	
MARIO ZORZOLI	DOCTOR AND SCIENTIFIC ADVISER	INTERNATIONAL CYCLING UNION
FRANCESCA ROSSI	PhD, director of UCI ANTI-DOPING SERVICES	INTERNATIONAL CYCLING UNION (UCI)
Stephane BERTON 02/10/12	MD, PhD MEDICAL AND ANTIDOPING COMMISSION	INTERNATIONAL ASSOCIATION OF ATHLETIC FEDERATION (IAAF)
Talgat Talbayev	athletes' Anti-Doping Laboratory	

USADA

Preserving the integrity of competition. Inspiring true sport. Protecting the rights of athletes.

Even more, the scientific literature does not support the effectiveness of hGH as an ergogenic aid in normal males. The literature does, however, demonstrate that hGH can cause serious medical problems including diabetes, abnormal bone growth, increased risk of cancer, and hypertension. There is also the risk associated with introducing contamination or contaminated products and serious risks associated with botched injections.

Concluding, we appreciate your desire to be well-educated on the matter of hGH testing prior to incorporating it into the NFL anti-doping program. We hope that this letter will serve to reassure you that from a scientific standpoint, the NFL and its players should be fully confident that the hGH test currently in use is accurate and reliable, and that it will effectively deter players from using hGH to the benefit of those who compete with integrity.

We appreciate your attention to this letter.

C. Ayotte	PROF-T DIRECTOR	Doping Control Lab Montréal
Name	*Title*	*Organization*
Name	*Title*	*Organization*
Name	*Title*	*Organization*
Name	*Title*	*Organization*
Name	*Title*	*Organization*
Name	*Title*	*Organization*

USADA

Preserving the integrity of competition. Inspiring true sport. Protecting the rights of athletes.

Even more, the scientific literature does not support the effectiveness of hGH as an ergogenic aid in normal males. The literature does, however, demonstrate that hGH can cause serious medical problems including diabetes, abnormal bone growth, increased risk of cancer, and hypertension. There is also the risk associated with introducing contamination or contaminated products and serious risks associated with botched injections.

Concluding, we appreciate your desire to be well-educated on the matter of hGH testing prior to incorporating it into the NFL anti-doping program. We hope that this letter will serve to reassure you that from a scientific standpoint, the NFL and its players should be fully confident that the hGH test currently in use is accurate and reliable, and that it will effectively deter players from using hGH to the benefit of those who compete with integrity.

We appreciate your attention to this letter.

Name	*Title*	*Organization*
Shinji Kageyama	Director of Anti-Doping Lab	Mitsubishi Chemical Medience Corporation

Seibersdorf, October 5th, 2011

For the attention of:

Prof. Dr. Larry D. Bowers
Chief Scientific Officer
U.S. Anti-Doping Agency

Dear Prof. Bowers,

it came to our attention during the 10th Annual USADA Symposium on Anti-Doping Science on the topic of "Detection of Growth Factors" that there is intense discussion in the United States about growth hormone testing in the National Football Leagues.

We are a world-wide acting organisation of Anti-Doping Scientists, consisting of Toxicologists, Pharmacologists, Chemists, Biochemists and experts from related disciplines. We have years of experience with the isoform test to detect GH abuse, currently applied in doping control by the WADA accredited laboratories. Several thousands of samples have been analysed in the period of time after test implementation.

We want to take the opportunity to confirm that the test itself is scientifically accepted and has undergone extensive validation. Several publications in peer-reviewed journals confirm the acceptance of this test within the scientific community. The test is able to reliably detect GH misuse within its window of opportunity.

In view of the limited medical use of growth hormone and associated negative health consequences by its misuse by healthy athletes, especially due to the often untraceable quality of the GH preparations used, testing in general and the isoform test in particular serves as a strong tool to reduce or even diminish GH misuse in sports and thereby protecting the health of all athletes.

This opinion is shared by the Directors of WADA accredited laboratories listed by name in the annex of this letter.

