INTEGRATIVE MEDICINE FOR ANTI-AGING e-Journal™

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Anti-Aging Industry Responds to JAMA HGH Article

By Jeff Morris

An article in the October 26 issue of the *Journal of the American Medical Association* has stirred up a huge amount of discussion and controversy in the anti-aging community. The article, “Provision or

Distribution of Growth Hormone for 'Antiaging'- Clinical and Legal Issues" by Thomas T. Perls, M.D., MPH, Neal R. Reisman, M.D., JD, FACS, and S. Jay Olshansky, Ph.D., appears in JAMA, Vol. 294 (16), pp. 2086-2090.

The article claims that because of 1988 and 1990 amendments to the Food, Drug and Cosmetic Act, off-label distribution or provision of human growth hormone (HGH) to treat aging or age-associated illnesses is illegal in the United States. The findings were peer-reviewed by independent experts and by *JAMA's* legal counsel. According to co-author Olshansky, professor of epidemiology at the University of Illinois at Chicago School of Public Health, "Off-label use for many drugs is a normal and accepted practice in medicine, but that is not true for growth hormone. According to laws instituted by Congress more than 10 years ago, HGH can only be distributed for indications specifically authorized by the Secretary of Health and Human Services, and aging and its related disorders are not among them. The use of HGH as an alleged anti-aging intervention is a major public health concern not just because it is illegal, but also because its provision for anti-aging is not supported by science and it is potentially harmful."

Co-author Perls, director of the New England Centenarian Study at Boston Medical Center and associate professor of medicine at Boston University School of Medicine, said that "there is no evidence that HGH administration stops or reverses aging…on the contrary, responsibly conducted and peer-reviewed science indicates that HGH could in fact accelerate aging and shorten lifespan. It is associated with very high rates of serious adverse effects, and long-term use could increase one's risk of cancer." Dr. Olshansky told United Press International, "Initial clinical trials conducted indicate HGH might cause significant problems, including diabetes, carpel tunnel syndrome and an elevated risk of cancer. In what could be the greatest irony of all for those taking the compound as an anti-aging remedy, animal studies suggest it actually may shorten lifespan." HGH has yet to be studied in significant long-term trials to determine whether it actually has anti-aging properties, said Dr. Olshansky, adding, "Maybe there is a place for growth hormone in the future to influence age-related problems, but we won't know that until the clinical trials are conducted."

In an October 28 *Medscape* article, Laurie Barclay, M.D. reported that when sold through Web sites, HGH may be expensive; formulations including tablets, sprays, or injectables may range in cost from $200 to $1,000 monthly. The Federal Trade Commission estimated that one Internet site generated more than $70 million in sales of pills and sprays purported to contain GH or to stimulate its production. In 2004, U.S. sales of GH totaled $622 million for nearly 213,000 prescriptions, not including Web site sales. Worldwide annual sales of GH are estimated at $1.5 to $2 billion. "Millions of dollars in profits are made off of

useless pills and sprays like these," Dr. Perls told *Medscape*. "Pills with GH are destroyed in the stomach, and because the molecule is too large to enter the blood stream via sublingual and nasal sprays, such products have absolutely no biological effect. You might as well be paying hundreds of dollars for sand and water."

The section of the law cited by the *JAMA* article states that, "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 ... is guilty of an offense punishable by not more than 5 years in prison." The law also provides for imposition of fines. In an October 25 Forbes.com article, Robert Langreth reported that Dr. Perls came across the law while surfing the Internet a few years ago and recalled that he “was blown away.” After having confirmed details of the law with the FDA, it took Dr. Perls and his co-authors over a year to get the study published, wrote Langreth, because some reviewers couldn't believe their conclusions. Dr. Olshansky told UPI that the finding was so shocking, the experts who reviewed the article for accuracy before it was published didn't believe it at first. “One of them actually said, ‘This can't be right,’” said Dr. Olshansky.

