GROWTH HORMONE

Human Tragicomedy in Three Acts

INTERNAL MEDICINE GRAND ROUNDS

23 APRIL 2010

WILLIAM J. KOVACS

This is to acknowledge that William J. Kovacs, M.D. holds one (1) share of common stock in Pfizer, Inc. (a manufacturer of a recombinant human growth hormone product) and that he has squandered untold sums on Major League Baseball tickets in his lifetime. Dr Kovacs has no other financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Kovacs will be discussing off-label (well, actually illegal) uses of growth hormone in his presentation.

ACT I

Saepius ventis agitatur ingens
Pinus et celsae graviore casu
Decidunt turres feriuntque summos
Fulgura montes

Q. Horatius Flaccus
Lib. II Carm. X

Scene 1: Atlanta, Georgia (1985)

CDC | CDC Home | Search | Health Topics A-Z

MMWR

Weekly

June 21, 1985 / 34(24);359-60,365-6

Fatal Degenerative Neurologic Disease in Patients Who Received Pituitary-Derived Human Growth Hormone

Reports of rapidly progressive and fatal degenerative neurologic disorders in three recipients of human growth hormone (hGH) have been received by the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH). In two cases, diagnoses of Creutzfeldt-Jakob disease (CJD) were made at autopsy.

Figure 1. *The announcement in Morbidity and Mortality Weekly Reports on the development of Creutzfeld-Jacob Disease in individuals treated with growth hormone from human pituitaries*

A notification appeared on June 21, 1985 in the Center for Disease Control's *Morbidity and Mortality Weekly Reports* on a rapidly progressive and fatal neurodegenerative disorder observed in three young patients who had received treatment with human growth hormone. These patients had been taking a form of human growth hormone prepared between 1963 and 1988 by an organization called the National Pituitary Agency (later the National Hormone and Pituitary Program). The NPA had been funded as a contract organization since 1963 to provide (among other scientific research materials) a preparation of human growth hormone derived from cadaver pituitaries. The purified preparation had been used under an Investigational New Drug protocol to treat nearly 7,700 children with diagnosed growth disorders. Histopathologic evidence in each of the initial reports, including one from Dr. Ron Tintner, a neurologist then on the faculty of UT Southwestern, was consistent with Creutzfeld-Jacob disease, a transmissible spongiform encephalopathy that was almost never observed in young persons and had previously been reported to be transmitted by transplantation of human corneal tissue and by neurosurgical instrumentation.

The NPA program had been built on the best of intentions. The scarcity of material led to "black-market" conditions that the National Institutes of Health sought to remedy in 1961 by creation of an organization to coordinate the collection of pituitaries, the extraction of the growth hormone preparation, and its equitable distribution to investigators for research purposes and to physicians for the treatment of patients. Dr. Robert Blizzard, then at The Johns Hopkins University, led the delicate negotiations to cobble together the consortium of players—research scientists to purify the hormone, pathologists to collect the pituitaries, and the concerned parents of children with growth disturbances. The pathologists were rewarded with $2 for every pituitary provided to the program: the investigators who extracted the glands were allowed to keep some of the hormone preparation for research. Parents assisted the program in various ways: Mr. Fred Mahler was a TWA pilot who arranged transporting the frozen pituitaries in the cockpits of his airline's planes on flights to Baltimore. His wife, a former flight attendant with the airline, helped organize an advocacy group, the Human Growth Foundation, and raised funds to support the NPA before the promised NIH funding began.

Figure 2. *Dr Robert Blizzard built the consortium that provided human growth hormone treatments to over 7000 children with growth disorders*

The methods used in the preparation of the growth hormone were primitive. Dr. Blizzard recounts: "the hGH was received from extractors at the NPA in small mason jars. It was transferred by spatula to wax paper and placed on a simple analytical balance. One milligram of hGH (one day's dose) was weighed and placed in small sterile screw cap vial which then was sealed." No radioimmunoassay for growth hormone existed until 1962 and even

bio-potency estimates were not performed on the preparations until 1965. Solubility of preparations varied—the 0.1% HCl required for dissolution of one labs' preparation made it the least popular among patients.

The NPA program had successfully demonstrated that growth-promoting activity of anterior pituitary extracts accelerated linear growth dramatically in patients with growth disorders. On a national therapeutic scale, however, it was obvious to all that the effort could only be insufficient. Blizzard estimated as early as 1963 that, even if a pituitary were harvested from every autopsy performed in the United States, sufficient hormone could only be obtained to treat about 4000 individuals per year. Awareness was dawning that other patients with short stature conditions such as Turner's syndrome could also benefit from therapy. In 1977 Dr. Albert Parlow at Harbor-UCLA Medical Center became director of the National Hormone and Pituitary Program and the yields per pituitary and available supplies of growth hormone increased. Nevertheless, by 1985 only the 7,700 individuals were treated in the U.S. program. Then came recognition of the CJD disaster.

The United States experience was mirrored in other countries with programs to produce growth hormone for treatment. In France 115 cases of Creutzfeld-Jacob disease were indentified among the 1,700 recipients of growth hormone therapy. In the United Kingdom 56 of 1,849 treated persons were affected. With the CDC's report in 1985 the US and UK organizations immediately stopped distribution of their preparations of growth hormone and patients were left without therapy.

