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Growth hormone and anabolic steroids: athletes are the tip of the iceberg

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Professional Athletes' misuse of anabolic steroids, growth hormone and other drugs are the tip of a very large, mostly ignored iceberg, made up of people who receive these drugs for such non-medical uses as body-building, school sports and "anti-aging". Although these drugs are often used in combination, this article focuses on growth hormone. Fuelling the demand for these drugs are drug manufacturers, pharmacies, websites, clinics and their doctors. Copyright © 2009 John Wiley & Sons, Ltd.

Athletes are the Tip of the Iceberg

The Mitchell Report and Congressional hearings have successfully exposed the use of androgenic anabolic steroids (AAS) and human growth hormone (hGH) by professional athletes^[1,2] but much more must be done to inform legislators and the public that (a) professional athletes are only the tip of an iceberg made up of hundreds of thousands of users (Table 1); (b) numerous AAS and hGH manufacturers, pharmacies,^[3] doctors, clinics, gyms and Internet sites are involved in the distribution of these drugs, which generate huge profits; (c) in non-medical use the health risks of these drugs are much greater than their benefits;^[4,5] (d) murders,^[6] other violent behaviour,^[7] psychological disorders^[8] and suicides^[8–10] have been associated with the use of AAS, which frequently accompanies hGH use in this setting; and (e) distribution and sale of AAS and hGH for non-medical uses is illegal.^[11–12] This article will hopefully shed light on those who deceptively distribute and sell hGH for non-medical uses.

Marketing and Selling Growth Hormone to Adults

Unfortunately, the media often categorize hGH as an anabolic steroid, which it is not. However, the media are correct in assuming that the medically inappropriate (and illegal) distribution of hGH nearly always accompanies AAS use. Though hGH alone may have some anabolic effect,^[26] clinical studies of normally aging subjects demonstrate that hGH alone provides minimal improvement in muscle mass^[27,28] and fat loss,^[29] while subjecting them to unreasonably high rates of adverse events.^[4,30–33] AAS are accompanied by medical risks (some of them potentially lethal) but they nonetheless promote increased muscle mass and at least one short-term study of older men with lower than average age-specific IGF-1 and testosterone levels suggests that hGH may increase the anabolic effect of AAS in such subjects.^[34] The authors of the latter study noted hypertension as a side effect of this combination regimen and cautioned that such treatment may be specifically beneficial in frail, sarcopenic elderly and that longer term study is still needed. Thus, anti-aging clients or athletes experience increased muscle mass due to the anabolic steroid(s) but may be told that the hGH is important to the success of their programme. This scheme results in much greater profits than selling AAS alone.

Numerous animal and human studies demonstrate that impairment of the hGH-IGF-1 axis actually enhances lifespan.^[35–40] Lifespan increases that are due to caloric restriction may result from decreased IGF-1.^[41,42] At least one study demonstrates that hGH administration shortens lifespan in rats.^[43] Several hGH clinical trials have revealed numerous adverse effects (Table 2). It is theoretically possible that reductions in hGH experienced as a function of age are an adaptive response to accumulating cell damage^[44,45] and offer protection from various age-related diseases (such as cancer). In a 2002 Johns Hopkins study published in JAMA, about 50% of subjects experienced side effects, primarily joint pains and extremity swelling. Thirteen per cent developed elevated blood sugars or diabetes.^[30] In other words, except for rare cases, in the adult, the risks of hGH far outweigh what little if any benefit might exist, particularly in normally aging adults.