Distributing HGH via the Internet is in violation of another law, reported *Medscape*, because the Food, Drug and Cosmetic Act requires that GH must be prescribed by a physician who, "'based upon an individualized determination of a proper course of treatment, authorizes the drug's distribution to a patient under his supervision.'" Numerous Web sites reviewed by the authors showed either no evidence of such supervision, or purported supervision in which the supervising physician never met the patient. Distributors may also be in violation of laws against false advertising or deceptive promotion.

According to Forbes.com, exactly how much growth hormone is used for anti-aging and other off-label purposes is unclear, but one 2003 *New England Journal of Medicine* paper estimated that as much as one-third of all growth hormone prescriptions are for off-label uses. Overall, 74% of growth hormone prescriptions went to adults, the new *JAMA* study found, despite the fact that only one in 10,000 per year suffer from a deficiency of the hormone. Companies that sell growth hormone, reported Forbes, include Pfizer, biotech stalwart Genentech, and Swiss biotech firm Serono:

> Pfizer says that, in 2003, it stopped selling to clinics it suspected might be using growth hormone for antiaging purposes and ended all sales of growth hormone directly to physicians. The vast majority of its sales are now for children with short stature. A Genentech spokeswoman said that it "tightly controlled" growth hormone distribution to prevent misuse, requiring distributors to verify a proper indication before sending out the drug. A spokesman for drug distributor McKesson said that the company only distributes growth hormone to pharmacies and other parties that have

> been preapproved by manufacturers. Serono stated that it obeys "applicable laws."

Forbes quoted Dr. Perls as saying, "There is no such thing as legal off-label use of this drug," and Dr. Olshansky was reported to say that the law "has rarely been enforced, but my guess is after tomorrow [October 26] that is going to change. Probably thousands of physicians and others have been distributing it [for antiaging purposes] without knowing it is illegal to do so. Physicians who are illegally administering growth hormone should stop."

Factoring into the discussion is the continuing contentious and litigious relationship between Drs. Perls and Olshansky and Drs. Ronald Klatz and Robert Goldman of the American Academy of Anti-Aging Medicine (A4M). A4M has been among the leading proponents of HGH use, and Drs. Perls and Olshansky have disclosed that they are defendants in a lawsuit brought against them by the A4M and others. (By way of full disclosure, we should mention that Drs. Klatz and Goldman were formerly associated with the anti-aging conference run by PBI Media Holdings, Inc. (formerly known as Primedia), publisher of this *e-Journal*. Drs. Perls and Olshansky do not and never have had any association with the publisher of this journal or owners of the *Integrative Medicine for Anti-Aging Conference*. They, along with Dr. Reisman, have disclosed various financial arrangements with The American Federation of Aging Research, the Alliance for Aging Research, and/or the National Institute on Aging and Boston University School of Medicine's Evans Medical Foundation in Massachusetts.) A request for comment sent by the e-Journal to Dr. Klatz went unanswered. However, in a preliminary response to the JAMA article issued on October 28 to its members, A4M stated:

> We have assembled international scientific and legal teams to prepare a response to JAMA as a letter to the editor, as well as press release responses to this poor attempt at damaging the profession. No efforts will be spared in defending the rights of our member physicians. It is shocking that this paper ever passed peer review in such a prestigious publication as JAMA. This article will now be used as a weapon by those with an agenda to damage the rights of physicians to provide high level care to their patients. We are also assembling a legal team with the assistance of the insurance industry to protect physicians against untoward prosecution by state medical boards and other agencies and protect your right to practice advanced preventative medicine for the benefit of your patients.