Scene 2: Boston, Massachusetts (1928)

Whether human growth hormone even existed was a matter of conjecture in the early twentieth century. In 1886 Pierre Marie had described the symptom complex of "acro-megalie" in association with tumors of the pituitary. He reported 2 patients with rapid growth in height or enlargement of hands, feet, and facial structures as well as headaches and visual problems. The function of the pituitary was essentially unknown at the time (no one was even sure if the gland was essential for life) and as more acromegalic patients were recognized their presentations only confused the issue because some aspects of their disorder suggested hormonal deficiency states. By 1928 Harvey Cushing had figured it out. In 1909 he had reported at a meeting in Budapest a case of a man with acromegaly who was referred to him (then at Johns Hopkins) by Dr. Charles Mayo. The man had obvious acromegaly and Cushing ventured surgically into the man's sella turcica--which he incised longitudinally and "a considerable portion—possibly one-half of the exposed gland—was removed piecemeal with the aid of a delicate, long-handled cuvette."

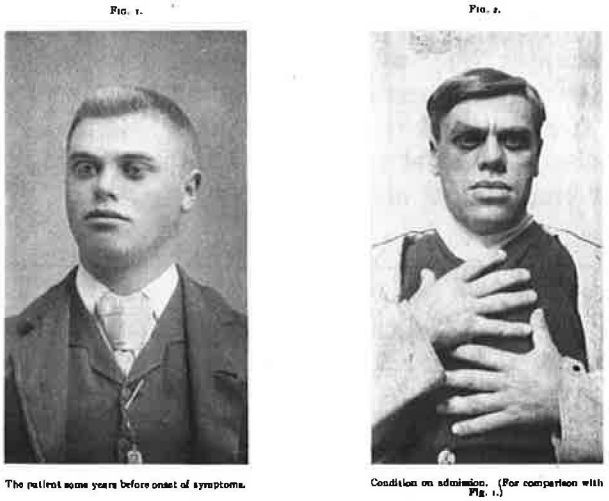


Figure 3. *Harvey Cushing postulated that this man's acromegalic state was the consequence of pituitary overactivity—and that the adenomas observed in such cases secreted an excess of some hormone.*

It worked. Within about two weeks of the operation the patient reported that his hands seemed less stiff, and Cushing felt the objective thickening of tissues was diminished. The fingers were 1-1.5 mm thinner. The man returned to his farm and came back to Baltimore that summer. Cushing then noted "considerable change... in his appearance" and some objective measurements seem improved (Cushing, ever the perfectionist considered them to "lay possibly within the margin of error, so that it would be unjust at this early date to lay emphasis upon them"). The case supported his contention that acromegaly was a hypersecretory state of the pituitary—not a deficiency state. Just what might be secreted in excess was, of course, totally unknown.

By 1928 Cushing had operated on more than 100 pituitary tumors for which he had sufficient pathological material for analysis. Sixteen of those cases were clearly acromegalic patients whose tumor specimens were eosinophilic adenomas with cells packed with acidophilic "alpha" granules. A rough correlation was observable between the amount of alpha granules in the tumor and the severity of the clinical features. Something in those granules was the offending hormone.

Scene 3: San Francisco, California (1921)

Cushing was well aware of experimental work that supported his construct. In 1921 Herbert Evans and J. A. Long at the University of California had reported "a characteristic acceleration of growth in rats treated intraperitoneally with the finely ground, fresh anterior lobe of the hypophysis of beef." It didn't work when given orally, even in very large amounts, but after a year's intraperitoneal administration one animal weighed twice as much as her matched normal littermate! Some of this was increased fat deposition, but the skeleton was "invariably larger and heavier."

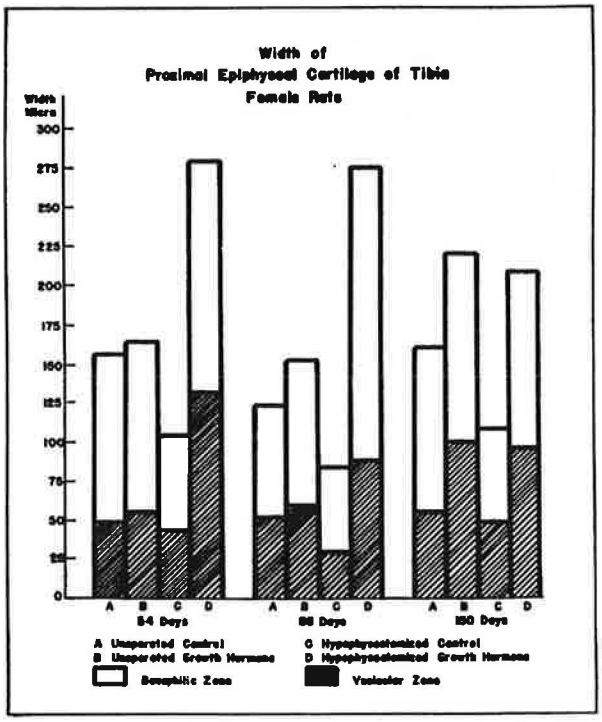


Figure 4. *Evans's experimental data showing the effects of growth hormone administration on the tibial epiphyseal cartilage of intact and hypophysectomized female rats.*

This was only in the beginning of the growth hormone research at UCSF. Evans' work encompassed studies of all the hormones of the anterior pituitary as the fields of peptide chemistry and protein purification techniques were born. In 1938 Evans hired a newly minted PhD in organic chemistry name Choh Hao Li. Jobs were scarce and Evans offered Li space to work in the basement of the UC Berkeley Life Sciences Building. There, Li developed purification and sequencing techniques for all of the anterior pituitary hormones. For growth hormone, it took 32 years. Meanwhile, with less pure preparations of the hormone Evans and others had proven its effects on skeletal growth.