Many marketers and sellers of hGH often point to a small, very short-term study that appeared in the *New England Journal of Medicine*, which claimed that administration of growth hormone to nine men over six months resulted in body composition changes that were akin to making the subjects 20 years younger.^[62] The first author of that study, Daniel Rudman^[63,64] as well as the journal's editor^[65] and others^[29,66] decried the anti-aging industry's misuse and misinterpretation of that study's findings and clinical implications. To make the anti-aging industry's case, Ronald Klatz claimed that 'thousands of published studies on hundreds of thousands of patients have demonstrated the clear benefits of adult GH replacement therapy, when utilized under proper clinical guidelines and at proper physiological dosages.'^[67] In response to the deceptive and prevalent distribution of hGH for purported anti-aging and muscle building effects, multiple worldwide endocrinological organizations leading endocrinologists and the FDA have produced warnings and consensus statements making it clear that hGH is neither indicated nor safe for body building, athletic use or anti-aging.^[66,68–72]

Human growth hormone levels gradually decline in adults with minimal or no negative health consequences for the vast majority

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Table 1. Non-medical users of growth hormone and anabolic steroids

Military personnel^[13]
 Police^[14]
 Firemen^[14,15]
 Middle school^[16,17] and high school students^[17–20]
 Body builders^[21] and professional wrestlers^[22]
 Athletes^[1,2,23]
 Gym users^[24]
 'Anti-aging' and 'age-management' customers^[5,11,25]

Table 2. Adverse effects of growth hormone in normally aging adults

Cancer^[46–59]
 Diabetes^[30,31]
 Hypertension^[30,31]
 Arthralgias^[60]
 Edema^[60]
 Carpal tunnel like syndrome^[30] and other parasthesias^[60]
 Increased pressure around the brain (called pseudotumor cerebri)^[61]

of the population. Many pushers and sellers of hGH claim and advertise that normal declines in hGH cause aging and a reduction in strength, muscle mass, sleep and sexual performance. They further claim that replenishing hGH to levels present at younger ages stops or reverses these problems as well as aging itself.^[73–76] As noted above, there is little scientific evidence supporting these claims; on the contrary, there is a rapidly growing body of evidence that hGH administration in normally aging adults is contraindicated.^[11,29,44,66]

United States Federal Law Regarding Growth Hormone

Medical conditions in adults that merit the use of hGH are few and rare. According to the FDA, hGH has serious, known risks. Among the possible long-term side effects of hGH is an increased risk of cancer, and other dangerous side effects have been reported, including nerve pain and elevated cholesterol and glucose levels. For this reason, hGH is carefully regulated in the U.S.^[72] Recognizing the potential for hGH abuse and adverse effects, Congress amended the Food Drug and Cosmetic Act (FDCA) in the late 1980s and early 1990s to enact stringent controls involving the distribution of AAS (the anabolic steroids act) and hGH (see Table 3).

Thus, the only medical indications allowed for distributing hGH to adults (and there is no such thing as legal 'off-label use' of hGH) are:

- AIDS wasting syndrome (this does not include lipodystrophy)^[78]
- short bowel syndrome
- growth hormone deficiency (GHD)

When it became widely understood that distributing hGH for anti-aging is illegal,^[11,72] some consultants to the industry and anti-aging and age-management entrepreneurs suggested that they redefine GHD as problems they claim to be associated with declines in growth hormone production.^[5] Redefining GHD in this manner is medically unethical and outside the realm of the standard of care of

Table 3. The law concerning growth hormone distribution that appears in the Food, Drug and Cosmetic Act (FDCA) [72]

Section 303(e) (1) of the FDCA, 21 U.S.C. § 333(e) (1), prohibits knowingly distributing, or possessing with the intent to distribute, hGH for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services (HHS) under section 505 of the FDCA (21 U.S.C. § 355) and pursuant to the order of a physician. The Secretary of HHS has not authorized, for example, any hGH use for anti-aging, bodybuilding, or athletic enhancement. Thus, distributing, or possessing with the intent to distribute, hGH for these uses or any other unapproved use violates section 303(e) (1) of the FDCA. With regard to the penalties chapter of the FDCA, section 333 (e) states:^[77]