The A4M statement also claimed that 21 U.S.C. § 333(e), the federal statute that criminalizes the unlawful distribution of human growth hormone, must be analyzed in its historical context and legislative intent:

> The statute, passed as part of the Anti-Drug Abuse Act of 1988, originally applied to anabolic steroids, not hGH. It was enacted at a time when concerns over steroids in sports had reached national consciousness (coincidentally, enacted the same year that Canadian sprinter Ben Johnson tested positive for steroids), and was intended to combat steroid

> trafficking to cheating athletes by coaches, trainers and non physicians. When, in 1990, Congress took a more aggressive approach to anabolic steroids by passing a new law (the Anabolic Steroid Control Act of 1990) to elevate them to the status of controlled substances, concerns over the use of hGH in sports resulted in hGH being inserted to replace anabolic steroids in 21 U.S.C. § 333(e).

In his comments to UPI, Dr. Olshansky said that his team had initiated an effort more than three years ago to inform those in the HGH industry of the legal issues pertaining to the practice of dispensing the drug for reversing aging, and had unexpectedly stumbled across the language added in 1988 and 1990 that "basically…made it crystal clear that it is illegal to use growth hormone as an anti-aging intervention." In its response, A4M says:

> This is a very odd statement, considering the fact that when the law was written there were no anti-aging doctors or profession in existence. In fact the profession did not even birth until 5 years after it was first put in place in 1988. Such bias and clear agenda to harm a large population of dedicated physicians should have no place in a publication like JAMA.

One thing that is clear is that this same dispute has been ongoing for years. In an “Expert Roundtable” that appeared in the May-June 2003 issue of *Natural Health*, the topic “Are anti-aging hormones safe?” was addressed by some of these same players. The following exchange took place after the moderator posed the question, “Dr. Klatz, you've said that aging as we know it can be avoided. Are you saying we could all live to be 120?”

> Klatz: No, I'm not saying that at all. What I'm saying is that aging as we know it is really a constellation of degenerative processes that lead to chronic disease and finally to death.... You can ... prevent and treat the conditions of aging, such as osteoporosis, Alzheimer's disease, macular degeneration, and cognitive decline [using diagnostic techniques, drugs, and other therapies]. And by treating them, you change what you can expect to look like at age 50 ... or 90. By improving the quality of life and avoiding things that are going to kill you, such as heart disease and cancer, you live longer.
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> Perls: I actually also agree that we should do everything we can to allow people to maximize their time of good health. And whatever therapies can do that should be applauded. But they need to be proven and safe. We already have ways to maximize health that are not potentially dangerous: strength training, not smoking, and [following a sensible] diet. To me, those are the way to go. They require a lot of work. But if we can show that a healthy old age is worth fighting for, I'm hoping that people will do the work.
>
> I think it's important to not lead people down a path of [believing that you can] get injected with this stuff and get to very old age in good health, because then people ignore some of these other things that they really should be doing.... I think that media campaigns, including the kind of books that Dr. Klatz puts out, deliver only one part of that message, and that is to take HGH. People don't hear about these other things.... I also think that the anti-aging industry uses marketing tools to try and equate its

> credibility with those of us in academia, whether it be calling things the American Academy of This, or the National Academy of That.
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> Klatz: I find it reprehensible that Dr. Perls and his ilk in the gerontological establishment try to diminish the message of anti-aging medicine by their false attacks upon our credibility and our credentials, which are excellent. We have a society of 11,500 physicians and scientists, many of whom are members of universities, who hold academic positions, including myself, who are well published, who have all the credentials and accolades that Dr. Perls and his ilk have. However, our members have a different position, that aging is a treatable condition, which is in conflict with the gerontological establishment that says, "Just grow old and die."
>
> Perls: Dr. Klatz has misrepresented the gerontological community. We are advocates of older people. We strive to improve their quality of life and minimize the diseases associated with aging. My problem is that the anti-aging community often takes inaccurate views of aging, thus biasing society against older people.