ACT II

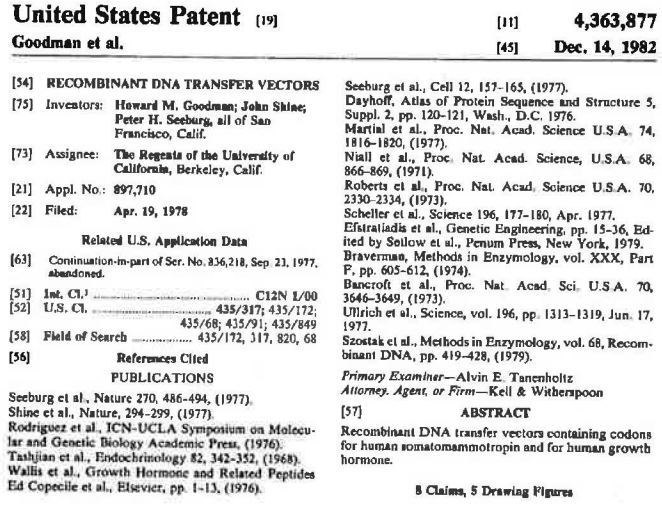
There is a human growth hormone on the market today—by prescription only—that could pump Nancy Reagan up to the size of John Madden in about three months, if that's what she really wants

Hunter S Thompson
Welcome to the Tunnel
In: Generation of Swine
Gonzo Papers Vol 2 (1988)

Scene 1: San Francisco, California (1978)

On New Year's Eve 1978, Axel Ullrich and Peter Seeburg, two postdoctoral fellows at the University of California San Francisco, were at a party when they decided to drop by their lab at UCSF to pick up some reagents. Ullrich and Seeburg had been offered jobs at Genentech, a 2-year-old biotechnology company that had just successfully prepared the first recombinant human gene product, insulin. Genentech was now ready for a larger challenge and human growth hormone (ten times larger than insulin) was to be it. What happened during their late night visit to UCSF has been the subject of a fascinating variety of accounts that emerged over the ensuing decades.

In that same month (December, 1978) Seeburg, Ulrich, and their mentors, John Baxter and Howard Goodman, had published the molecular cloning of a construct of the rat growth hormone gene that they had "engineered" to be expressed in the bacterium Escherichia coli, and they were actively involved in a project to achieve such "cloning" of the human growth hormone gene.



United States Patent [19]
Goodman et al.

[11] **4,363,877**
[45] **Dec. 14, 1982**

[54] RECOMBINANT DNA TRANSFER VECTORS

[75] Inventors: Howard M. Goodman; John Shine; Peter H. Seeburg, all of San Francisco, Calif.

[73] Assignee: The Regents of the University of California, Berkeley, Calif.

[21] Appl. No.: 897,710

[22] Filed: Apr. 19, 1978

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 836,218, Sep. 23, 1977, abandoned.

[51] Int. Cl.³ C12N 1/00
[52] U.S. Cl. 435/317; 435/172; 435/68; 435/91; 435/849
[58] Field of Search 435/172, 317, 820, 68

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Primary Examiner—Alvin E. Tanenholtz
Attorney, Agent, or Firm—Kell & Witherspoon

[57] ABSTRACT

Recombinant DNA transfer vectors containing codons for human somatomammotropin and for human growth hormone.

8 Claims, 5 Drawing Figures

Figure 5. *The " '877" patent from UCSF on their human GH clone--filed in April 1978.*

By the summer of 1978 Seeburg had already moved to Genentech and was working to isolate a human cDNA clone for growth hormone using human pituitary mRNA as a template. It was not going well. The Genentech source of cadaveric pituitaries (a company called Kabi) had not prepared them particularly well and the RNA was degraded. But, as Seeburg testified in later court proceedings, a human clone already existed that he knew he could use. It was in the lab at UCSF, and he was a co-inventor on the patent with Dr Howard Goodman.

At the time there were no PCR machines and no human genome database. So the molecular cloners stood on the shoulders of the giants who had purified and sequenced the protein as well as those who developed assays for its detection. Using partially purified hormone preparations William Daughaday (working with Mary Parker, the mother of our late division director) and Solomon Berson independently developed new radioimmunoassays for the hormone. For the first time the hormone could be quantitated in serum in physiologic amounts.