Yours faithfully,

Dr. Günter Gmeiner
President WAADS

List of Directors of WADA accredited Laboratories supporting the Statement about the reliability of the GH isoform test

Name, Title	Laboratory Location
Talgat Talbayev, Prof. Dr.	Almaty, Kazakhstan
Manolis Lyris, Dr.	Athens, Greece
Jordi Segura, Prof. Dr.	Barcelona, Spain
XU Youxuan, Dr.	Beijing, China
Gloria Gallo, Dr.	Bogota, Colombia
Ileana VÂJIALA, Dr.	Bucharest, Romania
Wilhelm Schänzer, Prof. Dr.	Cologne, Germany
Peter van Eenoo, Prof. Dr.	Ghent, Belgium
Tiia Kuuranne, Dr.	Helsinki, Finland
Detlef Thieme, Dr.	Kreischa, Germany
Martial Saugy, Dr.	Lausanne, Switzerland
Michael Sekera	Lisbon, Portugal
David A. Cowan, Prof. Dr.	London, Great Britain
Anthony Butch, Prof. Dr.	Los Angeles, USA
Jesus A. Muñoz-Guerra Revilla, Dr.	Madrid, Spain
Christiane Ayotte, Prof. Dr.	Montreal, Canada
Grigory Rodchenkov, Dr.	Moscow, Russia
Shila Jain, Dr.	New Delhi, India
Peter Hemmersbach, Prof. Dr.	Olso, Norway
Francoise Lasne, PhD	Paris, France
Francisco Radler, Prof. Dr.	Rio de Janeiro, Brazil
Francesco Botré, Prof. Dr.	Rome, Italy
Kim M. Monti, CEO	Salt Lake City, USA
Günter Gmeiner, Dr.	Seibersdorf, Austria
Oh-Seung Kwon, PhD, Prof.	Seoul, Korea
Catrin Goebel, Dr.	Sidney, Australia
Shinji Kageyama, Dr.	Tokyo, Japan
Loueslati Mohamed Hédi, Dr.	Tunis, Tunisia
Dorota Kwiatkowska, Dr.	Warsaw, Poland

WORLD
ANTI-DOPING
AGENCY
play true

December 12, 2011

Via email: c/o Christopher_Bowlin@mccain.senate.gov

Senator John McCain
241 Russell Senate Office Building
Washington, DC 20510-0303

Dear Senator McCain,

Thank you for your letter of December 5, 2011 and your interest in promoting clean competition and in addressing an important public health issue. We too are concerned that the tactics of the NFL Players Association will leave the fans and public with the erroneous impression that the drug human growth hormone ("hGH") is not harmful and that players in the National Football League are competing clean. In reviewing this controversy, you might wish to take particular note of the fact that the NFL Players Association's ("NFLPA") questions and complaints are coming from lawyers, not scientists. The scientific community, both inside and outside of WADA, does not question the reliability of the hGH test. WADA cannot tell you what is really motivating the NFLPA's reluctance to accept the hGH test, but it is certainly not science. Our interaction with the NFLPA has not involved dialog with informed scientists, but rather lawyers.

Human Growth Hormone is a potentially dangerous performance-enhancing drug. WADA supports the NFL's efforts to test for hGH. Under our guidance the International Olympic Committee first conducted testing for hGH at the Olympic Games in 2004. By 2008/2009, many of the major national anti-doping agencies, including the United States Anti-Doping Agency and several International Federations, began widespread testing for hGH. Minor league baseball has conducted almost 600 hGH tests since 2010. The positivity criteria established for the hGH test are intentionally very conservative. Out of the thousands of hGH tests performed worldwide over the last seven years, there have been nine positive cases. One of these athletes had a doctor's therapeutic use exemption for the use of hGH; five athletes admitted that they had indeed doped with hGH; and three cases (two skiers and a cyclist) are at some stage of results management. In our experience with a wide variety of anti-doping cases, the fact that more than half the athletes who have tested positive for hGH have subsequently admitted using the drug is quite unique and remarkable. (We assume that the NFLPA's critique of "no fair appeals process" is not directed at WADA, since the appeal right to the Court of Arbitration for Sport is clearly set out in the World Anti-Doping Code, which has been recognized by the United States government in ratifying The International Convention Against Doping in Sport under the auspices of UNESCO).

