Testimony before the Committee on Oversight and Government Reform United States House of Representatives

hGH Testing in the NFL: Is the Science Ready?

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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.

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Dr. Tabak is the principal deputy director of the National Institutes of Health (NIH). He previously served as the acting principal deputy director of NIH (2009), and prior to that as director of the National Institute of Dental and Craniofacial Research from 2000-10.

Dr. Tabak has provided leadership for several trans-NIH activities, including the NIH Roadmap effort to support team science, the NIH Director's initiative to enhance peer-review, and the NIH's implementation of the American Recovery and Reinvestment Act. Most recently, he co-chaired working groups of the Advisory Committee to the Director of NIH on the Diversity of the Biomedical Research Workforce and Information Technology and Informatics.

Prior to joining NIH, Dr. Tabak was the senior associate dean for research and professor of dentistry and biochemistry & biophysics in the School of Medicine and Dentistry at the University of Rochester in New York. A former NIH MERIT recipient, Dr. Tabak's major research focus has been on the structure, biosynthesis and function of glycoproteins. He continues work in this area, maintaining an active research laboratory within the NIH intramural program in addition to his administrative duties.

Dr. Tabak is an elected member the Institute of Medicine of the National Academies. He received his undergraduate degree from City College of New York, his D.D.S. from Columbia University, and a Ph.D. from the University of Buffalo.

Committee on Oversight and Government Reform
Witness Disclosure Requirement – "Truth in Testimony"
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1. Please list any federal or contracts (including subgrants or subcontracts) you have received since October 1, 2012. Include the Source and amount of each grant or contract.

   None

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2. Please list any entity you are testifying on behalf of and briefly describe your relationship with these entities.

   I am testifying on behalf of the National Institutes of Health (NIH), a component of the U.S. Department of Health and Human Services. I am the Principal Deputy Director for the NIH.

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3. Please list any federal grants or contracts (including subgrants or subcontracts) received since October 1, 2010, by the entity(ies) you listed above. Include the source and amount of each grant or contract.

   None

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I certify that the above information is true and correct.
Signature: *Date: December 11, 2012*