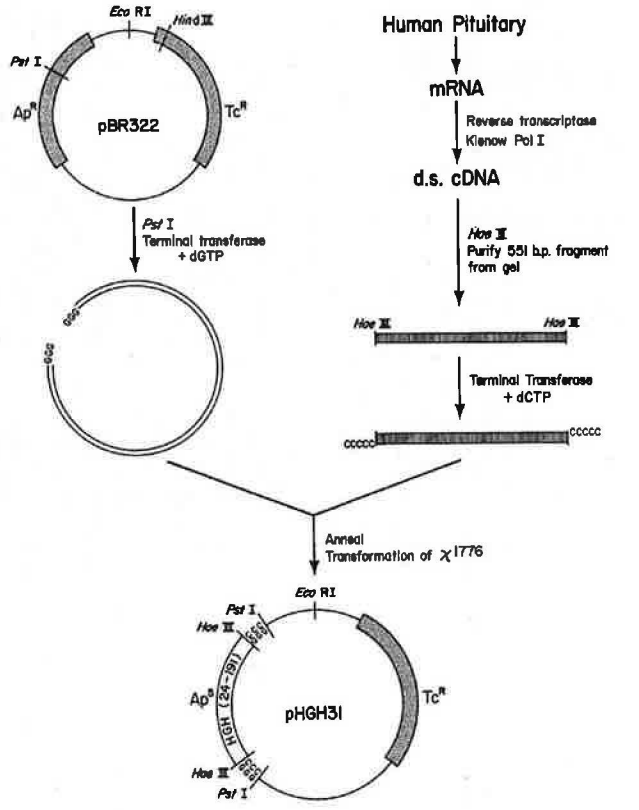

Figure 6. *The construction of pHGH31—drawing taken from Genentech's patent filed in July 1979. Peter Seeburg later testified that at Genentech he had failed to produce this construct, and instead used the clone that he had removed from his former UCSF lab.*

Even with these available tools Seeburg and his colleagues had no way to select the particular messenger RNA encoding the growth hormone transcript. The planned to use growth hormone-secreting tumors as a source of (hopefully more abundant) GH mRNA and relied on the isolation of a known restriction fragment that contained the transcript to create a plasmid construct lacking only the codons for the first 24 amino acids of growth hormone. This was to be used in combination with a synthetic piece of DNA encoding those first 24 amino acids to create a human clone which could express full length growth hormone in bacteria. It worked. On October 15, 1980 Genentech issued an initial public offering of its stock (the price rose by more than $50 per share in a single hour) and by 1985 Protropin® was approved for the market by the United States Food and Drug Administration. A bitter fight ensued over the origin of the Genentech growth hormone clone used in the production of their recombinant product. In 1990 the University of California sued Genentech for the alleged theft of intellectual property covered by their 1982 patent that included a plasmid containing a 550 base pair fragment of the growth hormone cDNA that encoded amino acid residues 24-191.

Scene 2: San Francisco, California (1999)

After nearly a decade the case finally came to trial. In 1999 Peter Seeburg testified that he had, in fact, removed a cDNA clone from his former UCSF lab on that New Year's Eve visit and that this clone contained the cDNA sequences needed by Genentech for their human growth hormone expression vector. The plasmid hGH31 reported in Genentech's 1979 paper could not be proved to exist and Seeburg stated: "Several attempts at Genentech by a colleague and me to obtain phGH 31 were unsuccessful, primarily due to the poor quality of the RNA starting material available to us at the time. With increasing pressure to complete the expression work, my colleague and I agreed to use the University of California 's cDNA clone for part of the work."

Dennis Kleid, one of Genentech's earliest employees, hotly disputes Seeburg's trial testimony, which he says contradicts both lab notebooks of David Goeddel (the "colleague" in Seeburg's trial testimony) as well as Seeburg's own prior depositions in the case. The trial ended in jury deadlock.

On November 19, 1999 The Regents of the University of California, San Francisco voted to

Figure 7 *Genentech Hall, donated to the University of California, San Francisco, as part of the settlement of the regents' law suit regarding growth hormone patents.*

settle the patent dispute for $200 million. This was reported to include $85 million in monetary awards to the inventors on the original UCSF patent as well funding for a new research building at UCSF. The building came to be named Genentech Hall. David Kleid, in his UCSF Oral History Program interview has lots to say about the impartiality of the judge in the case (Charles Legge) and even more about the motivations of Peter Seeburg in *Regents of the University of California vs Genentech*, but the last few lines of the transcript say the most:

Hughes [Interviewer M Hughes]: What a Story!
Kleid: [sighs]
Hughes: Is it over?
Kleid: Well, I don't think anything is ever over.

ACT III

My wife received a shot of HGH from Brian McNamee at my house. I think it was in our master bedroom. The year, I'm going to say 2003 possibly. I believe there was an article, from what I understand, about HGH in the USA Today that came out a couple days earlier that week. I don't know if it was the only article my wife had read. And he gave her a shot of HGH.

William Roger Clemens
Deposition
U.S. House of Representatives
Committee on Oversight and Government Reform
Washington, D.C.
February 5, 2008

Scene 1: Wakefield, UK (2010)

The Wakefield Trinity (Rugby) Football Club has a long and distinguished history dating back to its formation in 1873 by the members of the young men's society connected with Holy Trinity Church in Wakefield, a town near Leeds in West Yorkshire, England. On February 19, 2010, an unwanted chapter was added to that history. Terry Newton, one of the Wildcat players, received a two-year sanction from the UK Anti-Doping Agency in connection with a positive test for human growth hormone "doping" in a blood sample taken in November 2009. The test was reportedly run at the King's College London Drug Control Center. His was the first case of a sports sanction resulting from testing for illicit human growth hormone use by an athlete.