A hotbed of discussion on the HGH issue since release of the *JAMA* article has been the Gerontology Research Group (GRG), an online international discussion group based at UCLA and consisting of demographers, epidemiologists, physicians, and scientists focusing on longevity. The discussion illustrates that far from being a black-and-white issue, off-label use of HGH is a topic that has many shades of gray. On October 26, L. Stephen Coles, M.D., Ph.D., former medical editor of the *e-Journal*, posted these comments:

> Profs. Tom Perls, Neal Reisman, and Jay Olshansky claim the routine off-label use of hGH (outside the indication-scope of pediatric dwarfism, adult pituitary cancer, and AIDS wasting) is illegal and distributors can be punished under the law. Enforcement is to be done by the DEA (the same agency charged with responsibility to protect Americans against all sorts of addictive drugs). Remember that many of the retail Internet-based suppliers live off-shore, so the FBI/FDA can't get to them directly.
>
> I, personally, do not agree with Tom's statement of concern about hGH increasing the risk of cancer (we have had several lectures on this topic by pituitary-endocrine specialists here at UCLA, and there is no evidence for hGH promoting cancer that we know of; indeed, to the contrary, some patients with occult cancer were subsequently cured of their cancer following administration of hGH for other reasons, possibly by stimulating a tired immune system to increase its surveillance for cancer in the body), although many other things that Tom says are certainly true. However, the difference between marketing alleged oral secretagogues of hGH and IM injections of true hGH itself are quite different, and this needs to be articulated much more clearly before "throwing out the baby with the bath water." IGF-1 was approved by the FDA for even more specialized indications starting next year (2006), and that taken by itself may have cancer-promoting side-effects. This remains to be seen, however, and don't forget that IGF-1 is the major metabolic by-product of hGH in the liver.
>
> Also, we don't understand how it can be that older patients feel so much better on low-doses of hGH (maybe they're burning through their residual

> life-expectation at a faster rate?), but no one has factored in the rodent data from Prof. Richard Miller, M.D, Ph.D.'s Lab in Ann Arbor, MI that mGH-knockout mice live longer than wild-type mice into human clinical-trial data.

Dr. Coles also alluded to the litigation initiated by Drs. Klatz and Goldman against Drs. Perls and Olshansky, and provided this article that—coincidentally or not—appeared in the October 25 issue of *The Scientist:*

> **Aging Researchers Sued: Osteopaths Ask for US$120 Million After Being Criticized; Experts Question Limits of Scientific Debate**
> By Adam Marcus, *The Scientist*
>
> Two aging-science researchers are suing two other academics for $120 million, arguing that the defendants have damaged their reputation by accusing them of making inflated claims about the efficacy of anti-aging therapies they promote, a case that raises questions about when academic debate "crosses a line." The Plaintiffs in the lawsuit are Ronald M. Klatz and Robert M. Goldman, a pair of osteopaths who founded the American Academy of Anti-Aging Medicine (A4M) in Chicago, IL. The doctors, who also earned MD degrees in Belize, argue that their critics have defamed them as scientists and interfered with their business relationships. While A4M appears to be a clearinghouse of aging research and information, visitors to its website can quickly arrive at commercial sponsor pages selling all manner of products and services, many of questionable efficacy, according to some scientists. The two plaintiffs also have a company called Medical Development Management that sells anti-aging products, according to published reports…A4M's website emphasizes the anti-aging powers of several hormone treatments, including DHEA and human Growth Hormone.

The defendants in the suit are, of course, Drs. Olshansky and Perls. Neither they nor A4M would discuss the particulars of the suit, nor would they address which scientific issues are being contested, said the article. *The Scientist* continued:

> While hardly the only scientists to throw darts at perceived hype, Olshansky and Perls have been particularly aggressive at pointing it out -- a crusade motivated by what they believe is exaggeration's menace to legitimate aging science…They have mocked A4M directly, including presenting the group with a fake "Silver Fleece" award for the "most outrageous or exaggerated claims about slowing or reversing aging."