Stock Exchange Tower, 800 Place Victoria (Suite 1700), PO Box 120 – Montreal (Québec) H4Z 1B7 Canada
Tel: +1 514 904 9232 • Fax: +1 514 904 8650
www.wada-ama.org

The NFLPA gives no "credence" to either WADA's independence or its scientific findings, ignoring the fact that WADA is given both roles under the World Anti-Doping Code and that a representative of the United States Office of Drug Control Policy sits on our Foundation Board. Moreover, the NFLPA's claim that the hGH test has support only in WADA and WADA-accredited laboratories is simply misinformed. The test was developed by two internationally-regarded growth hormone researchers, Dr. Christian Strasburger (Campus Mitte Charité, Berlin) and Dr. Martin Bidlingmaier (Klinikum der Universitaet – Innenstadt, Munich). Neither had any association with WADA before they undertook the task of developing this test. Dr. Bidlingmaier, for example, is on the Organizing Committee for the Sixth International Congress of the Growth Hormone Research Society and IGF Research Society, to be held in Munich in October 2012—a conference that has nothing to do with WADA. The test has been published in peer-reviewed scientific publications, *Lancet* in 1999, the *Journal of Clinical Endocrinology and Metabolism* in 2001, and *Clinical Chemistry* in 2008. Both the method and the population studies that form the basis of the test's positivity criteria have been subject to ongoing review by a working group of scientists who come from both inside and outside of WADA. That working group has included numerous experts in the field of human growth hormone clinical research or statistics whose only involvement with WADA has been their development or review of hGH testing. Over two dozen external experts have provided specific input on different aspects of the test. Other hGH clinical researchers with no prior relationship with WADA or involvement in anti-doping were also involved in the 2004 USADA Conference on Detection of Human Growth Hormone Abuse and the 2011 USADA Symposium on the Detection of Growth Factors, both of which further validated this test.

The NFLPA is apparently contending that a new population study specifically of NFL players is required. Such a study is not necessary. Three different population studies have already been done in relation to the hGH test involving the statistical analysis of more than 2,400 male samples. All of these studies support the positivity criteria currently used in the hGH test.

There is nothing unique about American football players that requires a separate population study. The current hGH test compares the relative concentrations of the different hGH isoforms detected in an individual's blood, not the absolute amount of hGH present. Human growth hormone experts have consistently told us that there is no reason to believe that the current hGH test criteria are unsuitable for different types of athletes.

That conclusion has proved true, for example, in the testing conducted by USADA, which we understand has been recognized by Congress as the independent agency for Olympic Movement testing in the United States. USADA has conducted close to 1,000 hGH tests since 2008 on a wide variety of athletes, including sprinters, shot putters, hammer throwers, weightlifters, wrestlers, and boxers, with no positive tests. One other obvious flaw with the "NFL football player population study" demanded by the NFLPA is that to the extent there is a current problem of hGH use by NFL players, then the results of the population study would, of course, be skewed.

Unfortunately, the NFLPA is a latecomer to this effort to protect clean competition and public health from hGH abuse. Having arrived late to the party, they want the movie to start all over again now that they have arrived. They make that demand without scientific justification. Because WADA recognized that NFL players are role models and because we

supported the efforts by the NFL to close a significant loophole in its anti-doping program by instituting hGH testing, we went out of our way to meet with the NFLPA. The response that we have gotten from them has been frivolous argument from lawyers, not serious comments from scientists with credentials in the hGH area. Coincidentally, we also met with the Major League Baseball Players Association and, unlike their football counterparts, they agreed to hGH testing starting next year. We also are aware that USADA offered to meet with the players and inform them of the test and practical implications, as well as provide its scientific data on its testing. Unfortunately, we understand the NFLPA rejected this offer.