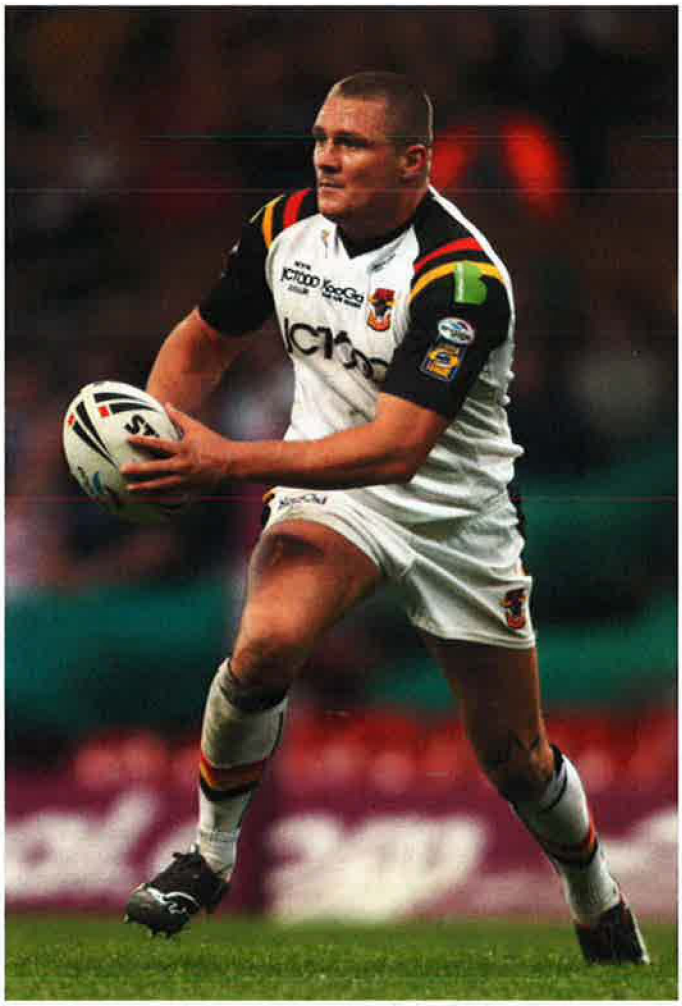

Figure 8 *Terry Newton of the Wakefield Trinity Wildcats made sports history in February 2010 by becoming the first athlete to test positive for illicit growth hormone use.*

Scene 2: Washington, D.C. (2008)

In the spring of 2006 the commissioner of Major League Baseball, Allan H. ("Bud") Selig asked former Sen. George Mitchell to conduct an investigation into allegations of the widespread use of performance enhancing drugs by Major League Baseball players. 68 former players agreed to speak with Sen. Mitchell. Not a single active player agreed to be interviewed.

In the course of that investigation, however, Mitchell heard allegations of growth hormone use by star pitchers Roger Clemens and Andy Pettitte. A former New York City police officer named Brian McNamee spoke to Mitchell's team. McNamee had entered into a written agreement to cooperate with United States Attorney for the Northern District of California. He was considered a sub-distributor for a man named Curt Radomski, a former clubhouse attendant for the New York Mets who came to operate a network supplying anabolic steroids and growth hormone to MLB players.

Roger Clemens had signed with the Toronto Blue Jays in 1997 after spending the first 13 years of his career with the Boston Red Sox. Brian McNamee began working for the Blue Jays in 1998 and both he and Clemens lived in the Toronto SkyDome. By McNamee's account to the Mitchell Commission, Clemens first approached him for assistance with anabolic steroid injections. Later, after Clemens had signed with the New York Yankees and McNamee continued to serve as a personal trainer, he suggested to Clemens that he try human growth hormone. McNamee told the commission that he subsequently administered growth hormone to Clemens on four to six occasions. In 2008 Clemens appeared voluntarily and testified under oath before the House Committee investigating use of performance enhancing drugs in MLB. He denied McNamee's allegations. Andy Pettitte, who was Clemens's teammate on the Yankees used McNamee as a personal trainer along with Clemens. Pettitte had testified before the same House Committee that McNamee injected him with growth hormone twice a day for two days in 2002 in an effort to speed his recovery from elbow problems. Pettite also testified that Clemens had reported to him that he took growth hormone in 1999.

Andy Pettitte didn't think that growth hormone helped him in any way. Is there any evidence to suggest that it might? The available data are not impressive. A systematic review of available literature from a Stanford group in 2008 is the best summary. These investigators limited their analysis to randomized, controlled trials that compared effects of growth hormone with no treatment in young healthy people. Whether the dosage (average of 36 μg/kg/day) or duration of therapy (average 20 days) has anything to do with regimens used by athletes is, of course, unknown. The data support an effect to increase basal metabolic rate and lean body mass but not strength.