- (1) Except as provided in paragraph (2), whoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under section 505 and pursuant to the order of a physician, is guilty of an offense punishable by not more than 5 years in prison, such fines as are authorized by title 18, or both.
- (2) Whoever commits any offense set forth in paragraph (1) and such offense involves an individual under 18 years of age is punishable by not more than 10 years imprisonment, such fines as are authorized by title 18, or both.
- (3) Any conviction for a violation of paragraphs (1) and (2) of this subsection shall be considered a felony violation of the Controlled Substances Act for the purposes of forfeiture under section 413 of such Act.
- (4) As used in this subsection the term 'human growth hormone' means somatrem, somatotropin, or an analogue of either of them.
- (5) The Drug Enforcement Administration is authorized to investigate offenses punishable by this subsection.

medicine. Furthermore, such redefinition is deceptive and does not meet the medico-legal definition of GHD. In fact, GHD is a very rare syndrome, occurring at a rate of about 1–3 adults out of 10,000.^[79] It is usually due to a cancer of the pituitary gland or surgical and/or radiation of the tumour leading to the pituitary gland's inability to adequately respond to hypothalamic stimulation. Thus, the legal diagnosis of GHD mirrors what endocrinologists regard as appropriate criteria for accurately making the diagnosis of GHD.

In response to misleading claims of GHD, the FDA recently made the labelling that accompanies the various US brands of hGH unambiguously clear about how a diagnosis of GHD must be made to legally justify the prescribing and distribution of hGH for this diagnosis. For example, the required diagnostic criteria that appear in the 2008 labelling for Humatrope are shown in Table 4^[80] (and, this labelling has been adopted for all of the other hGH brands that have approval for adult use as well).

Note that in this labelling, there is no ambiguity or doubt that a provocative (otherwise called a stimulation) test is required to make a diagnosis of GHD, except in the rare case (4–5 per 10 000 adults) of panhypopituitarism^[81] or an inborn hGH deficiency. A subnormal response to the standard hGH stimulation test is a peak hGH level of less than 5.0 ng/L. Anti-aging and other clinics distributing hGH for anti-aging or athletic uses would not, in general, perform such a test because in almost all cases the test result would not support the legal distribution of hGH.

Insulin-like growth factor (IGF-1) levels

Some doctors attempt to claim a diagnosis of GHD based upon IGF-1 levels without properly proving a diagnosis of GHD as out-

Table 4. Required diagnostic criteria for distribution of growth hormone for adult growth hormone deficiency that appear in package labelling for growth hormone (example comes from Humatrope, manufactured by Eli Lilly)

Humatrope is indicated for the replacement of endogenous GH in adults with GH deficiency who meet either of the following two criteria:

Adult-Onset (AO): Patients who have GH deficiency, either alone or associated with multiple hormone deficiencies (hypopituitarism), as a result of pituitary disease, hypothalamic disease, surgery, radiation therapy, or trauma; or

Childhood-Onset (CO): Patients who were GH deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes.

Patients who were treated with somatropin for GH deficiency in childhood and whose epiphyses are closed should be re-evaluated before continuation of somatropin therapy at the reduced dose level recommended for GH deficient adults.

According to current standards, confirmation of the diagnosis of adult GH deficiency in both groups involves an appropriate GH provocative test with two exceptions: (1) patients with multiple other pituitary hormone deficiencies due to organic disease; and (2) patients with congenital/genetic GH deficiency.'

lined above, which, in my opinion, is deceptive, inaccurate^[82] and also medically unethical and unprofessional. It is worth noting that more than 99% of adults would not meet the FDA's and American Association of Clinical Endocrinologists^[68] diagnostic criteria for GHD.^[83] Measurement of IGF-1 levels in older adults, when demonstrated to be lower than that of young adults, does not constitute a scientific^[68,84] or legally^[11] acceptable diagnosis of GHD.

Other pertinent federal and state laws

A number of states have their own statutes that specifically prohibit prescribing and distribution of hGH for non-medical uses, closely mirroring federal law. These are listed in Table 5.