We appreciate your efforts to resolve this issue for the National Football League. I hope that your decisions will be informed by the opinions of the scientists.

Sincerely,

David Howman

David Howman
Director General

BASIC
RESEARCH

5742 West Harold Gatty Drive
Salt Lake City, UT 84116
phone (801) 517-7000
fax (801) 517-7001
website www.BasicResearch.org

December 17, 2012

Congressman Jason Chaffetz
1032 Longworth HOB
Washington, DC 20515

Re: ***The House Oversight and Government Reform Committee Hearing, December 12, 2012, at 10:00 a.m., on "HGH Testing in the NFL: Is the Science Ready?"***

Dear Congressman Jason Chaffetz:

We wish to thank you for your attendance and input at the Committee Hearing, and for helping to set the record straight regarding the safety and efficacy of the proposed testing methods to detect illegal rhGH injections. We are relieved that the increase in hGH resulting from our SeroVital™-hgh formula will not result in a finding of illegal doping by the presently proposed testing protocol.

We echo the Committee's concerns about illegal doping and encourage you to continue to work to establish and maintain the verbal and legal distinction between these *illegal* rhGH injections and the body's own endogenous hGH increase that can be attained by natural supplementation and nourishment of the pituitary gland. This is of paramount importance to our industry.

Our SeroVital formula is an innovative new natural product shown to increase the body's own production of hGH. It was developed and studied in collaboration with Pennington Biomedical Research Center at Louisiana State University, and the research results were presented at the prestigious Obesity Society's 30th Annual Scientific Meeting. This specialized amino acid blend was shown to significantly increase natural, endogenous hGH to more youthful, healthy levels. Indeed, research shows that adequate, natural hGH levels are a health benefit to the general population.

The randomized, crossover, double-blind clinical trial conducted by Pennington recruited men and women of a wide age range and showed that our patent-pending product increased mean, serum hGH levels by 682%. Rather than bore you with the details, we've attached a summary of the study results presented at the Scientific Meeting.

We also wish to point out **several gross misrepresentations** that were made repeatedly during the hearing. We would like to set the record straight regarding the

BASIC
RESEARCH
5742 West Harold Gatty Drive
Salt Lake City, UT 84116
phone (801) 517-7000
fax (801) 517-7001
website www.BasicResearch.org

safety and Federal regulation of dietary supplements, and we would like to add this response to the Congressional record if possible.

Primarily, Mr. Mike Gimbel repeatedly referred to "unregulated supplements" and the "unregulated" dietary supplement industry. I'm sure the Food and Drug Administration would find this quite interesting, because as you are aware, the dietary supplement industry is *stringently* regulated by the FDA. Mr. Gimbel also characterized dietary supplements as potentially lethal and unavoidably addictive.

Some examples of this misrepresentation from Mr. Gimbel's written statement and oral testimony are found below; the video record of which may be viewed at http://www.c-span.org/Events/House-Hearing-on-NFL-Steroid-Use/10737436501/

- "Many athletes... are going to health food stores, GNC stores, buying tons of muscle supplements which are not regulated. The FDA does not regulate that industry." (oral testimony 1:11:39)
- "A whole industry... is not regulated. So it's a real Russian roulette crapshoot when it comes to what these kids are buying" (oral testimony 1:12:08)
- "the issue of unregulated supplements is a huge issue that needs to be addressed by the FDA" (oral testimony 1:40:48)
- "...unregulated supplements. Diet supplements. Muscle supplements." (oral testimony 0:38:55)
- "Many of these [dietary supplement] products have had hGH and anabolic steroids in them. We just don't know... it needs to be regulated." (oral testimony 1:11:49)
- [States over-the-counter protein powders or "muscle products" may have anabolic steroids or other illegal drugs in them] 1:40:20
- "... taking any form of dietary supplements is like playing Russian Roulette." (written opening statement/testimony)
- "People that use these supplements will get addicted... whether it's just psychologically, or whether it's physically as well." (oral testimony 0:40:10)

Again, we would like to set the record straight regarding the safety and Federal regulation of dietary supplements, and we would like to add this response to the Congressional record if possible.