The article quoted Daniel Perry, Executive Director of the Washington, DC-based Alliance for Aging Research, as saying he does “not hold much stock in A4M's findings,” and hopes the lawsuit doesn’t “give the organization more attention than it deserves.” But it also quoted Terry T. Fulmer, Dean of the New York University College of Nursing and President of the Gerontological Society of America, who said while she was not familiar with the lawsuit, she did know the people on both sides of the case, and rejects “the notion that groups like A4M are dangerous to the field of aging research…People disagree, and that's how we move the science ahead.” Still, *The Scientist* reported, “other aging researchers were reluctant to comment on the legal dispute,

suggesting that the suit may already be having a chilling effect." Said one past president of GSA, "I don't want to get sued."

Karlis Ullis, M.D. (medical director of the Sports Medicine and Anti-Aging Medical Group in Santa Monica, CA, faculty member of the UCLA School of Medicine, and a member of the scientific advisory board of LifeExtension Foundation) noted:

> I think it is no small coincidence that Perls and Olshansky and some others were sued by Klatz and Goldman of A4M for around $[120] million for defamation for having publicly received the [Silver] Fleece Award from them, and the publication of this most recent JAMA article…Interesting in the letter from the FDA from Steven D. Silverman to Tom Perls of Oct 4th 2004 was that Silverman used HGH as coined by Klatz in his book "Grow Young With HGH" in about 1997 and not the correct scientific terminology of "recombinant hGH".

Dr. Ullis was referring to information contained in the news stories about the *JAMA* article, which quoted Steven Silverman, director of FDA's Division of New Drugs and Labeling Compliance, as saying in a letter to Olshansky's team, "We are also concerned with the improper distribution of HGH products." He was also reported to have said that the FDA has been actively enforcing the provision since it was enacted, and that the agency has sent letters to several companies dispensing HGH over the Internet as an anti-aging treatment, warning them they are in violation. Silverman also noted HGH can cause "serious side effects, including bone and joint problems, worsening diabetes and increased cholesterol levels and blood pressure."

Steven B. Harris, M.D. (also on the scientific advisory board of LifeExtension, as well as president and director of research at Critical Care Research and chief medical advisor to Alcor Life Extension Foundation) posted this to the GRG:

> Growth hormone is the ONLY pharmaceutical in the entire armamentarium which it's illegal to prescribe for an off-label use. Even DEA CONTROLLED substances are legal to prescribe for off-label uses, if you can convince your state medical board of your case. Adult ADHD was treated for years that way.
>
> Some of the history of this particular legislation would have [been] good to track down for the JAMA article-- the article would then presumably have been published faster, instead of taking a year in review because no sensible physician believed it. For this is not how the rest of the medical system works. We doctors know about scheduled drugs, and ethical pharmaceuticals, and off label use of drugs approved already for one use (which is generally legal).
>
> Basically, I think the whole thing stinks. I'm guessing it was done by some[one] at FDA pissed off about importation of hGH for body builders and the like, who didn't see a prayer of getting it formally DEA scheduled and controlled, like anabolic steroids. So they inserted this rider about permitted uses of hGH in the PENALTY clause of a bunch of FDA code about other matters, where it sits hidden, because it really doesn't belong

> there. Whoever heard of making something illegal, by hiding the language to that effect in the punishment and penalty lists for other related crimes??
>
> It does not pass the sniff test. I wish the JAMA legal council had pointed that out. Laws are not made to be hidden in odd sections of code where they don't belong, and then rarely enforced, except at somebody's bureaucratic pleasure. That's not how a free society is supposed to operate.
>
> I hope this is (now) uniformly enforced, and some respected and academic endocrinologist treating some kid with congenitally short stature syndrome without hGH deficiency (where there is now mixed evidence of efficacy, and no current label indication), is sentenced to prison.
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> Right before the FDA approves the stuff for this use, based on a new study.
>
> When your government determines for you, on penalty of long prison sentences, what is scientifically and medically correct, even on issues where reasonable people disagree on the science, your society is in big trouble. But we've been in that kind of trouble for a long time. As it is, the science is bought by the people with money, and those without it (the big money or the science it buys) are increasingly threatened with prison. That's fascism with the face of capitalism. It's enough to make you a Marxist.