Compounding

Various compounding pharmacies combine hGH with other substances such as vitamin B12, perhaps with the intent of skirting the law by indicating that the compounded drug is not hGH per se and therefore can be legally provided to the client. It is clear, however, given various alerts published by the FDA, that the FDA considers distribution of compounded hGH as distribution of an unapproved drug.^[72]

Violating federal trade laws

Common marketing practices regarding hGH and related products are probably illegal. In a recent case brought before the US District Court by the Federal Trade Commission (FTC) regarding a defendant selling products that claimed to contain hGH, the FTC outlined several claims that illustrate findings that can lead to fines and disciplinary action:^[85]

- 'The dissemination of false advertisements for the purpose of inducing the purchase of a drug or device pursuant to 15 USC § 52(a) is an unfair or deceptive practice within the meaning of 15 USC § 45(a).'
- 'The defendant deceptively promotes and sells hGH products with claims that are wholly false and cannot be substantiated.'
- 'The defendant's claims are false and cannot be substantiated with competent scientific evidence.'

Table 5. States with laws that specifically address growth hormone distribution

Arizona: Arizona Revised Statute, ARS 32-1996E states 'A person who dispenses human growth hormone in violation of this chapter is guilty of a class 6 felony.' The chapter being referenced by this statute subsection is chapter 18, title 32.

Colorado: Colorado classifies hGH as an anabolic steroid and thus the laws under the state's Uniform Controlled Substances Act of 1992 [C.R.S. § 18-18-102] apply to hGH.

Florida: Under 458.331 of the Florida statutes: "ee) Prescribing, ordering, dispensing, administering, supplying, selling, or giving growth hormones, testosterone or its analogs, human chorionic gonadotropin (HCG), or other hormones for the purpose of muscle building or to enhance athletic performance. For the purposes of this subsection, the term "muscle building" does not include the treatment of injured muscle. A prescription written for the drug products listed above may be dispensed by the pharmacist with the presumption that the prescription is for legitimate medical use."

Idaho: Idaho classifies hGH as a schedule III controlled substance, similar to anabolic steroids, under Idaho Code § 37-2709

Illinois: Under this state's Food, Drug, and Cosmetic Act, Chapter 410, § 410 ILCS 620/3.22, it is a criminal offense to distribute hGH for anything but medical uses approved by the US Secretary of Health and Human Services.

Kansas: According to Statute 65-2837 (b), unprofessional conduct shall include: " (28) Prescribing, dispensing, administering or distributing an anabolic steroid or human growth hormone for other than a valid medical purpose. Bodybuilding, muscle enhancement or increasing muscle bulk or strength through the use of an anabolic steroid or human growth hormone by a person who is in good health is not a valid medical purpose."

Massachusetts: This state lists all prescription drugs (including growth hormone) as controlled substances

Maine: This state lists all prescription drugs (including growth hormone) as controlled substances.

Minnesota: Under Minnesota Statutes Health Code, Chapter 152, Drugs, controlled substances, Minnesota Statutes § 152.02, hGH is classified as an anabolic steroid and therefore a schedule IV substance.

Oklahoma: 'A licensed practitioner. . . shall not prescribe, dispense, deliver or administer an anabolic steroid or human growth hormone. . . except for a valid medical purpose. A valid medical purpose for the use of anabolic steroids or human growth hormones shall not include bodybuilding, muscle enhancement or increasing muscle bulk or strength of a person who is in good health.' [63 Okl. St. § 2-312.1]

Oregon: Oregon classifies hGH as a controlled substance.

Rhode Island: Rhode Island classifies hGH as a controlled substance, schedule III drug. Under Rhode Island General Laws § 21-28-4.01 (E): 'It shall be unlawful for a practitioner to prescribe, order, distribute, supply or sell an anabolic steroid or human growth hormone for (i) enhancing performance in exercise, sport, or game, or (ii) hormonal manipulation intended to increase muscle mass, strength or weight without a medical necessity. Any person who violates this subsection is guilty of a misdemeanor and upon conviction may be imprisoned for not more than 6 months or a fine of not more than \$1,000 or both.'