Under current law, any fly-by-night supplement maker who engages in illegal practices can and should be prosecuted. Putting drugs in dietary supplements is currently a felony. If a dietary supplement manufacturer is found to have placed anabolic steroids into a dietary supplement, that manufacturer should be criminally prosecuted.

BASIC
RESEARCH

5742 West Harold Gatty Drive
Salt Lake City, UT 84116
phone (801) 517-7000
fax (801) 517-7001
website www.BasicResearch.org

However, to imply, as Mr. Gimbel does that over-the-counter dietary supplements are the same class of substance as illegal steroids, rhGH injections, or other drugs, or to claim as Dr. Goldberg does (oral testimony 1:12:48), that, "because they're not regulated, they can put [anabolic steroids] in to make it work," is the kind of misunderstanding and misrepresentation that we need to fight against.

Contrary to Mr. Gimbel's repeated statements to the contrary during the hearing, dietary supplements are indeed regulated by the federal government, and manufacturers are under scrutiny to ensure the safety and validity of their formulations. We wish all to be made clearly aware of this fact. Perhaps the negative impact of the type of misinformation conveyed by Mr. Gimbel during the hearing would be lessened.

Thank you so much for taking the time to address these concerns.

Sincerely,

Dennis W. Gay, CEO

LIMITLESS WORLDWIDE™

December 17, 2012

Congressman Jason Chaffetz
1032 Longworth HOB
Washington, DC 20515

Dear Congressman Chaffetz,

We are writing to thank you for your participation in the recent House Oversight and Government Reform Committee hearing titled "HGH Testing in the NFL: Is the Science Ready?" We are grateful to you for addressing the issues surrounding hGH testing methods, and we would especially like to thank you for helping to raise the distinction between illegal, synthetic, recombinant human growth hormone (rhGH) injections and a new dietary supplement that supports pituitary health, and therefore raises hGH levels naturally.

These issues are extremely important to us, because they have the potential to directly impact our company, Limitless Worldwide, LLC. We are a Utah-based company that has secured the exclusive rights to distribute a patent-pending amino acid formula under the trade name THRIVE in the direct-to-consumer market. This formula has been proven in a clinical study to increase human growth hormone levels by an eight-fold mean. The study, which was presented at the prestigious Obesity Society's 30th Annual Scientific Meeting, is attached here, too.

Rather than introducing synthetic recombinant human growth hormone into the body, which is at the center of the HGH controversy, the orally administered THRIVE formula is a dietary supplement that encourages the pituitary gland to produce more hGH naturally through the use of a highly specialized, patent-pending amino acid formula.

We are, of course, very concerned about the negative press associated with the term "hGH" (almost exclusively resulting from illegal rhGH injections, but nevertheless the term "hGH" is used with abandon) and the effect it may have on the dietary supplement industry. Of particular concern is the almost universal association among the press of the term "hGH" with illegal doping in sports. These were major issues for our company, and we are very grateful to you for helping to clear up this misinformation. We are also thankful for your efforts to confirm that any testing methods put in place will not produce a false positive for consumers who are utilizing our dietary supplement rather than resorting to illegal rhGH injections.

P 800-429-4290 F 801-530-2951 LimitlessWorldwideLLC.com
5742 West Harold Gatty Drive, Salt Lake City, UT, 84116

LIMITLESS WORLDWIDE™

THRIVE is one of our premier products, so making the distinction between its capabilities and the dangers involved with illegal rhGH injections is vitally important not only to us, as cofounders of Limitless Worldwide, but to our many distributors. These direct-to-consumer distributors are basically a network of small business owners, and as you are very well aware, small business owners are the backbone of our economy and are always grateful for any support they receive from elected officials.