In a GRG post replying to Dr. Harris, Dr. Olshansky provided an account of the *JAMA* article's history:

> The original version of this manuscript was more than double its current length, and it contained considerably more detail – including a discussion of the history and some of the rationale we could discern behind this legislation. However, due to severe space constraints at JAMA we had to remove those sections.
>
> By the way, the reason the review process took so long was because the editors and reviewers put this through several additional layers of external and internal review -- a far more detailed process than any other manuscript I've worked on. Naturally, we appreciated this because it finally convinced those skeptical of our conclusions that our interpretation was indeed correct. The editors and external reviewers at JAMA were very meticulous -- requiring that we (mostly Tom) spend an inordinate amount of time in the library doing background research. I'll talk to Tom and Neal about publishing the material previously removed -- that would certainly address many of your questions.
>
> The history behind this paper is also of interest. The idea began some 3-4 years ago at a conference run by Brian Kinney -- a brilliant scholar/plastic surgeon who has been running educational conferences for plastic surgeons. Tom and I were invited to several along with Len Hayflick and Neal. Neal is a lawyer/plastic surgeon who spent a considerable amount of time educating fellow plastic surgeons about the various ways that plastic surgeons entering into the anti-aging industry should be protecting themselves legally [that is correct, the origin of this paper was devoted to informing/protecting physicians in the anti-aging industry]. His

presentations were thoroughly researched and balanced -- I was immediately drawn to him and have since discovered he is an excellent scholar. Some of his presentations focused on legal issues associated with GH. Some 3+ years ago I invited him to draft one of the articles for our special issues of JG:BS (along with Tom) on the legal issues associated with GH. He did so and it was an excellent article. This JAMA manuscript is an outgrowth of that effort that began some 3+ years ago and our accidental discovery of the language that makes off-label use of GH illegal. So, to answer your question about the possible linkage between this paper and the suit -- there is none. They are unrelated. Hope this clarifies things.

S. Mitchell Harman, M.D., Ph.D., Director and President of Kronos Longevity Research Institute, posted this on October 27:

Whether off-label prescription of GH for "anti-aging" purposes is or is not against the law is almost irrelevant. The fact is that there are no good data supporting functional benefits or improved quality of life in the "somatopausal" population (as opposed to patients with adult GHD due to pituitary disease) even at the "high doses" of GH reported in the literature. Furthermore, the benefit of GH replacement even in elderly aGHD patients may be attenuated, and the risks increased. The likelihood that lower doses, adjusted to reduce adverse effects, would produce significant benefits is thus very low. In addition, while a relationship to cancer is highly speculative, most data come from studies of younger patients, who are less likely than elders to harbor pre-clinical cancers. The published statistical associations between prostate, breast, and colon cancers and circulating IGF-I levels are consistent across multiple studies, and therefore troubling. Finally, the work by Bartke, Brown-Borg, Miller and others showing changes consistent with premature aging and early mortality with excess GH and prolonged lifespan in GH-deficient and GH-insensitive dwarf rodents, while of uncertain relevance to human aging, should give us pause. These findings are certainly not consistent with the idea the GH is an "anti-aging" hormone.

Given all of the above, it is my contention that, legal or illegal, no conscientious, well-informed physician would prescribe GH for an otherwise healthy elderly patient. I reiterate that administration of hGH for treatment of the "somatopause" should be limited to properly controlled research studies.

Whether patients need the government's protection from their own folly and the ministrations of sometimes well-meaning, but misinformed, and in other cases, venal and fraudulent doctors is a matter of political philosophy. My own opinion is that, in matters of medicine, patients trust doctors and most do not have sufficient information to make informed medical decisions (that's why we go to medical school and train for several postgraduate years). Medicine needs to be regulated, because "caveat emptor" is inadequate in situations in which consumers cannot distinguish between true and false/misleading information.