Washington: Washington state law classifies human growth hormone as an anabolic steroid, under RCW 69.41.300. RCW 69.41.320 in turn states: "(1)(a) A practitioner shall not prescribe, administer, or dispense steroids, as defined in RCW 69.41.300, or any form of autotransfusion for the purpose of manipulating hormones to increase muscle mass, strength, or weight, or for the purpose of enhancing athletic ability, without a medical necessity to do so. (b) A person violating this subsection is guilty of a gross misdemeanor and is subject to disciplinary action under RCW 18.130.180."

West Virginia: hGH is classified as a class III substance.

Sample of compounding pharmacies and anti-aging, age management, longevity, rejuvenation or wellness clinics advertising growth hormone on the internet

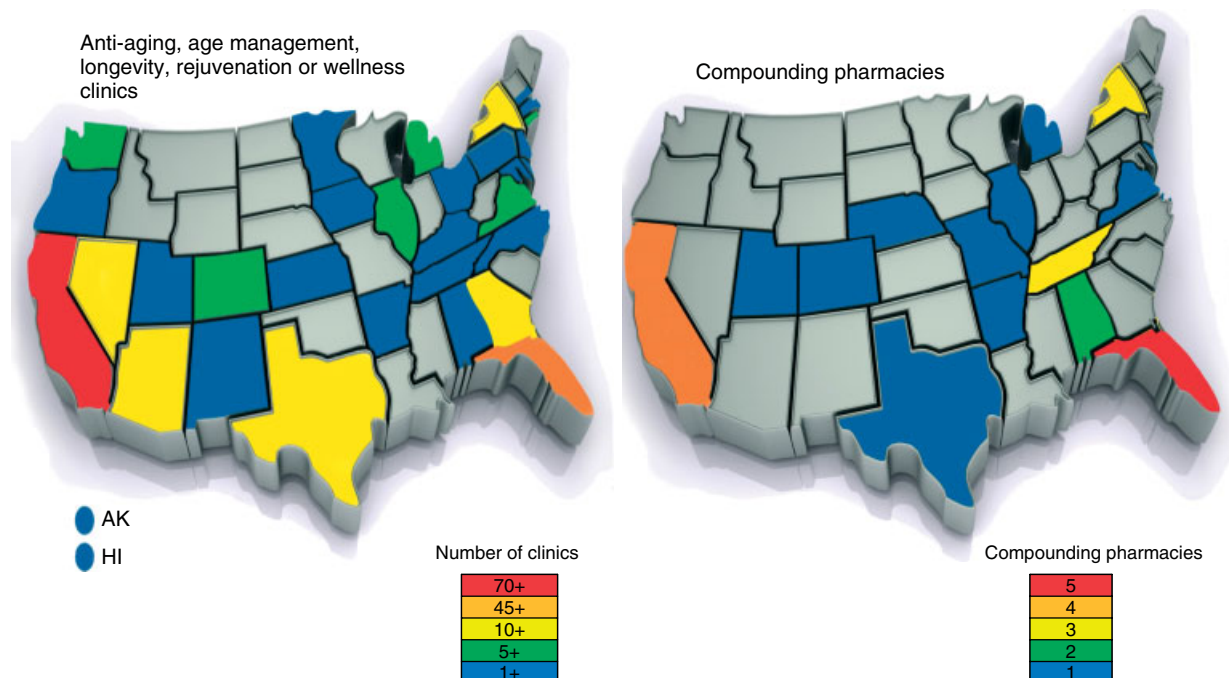


Figure 1. A guestimated 10% sample of compounding pharmacies (n = 26) and anti-aging, age-management, longevity, rejuvenation and wellness clinics (n = 276) advertising that they provide growth hormone. Note the high concentration of clinics in California, Nevada, Texas, Arizona and Florida.^[1]

Illegal and medically inappropriate distribution of hGH

Since 1990, networks of compounding pharmacies, anti-aging, age-management and other clinics, and physicians have developed a huge hGH business.^[64] The distribution network involves weight-training enthusiasts, anti-aging medicine entrepreneurs and those who have fallen victim to hGH replacement scams. My own research has found websites for 279 anti-aging or other clinics that advertise hGH treatment and 26 pharmacies throughout the US that distribute the drug to clinics or sometimes directly to users (see Figure 1). This is probably only a fraction of the total number of clinics and pharmacies distributing hGH for non-medical uses.^[1]

Human Growth Hormone Distribution in the U.S.