Please accept a sincere thank you both from us personally, as well as from our many distributors. Your support is very much appreciated.

Steve and Melyn Campbell

Limitless Worldwide™, LLC

P 800-429-4290 F 801-530-2951 LimitlessWorldwideLLC.com
5742 West Harold Gatty Drive, Salt Lake City, UT, 84116

Elevated Growth Hormone 120 Minutes Following a Single Low-Dose of Amino Acids in Healthy Subjects

ABSTRACT

Background: The use of amino acid supplements to provoke growth hormone (GH) secretion in athletes and entertainers now extends to the general public. Not only do they have a goal of building lean tissue and reducing fat, but also in improving skin quality and other rejuvenating qualities that they believe GH can provide. Despite increasing mainstream use, evidence for whether oral amino acids stimulate GH is not clear.

Methods: This was a cross-over, placebo-controlled randomized study. 16 (12 males; 32±14 years; 26.4±5.0 kg/m^2) healthy subjects had serum GH measured at baseline and 15, 30, 60, 90 and 120 minutes after taking a single low dose proprietary amino acid supplement blend (Somatodyne™ formula) or placebo.

Results: After 120 minutes, GH levels had increased 8-fold from baseline (0.17 to 1.33ng/ml) and were significantly higher than placebo (P=0.01). In addition, a significantly higher mean AUC was observed after taking the supplement [20.4 (95% CI: 19.9-21.0ng/ml) vs. 19.7 (95% CI: 18.7-20.6ng/ml); P=0.04].

Conclusion: Our results show that a single oral dose of these amino acids can significantly increase GH levels after 120 minutes in healthy men and women. Whether these GH changes persist over a longer duration or have other positive effects is being further examined.

September 2012
Obesity Society's 30th Annual Scientific Meeting - San Antonio, TX

INTRODUCTION

GH-deficient adults have marked reductions in lean body mass, and within months of GH treatment, gains in lean body mass, skin thickness and muscle mass were observed.[1-3] It is well-established that intravenous (IV) administration of some amino acids results in significant GH secretion[4,5] presumably via inhibition of somatostatin (SS), Figure 1, (also known as Growth Hormone Inhibiting Hormone). Such studies prompted testing of oral amino acids supplements (mainly arginine, lysine and orthinine) to stimulate GH secretion,[6-10] albeit with mixed results and limitations in the study's designs. Our aim was to rigorously determine whether oral amino acids can stimulate GH secretion, since athletes, entertainers and even the general public commonly take these supplements and believe GH has rejuvenating properties.

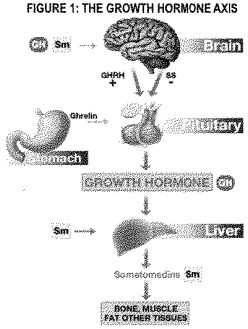
METHODS

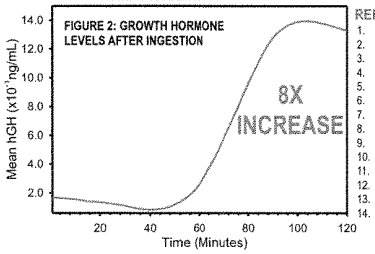
This cross-over, placebo controlled, double-blind study involved 16 healthy subjects [12 males, 4 females; 9 Caucasian, 6 African American, 1 other; mean age= 32±14 years; body mass index=26.4 ± 5.0 ranging from 19.1 to 36.8kg/m^2] (IRB Number 10043). Each subject reported to the Inpatient Unit on two occasions one week apart. After an overnight fast, subjects had an IV line placed and baseline bloods samples were drawn at -30, -15, and 0 minutes. Subjects were then asked to swallow the capsules of supplement (Somatodyne™ formula) or an identical looking placebo. The Somatodyne formula is a novel 2,911 mg/dose blend of (S)-2,6-Diaminohexanoic Acid HCl, (S)-2-Amino-5-Guanidinopentanoic Acid HCl, Pidolic Acid, (S)-2,5-Diamino-5-Oxopentanoic Acid, L-Alpha-Acetamido-Beta-Mercaptopropionic Acid, and *Schizonepeta tenuifolia* Benth. L. (aerial parts) powder. Blood was drawn at 15, 30, 60 and 90 and 120 minutes for assay. Human GH was measured at each time point using the Siemens Immulite 2000 (intra-assay CV was 3.72%, inter-assay CV was 5.70%, and the detection limit for GH was 0.05ng/ml.