Table 3. **Summary Effect Sizes for Body Composition, Strength, and Basal Metabolism***

Clinical Area and Clinical Outcome	Study Samples, n†	Weighted Mean Difference (95% CI)‡
Body composition		
Change in body weight	9	0.3 kg (−0.5 to 1.1 kg)
Change in fat mass	10	−0.9 kg (−1.9 to −0.0 kg)
Change in lean body mass	11	2.1 kg (1.3 to 2.9 kg)§
Strength		
Change in biceps 1RM	2	−0.2 kg (−1.5 to 1.1 kg)
Change in quadriceps 1RM	2	−0.1 kg (−1.8 to 1.5 kg)
Basal metabolism		
End basal metabolic rate	7	141 kcal/d (69 to 213 kcal/d)‖
End resting respiratory exchange ratio or respiratory quotient	7	−0.02 (−0.03 to −0.01)‖
End resting heart rate	11	3.8 beats/min (0.2 to 7.4 beats/min)¶

* 1RM = 1 repetition maximum.
† Includes subsamples based on sex and dose.
‡ Growth hormone–treated group minus non–growth hormone–treated group. The weighted mean difference provides summary effect sizes in the same units as the outcome of interest. A positive value indicates that the weighted mean value in the growth hormone–treated group was higher than the value in the group not treated with growth hormone.
§ $P < 0.01$.
‖ $P < 0.001$.
¶ $I^2 > 50\%$; $P < 0.05$.

Figure 9 *Table summarizing data on body composition, strength, and basal metabolic rate from the systematic review by Liu and colleagues at Stanford in 2008.*

Scene 3: Seoul, South Korea (1988)

In 1988 the Canadian sprinter Ben Johnson was disqualified after his victory in the Olympic 100 meter final in Seoul when stanozolol was detected in his urine sample. Both he and his coach admitted under oath that he had also taken human growth hormone. Attention turned to the widespread use of growth hormone among athletes and the International Olympic Committee added to its list of prohibited substances in 1989. There was no reliable test to detect its illicit use by athletes.

The obvious approach would be simply to measure growth hormone itself in body fluids. This, however, presents a number of technical challenges. Five genes encoding growth hormone and related proteins reside in a cluster on chromosome 5. Two of these, GH1 and GH2, encode growth hormone variants (GH1 is the gene expressed in the pituitary and GH2 is expressed in placenta). The other three genes encode the placental protein chorionic somatomammotropin.

The GH1 gene itself comprises 5 exons and 4 introns and the transcribed RNA encodes a 191 amino acid product of 22,191 daltons molecular weight. Alternate splicing of exon three yields a second GH1 isoform of 20, 274 Daltons (176 amino acids).

The 22 kDa form of growth hormone is the most aboundant isoform in the pituitary and in the peripheral circulation (about 10-20 times more abundant than the 20kDa molecule. These proteins can also dimerize or aggregate and they can be post-translationally modified. The result is a remarkably heterogeneous population of molecules secreted by the pituitary into the circulation. In contrast, the recombinant preparations of human growth hormone consist of monomeric 22kDa growth hormone. Administration of recombinant human growth hormone suppresses endogenous growth hormone secretion and the 22kDa monomeric form of the hormone becomes even more predominant in circulation.

Table 2
Representative estimates of GH isoforms in the pituitary gland.

Monomeric GH	
22K GH	55%
20K GH	6%
Deamidated GH	
22K-GH-Asp^{152}	6%
22K-GH-Glu^{137}	2%
N-acylated 22K-GH	4%
Glycosylated GH	unknown (minor form)
Dimeric GH	
Non-covalent dimers (homo- and heterodimers)	10%
Disulfide dimers	7%
Other non-dissociable dimers	1%
Oligomeric GH	
Non-covalent oligomers	5%
Disulfide linked oligomers	2%
Other non-dissociable oligomers	<1%

Figure 10 *Table summarizing the circulating forms of growth hormone in humans. (From Baumann GP, in Growth Hormone and IGF Research 19:333 (2009)*

Assays based on these observations (the "isoform method") were validated in several laboratories of the World Anti-Doping Asociation (WADA) and these methods were used during the Athens Games of the XXVIII Olympiad (no positive tests), the Torino XX Winter Olympic games (no positive tests), the Beijing 2008 Olympic Games (no positive tests), and the Vancouver 2010 Winter Olympics (no positive tests). When Terry Newton made history by testing positive by this method he overcame remarkable odds. With a GH circulating half-life of 15 minutes the method is obviously only applicable for unannounced "out of competition" testing. So Newton's visit from the Rugby Super League's testing crew surely took place within 24 hours of his last dose of recombinant growth hormone. He did not contest his suspension.

Scene 4: St Louis, Missouri (1956)

A second approach to detecting illicit growth hormone use has its origins in one of the most famous experiments in the history of studies of growth hormone physiology, done in the mid 1950s by William Salmon and William Daughaday at Washington University in St. Louis.