Recent high-profile cases have revealed clinics and compounding pharmacies violating the law with regard to the distribution of hGH. In 2007, Pfizer Pharmaceuticals was fined \$34 million for promoting hGH as an anti-aging and athletic-enhancing intervention.^[86] Specialty Services Distribution, Inc. was fined \$10 million for distributing hGH for athletic enhancement, cosmetic, or anti-aging uses.^[87] The FDA, DEA, and FBI conducted crackdowns (Operation Phony Pharm^[88] and Operation Raw Deal^[89]) on national and international trafficking in AAS and hGH. Operation 'Which Doctor' led to the prosecution of doctors being paid by pharmacies to write prescriptions for hGH without having ever seen the patients.^[90] The cash-only business of web sites or clinics working closely together with compounding pharmacies can result in the generation of huge profits.^[3,24,91–93] Despite these government actions, the

marketing and selling of hGH remains pervasive and staunchly defended by some within the anti-aging industry.

As an illustration of how profitable illegal sales of hGH have become, consider the recent example of Lowen's Compounding Pharmacy, which was investigated by the New York State Bureau of Narcotic Enforcement. The investigation revealed that the pharmacy would purchase 25 g of imported hGH for \$75 000 and convert each gram into 3000 IUs of hGH. It would then sell the drug for \$6 to \$18 per IU (a weekly regimen for a single patient is 2–19 IU) netting a profit of \$375 000 to \$1.34 million dollars.^[94] Narcotics officials ultimately seized 90 g of hGH powder worth \$7.2 million, including a shipment destined for The Health and Rejuvenation Center, an anti-aging clinic in Palm Beach Gardens, Florida.^[3]

An important feature of hGH distribution for anti-aging and body building is that the vast majority of users pay cash for the drug. As a result of these cash-only transactions and the fact that hGH is often misbranded (for example, illegally imported or made into a 'new drug' by combining hGH with another compound),^[72] the actual number of people receiving hGH as part of an anti-aging or body building regimen is likely to be much higher than a previous estimate of 30 000 users.^[92] Another consequence of a cash-only business is that government or insurance agencies cannot detect or monitor adverse events. People who might have experienced side effects might simply stop taking the drug and end their relationship with the web site or clinic without reporting the problem, especially when the side effects are reversible. If hGH caused more severe health consequences, including cancer and death, there is little incentive for clients to pursue legal action when causation is difficult to prove, or because clients are often required to sign contracts that supposedly absolve the provider of any potential wrong-

Table 6. Suggested additional considerations for greater fines and jail time (otherwise known as 'level enhancements')

1. Engaging in monetary transactions over \$10 000 per patient per year.
2. Physical or mental harm to a patient resulting from illegally distributed growth hormone.
3. Contracting with a person to provide a testimonial, either public or private.
4. Receiving money or gifts of any form from a distributor of what will ultimately be illegally distributed growth hormone in exchange for a patient's or client's purchase of that growth hormone.
5. Providing money or gifts to others who refer patients or clients that ultimately receive illegally distributed growth hormone.
6. Inadequate record keeping, including the omission of major components of a medical record such as history of present illness, physical examination, assessment and plan, laboratory results, and/or medical justification for the administration of growth hormone.
7. No intent by the physician to see the patient again, once they have received illegally distributed growth hormone.
8. Never seeing the patient.
9. Interstate commerce (e.g. mailing illegally distributed growth hormone to out-of-state clients or patients).
10. Two-level enhancement for creating a reckless risk of bodily injury to clients or patients. Increasingly greater levels for, respectively, actual reversible harm, permanent harm, or death.
11. Two-level enhancement for illegally distributing growth hormone to 10–49 patients within a single year and a three-level enhancement for doing so for 50–99 patients and a four-level enhancement in the case of > 100 patients in a single year.

doing. Finally, there is an explicit disincentive for at least some anti-aging practitioners to report adverse experiences with hGH.