RESULTS

Mean growth hormone increased eight-fold over baseline after the supplement from 1.7x10^{-1} at baseline to 13.3x10^{-1}ng/ml at 120 minutes (Figure 2) compared to a mean decrease after placebo from 9.3x10^{-1} to 4.5x10^{-1}ng/m. Mean change in GH levels from baseline to 120 minutes (GH at 120 minutes minus GH at 0 minutes), was 11.5 x10^{-1}ng/ml (95% CI: 1.7, 21.4) after the supplement versus -4.8 x10^{-1}ng/ml (95% CI: -14.7, 5.0) after the placebo, demonstrating a statistically significant differential effect (P=0.01). After the supplement, the mean AUC for GH across 120 minutes was 20.43 (95% CI: 19.90, 20.95) ng/ml/min which was significantly higher (P=0.04) than placebo at 19.67 (18.74, 20.59) ng/ml/min. Overall, 120 minutes after taking the supplement, GH levels were significantly higher in both absolute levels and by AUC.

FIGURE 1: THE GROWTH HORMONE AXIS





DISCUSSION and CONCLUSIONS

The absolute magnitudes of these results are somewhat difficult to directly compare among past studies, as commercial GH assays use different antibodies to target specific GH epitopes resulting in differential sensitivities towards specific isoforms and fragments of the GH molecule. This results in variability of the normal range of the GH measurements in different assays. Indeed, the same GH sample measured using different assays can vary 2-3 fold.[11,12] Yet mean levels of GH reached after the subcutaneous injection of 0.06 IU of HGH in the treatment of GH deficient subjects was 0.4ng/ml, a value that was clearly in the range of values seen in our study with oral amino acids.[13] Furthermore, our normalized percentage increase matches the magnitude increase of previous positive study results on GH secretion.[6-10,13,14]

Overall, we report an eight-fold increase in GH levels 120 minutes after a single oral supplement of the Somatodyne™ formula. Our study had a broad range of ages and BMI's and included both genders. An additional advantage of our study over previous GH evaluations is that it contained a placebo control group and was randomized and double-blinded. Future studies will examine whether regular increases in GH with oral amino acids increase strength and vitality. This indeed may be the case, since elderly subjects administered oral GH secretotgogues for 6 and 12 months have sustained increases in lean body mass and improved physical function.[14]

REFERENCES

1. Cuneo RC et al. *J Appl Physiol* 1991;70:695-700
2. Cuneo RC et al. *J Appl Physiol* 1991;70:688-694
3. Rudman D et al. *N Engl J Med* 1989;280:1434-1438
4. Merimee TJ et al. *N Engl J Med* 1969;280:1434-1438
5. Alba-Roth J et al. *J Clin Endocrinol Metab* 1988;67:1186-1189
6. Suminski RR et al. *Int J Sport Nutr* 1997;7:48-60
7. Lambert MI et al. *Int J Sport Nutr* 1993;3:298-305
8. Corpas E et al. *J Gerontol* 1993;48:M128-M133
9. Isidori A et al. *Curr Med Res Opin* 1981;7:475-481
10. Fogelholm GM et al. *Int J Sport Nutr* 1993;3:290-297
11. Nindl BC et al. *J Appl Physiol* 2001;91:163-172
12. Bidlingmaier M et al. *Pituitary* 2007;10:115-119
13. Janssen YJ et al. *Br J Clin Pharmacol* 1999;47:273-278
14. White HK et al. *J Clin Endocrinol Metab* 2009;94:1198-1206