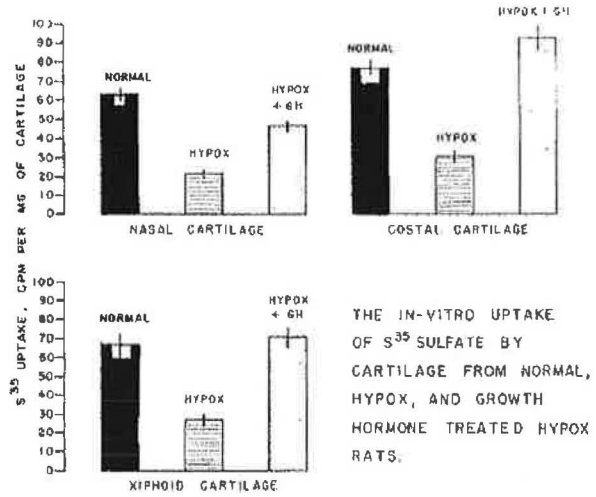

Figure 11 *Salmon and Daughaday described evidence for a systemically circulating mediator of growth hormone action. Figure taken from Salmon and Daughaday in J Clin Lab Med 49: 825 (1956).*

Salmon and Daughaday discovered that the serum of rats contained a growth hormone-regulated substance that stimulated the incorporation of sulfate into cartilage cultured *in vitro*. The substance disappeared from the serum of rats who had undergone hypophysectomy. Growth hormone treatment of the animals restored the activity but growth hormone added directly to the culture system had no effect. They named the substance "sulfation factor." In addition to its scientific importance in opening the field of "growth factor" research (it was subsequently agreed that the molecule be called insulin-like growth factor 1 or IGF-1) assays for the factor became an essential tool in the clinical assessment of pathologic states of growth hormone deficiency and excess.

After the International Olympic Committee banned growth hormone use by athletes in 1989 two more year passed before an advisory subcommittee was formed to examine the issues of detecting illicit growth hormone use. The Olympic Committee, however, was opposed to involving athletes in the research needed to develop testing methods. And the Olympic Committee provided no funding for such a project. Eventually the European Union agreed to fund research in this area and a consortium led by Dr Peter Sönksen, an endocrinologist at St. Thomas's Hospital and King's College, London sought to develop testing based on "biomarkers" of growth hormone action from either the growth hormone-IGF-1 axis or from collagen metabolism. They chose biomarkers with

long serum half-lives for study and their "GH-2000" study proposed a test based on two of these markers—IFG-1 and a procollagen N-terminal peptide called P-III-P. The latter is a marker of Type 3 collagen formation in soft tissues.

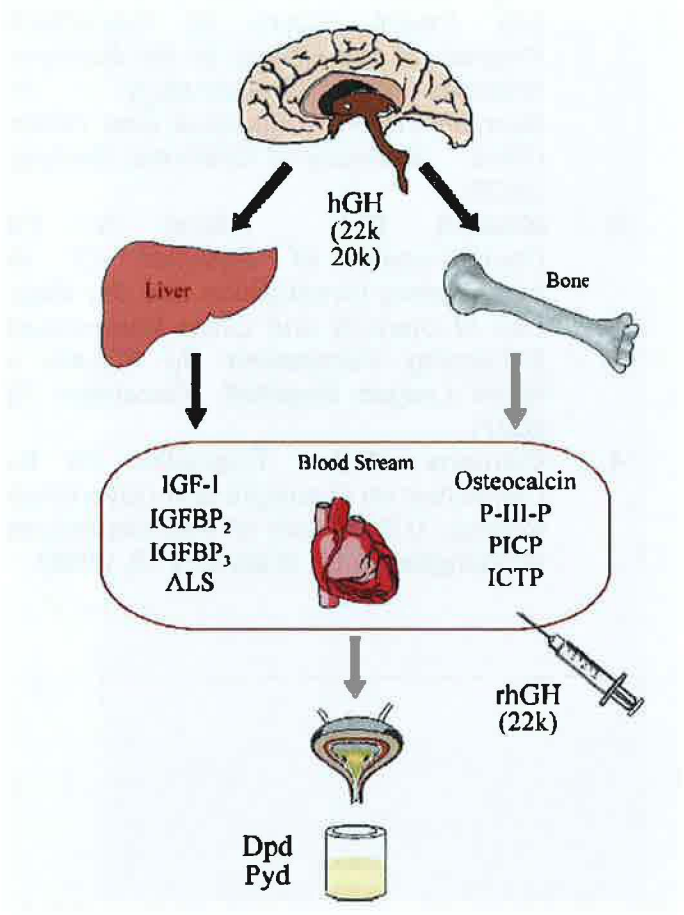

Figure 13 *Biomarkers considered for evaluation by the GH-2000 research team. From Sönksen P, in Growth Hormone and IGF Research 19: 341 (2009)*

They found IGF-1 and P-III-P as ideal markers because they exhibit little diurnal or day-to-day variation, and were not affected by exercise. The resulting test looked quite good. The data were reviewed by the EU and IOC and a workshop was convened in Rome in March 1999. Sönksen recalls strong support for the proposed test, with one lawyer from the Court of Arbitration in Sport stating that he would be happy to prosecute offenders on the basis of results of the test, but only if the athlete were a white European man.

The researchers returned to work to validate the tests in women, across a broader ethnic spectrum, and in the setting of recovery from injury. Some bizarre Olympic politics intervened, and the next phase of the study was delayed until the United States Anti-Doping Agency agreed to support the research project (now known as "GH-2004") at the end of 2002.