Human growth hormone and AAS are no longer distributed and sold to users in back alleys and locker rooms. The black market for extra doses of hGH sold by sufferers of AIDS wasting syndrome is no longer necessary. Opulent anti-aging clinics and Beverly Hills doctors appear on television shows such as 60 Minutes professing the health enhancing wonders of hGH. With no medical credentials, Susanne Somers has become an anti-aging industry spokesperson proclaiming the wonders of hormones including hGH on *Oprah!* and at anti-aging conventions.^[95] There are also at least hundreds of websites selling hGH, many without ever arranging for a physician to see the patient and some of which pay physicians to write prescriptions without ever seeing or even speaking with the patient.^[96]

What Should be Done?

A great deal of attention has been paid to professional athletes abusing AAS and hGH to enhance their performance unfairly. However, the most important players in this situation are the doctors and the rest of the distribution chain, who are making millions of dollars at the often times physical and financial expense of their far-too trusting patients. Because of sophisticated, deceptive and widespread marketing practices and the influence a doctor can wield, users become the victims while the co-conspirators of AAS and hGH distribution rings are the perpetrators. A number of doctors, clinics, a pharmaceutical

company and compounding pharmacies have been prosecuted and/or indicted and an up-to-date list with specific details can be found at the website: <http://www.hghwatch.com>.

This new environment for distributing growth hormone therefore merits a number of special considerations:

- Androgenic anabolic steroids and hGH are increasingly abused drugs. The prevalence and severity of the medical and financial consequences of this abuse are likely greatly underestimated. Policy makers need to devote adequate resources via the National Institute of Drug Abuse and the National Institute of Justice to much better quantify and understand the scope of this public health threat.
- Federal and State agencies need an aggressive mandate and adequate funding to investigate and prosecute the distribution chain from the top down.
- Numerous clinics and websites market their services, including hGH 'replacement', on the Internet and at times via other media such as newsletter advertisements, radio and magazine features. Under these circumstances, prosecutors should consider §2D1.1(b)(5): 'Distribution of a controlled substance through mass-marketing by means of an interactive computer service leads to a two-level-enhancement.'^[97] Also pertaining to such advertising is 21 U.S.C. § 843(b): §2D1.6. Use of Communication Facility in Committing Drug Offense; Attempt or Conspiracy.
- Given the brazen attitudes of those who openly and deceptively market hGH for anti-aging, body-building or other non-approved uses, and make it so easy for patients to obtain the drug by providing free-standing clinics, I suggest that physicians and others who illegally distribute at least AAS (which are controlled substances) out of offices or clinics be regarded as managing a drug establishment. For example, in §2D1.8. Renting or Managing a Drug Establishment; Attempt or Conspiracy (*Statutory Provision: 21 U.S.C. § 856*), per the US Sentencing Commission's guidelines, 'This section covers the offense of knowingly opening, maintaining, managing, or controlling any building, room, or enclosure for the purpose of manufacturing, distributing, storing, or using a controlled substance contrary to law (e.g., a 'crack house').' The result would be additional fines and jail time. In the case of clinic chains, where an offender owns and manages multiple clinics, additional fines and jail time would be indicated.

Summary

Just the name 'growth hormone' invokes visions of the fountain of youth. Thus, with deceptive marketing, illegal and dangerous hGH distribution has become pervasive. Many people have been misled into believing in the purported magical powers of hGH, whether they be anti-aging, body building or injury repairing. Profits from the sale of hGH, particularly at the level of secondary wholesalers and compounding pharmacies rival those seen in the crack cocaine trade. For up-to-date details, visit the website, <http://www.hghwatch.com>.

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