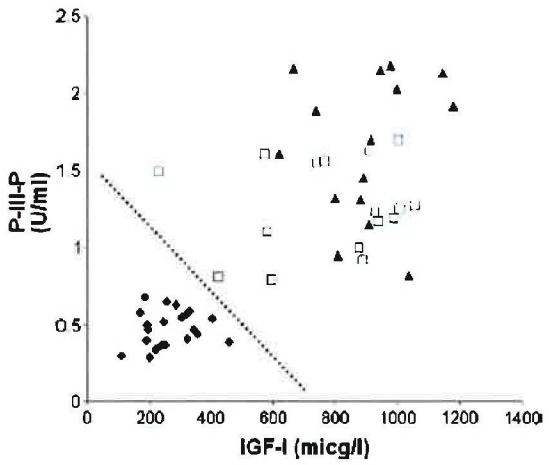

Fig 2. Individual datapoint plot of P-III-P against IGF-I levels in male subjects after 3 weeks treatment with low dose (□) or high dose (▲) GH or placebo (♦).

Figure 14. *Validation from the GH-2000 study. Taken from Sönksen P, Growth Hormone and IGF Research 19:341 (2009)*

This validation project was considered to have successfully addressed the issues of ethnic variance and the influence of injury on P-III-P levels. However, development of commercial assays to be used specifically for the purpose of testing athletes lagged and no biomarker test is in use today. On March 28, 2010 The New York Times quoted David Howman, Director General of the World Anti-Doping Agency, as saying that the implementation of a biomarkers test was only months away. WADA's official website indicates that "Following its policy, WADA does not disclose the moment when new detection methods are implemented."

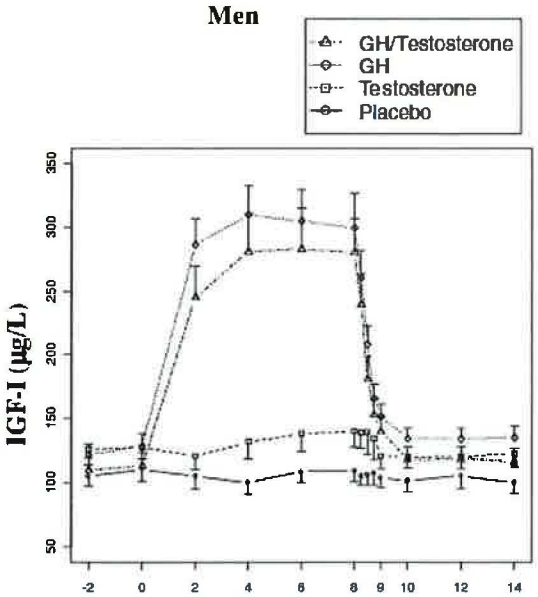

Figure 15 *IGF-1 data in men treated with growth hormone, testosterone, the combination, or placebo over 8 weeks. From the GH-2004 biomarker project. Nelson et al J Clin Endocrinol Metab 93: 2213 (2008)*

EPILOGUE

1. In 1993 a 33 year old woman named Tracia Hagy died in Bellevue, Washington after a 10 month illness that had been diagnosed as Creutzfeld-Jacob disease. She had been treated for pituitary dwarfism at the University of California, San Francisco from 1975-1977 with growth hormone from the National Hormone and Pituitary Program.

Tracia's surviving husband, Daniel, brought an action for wrongful death against the United States pursuant to the Federal Tort Claims Act (FTCA), 28 U.S.C. §§ 1346(b), 2671-80. He claimed that the government was liable for having provided UCSF with the contaminated hGH, and for having failed to discover and warn of the danger the hGH treatments posed to recipients. The United States moved to dismiss, contending that plaintiff's claims fall within exceptions to the FTCA's general waiver of sovereign immunity.

The court ruled that the United States could not be held liable for the negligence of either the NHPP or the hGH extractors because it had not waived immunity for the torts of its contractors and grantees. The discretionary function exception prevented the FTCA from being applied to hold the United States liable for its own alleged failure to discover the danger of using human hGH to treat dwarfism, or for an alleged failure to warn the public of it. For the reasons stated, the court granted the motion of defendant United States for dismissal pursuant to Federal Rule of Civil Procedure 12(b)(1).

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2. Worldwide annual sales of 8 different recombinant human growth hormone products from seven different manufacturers are currently estimated to exceed $3 billion. Most of the products are believed to have originated from the UCSF "clone".

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3. Roger Clemens becomes eligible for election to the Baseball Hall of Fame in 2013. As of April 22, Andy Pettitte was 2-0 in three starts for the New York Yankees and had an earned run average of 1.35.

Recommended Reading

1. **Blizzard, R.M.** Growth Hormone as a Therapeutic Agent. *Growth, Genetics, and Hormones 21: 49-54 (2005).*
2. **Hughes, S.S**. Dennis G Kleid: Scientist and Patent Agent at Genentech. *Program in the History of the Biological Sciences and Biotechnology. The Bancroft Library. Regional Oral History Office. University of California, Berkeley (2002).*
3. **Mitchell, G.J.** *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.* (December 13, 2007).
4. **Clemens, W.R**. Deposition for the Committee on Oversight and Government Reform, U.S. House of Representatives, Washington, D.C. (February 15, 2008).