Rashid A. Buttar, D.O., Medical Director of the Center for Advanced Medicine in Cornelius, NC, agreed with criticism of HGH use:

The use of paraentral recombinant HGH introduction is potentially dangerous, simply because it violates the negative inhibitory feed back loop vital for our physiology to maintain homeostasis. The use of any

> paraentral hormone induces a super physiological dynamic to occur. Most importantly with HGH, this will most often result in a disturbance of the hypothalamic-pituitary-adrenal axis and may potentially induce oncogenesis and contribute to a higher incidence of cancer secondary to increasing IGF-1 beyond physiological range and without the mitigation by somatostatin. I know that many on this list will again be outraged by this comment (and I'm sure I will loose a lot of sleep over that) but I treat cancer and NONE of my critics do. Ref: Journal of the National Cancer Institute, Vol 92, No 18, Sept 20, 2000, just as one major reference.
>
> I also find it very interesting that even the archaic conventional cancer literature ABOUNDS with using various strategies all revolving around the reduction of IGF-1 to achieve better efficacy of conventional chemotherapeutic agents such as tamoxifen for example. Ref: Nature, Cancer Update, April 2002, Research by Aleck Hercbergs at Cleveland Clinic Cancer Center, just as one recent reference.

Dr. Perls subsequently posted the following:

> Thought I'd weigh in here.
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> 1. I wrote an article on the tell-tale signs of quackery in general and in the anti-aging arena that was accepted by independent peer review in the J. Gerontology, 2004. It was while researching for that article in the previous year and a half, long before any law suit, that I discovered the amendments to the food drug and cosmetic act, and with the encouragement of Neil Reisman and Jay Olshansky, we felt this was of significant enough interest to further research (again before any lawsuit) along with having the opportunity to update the public on how little evidence there actually is for the utility of GH as an anti-aging treatment.
>
> 2. The legislative history behind those amendments is actually fascinating and indeed was requested by the JAMA reviewers. I wanted to provide this in the article however, the space limitations (which we were stretching-as is) prevented us from doing so. Many hours in the Boston College Law Library going over the congressional records with the help of some wonderful law librarians, basically reveals I believe that it was both the Senate's and the House's intentions (in separate Senate and HR Bills) to make GH as similar to anabolic steroids as possible in terms of restrictions on distribution and penalties. It seems to me that Congress did not want to put the restrictions of a controlled substance (anabolic steroids are a schedule III substance) on GH because of the disproportionate obstacles that would place on families who needed to obtain GH for their kids with the various syndromes that lead to short stature (renal failure, turner's, idopathic, prader willie etc). Thus the subcommittee instead imposed the restrictions and penalties outlined in the JAMA paper.

On October 26—the official release date of the *JAMA* article—Las Vegas-based Cenegenics Medical Institute was scheduled to hold a physician conference call on the topic, “Risk Associated with Prescribing hGH Obtained from Unregistered Manufacturers.” Given the events of the day, Cenegenics president John E. Adams spent much of the time discussing ramifications of the *JAMA* article. His basic message was, “We are in compliance at Cenegenics. What the *JAMA* paper concluded is that inappropriate prescriptions are being issued

over the Internet. The FDA is using the law appropriately to prosecute those using growth hormone inappropriately." Adams, who acknowledged that Cenegenics is associated with Primedia's conference, said that while Cenegenics is generally in agreement with the law, they do have a problem with the article "in the way they're expanding the law."

Dr. Alan Mintz, Cenegenics' chief medical officer and CEO, expanded on that point by telling us, "The article misstated the legal standard for prescribing hGH because a challenge test is not required to prescribe. Rather, if physicians have a legitimate, clinically based rationale for diagnosing a patient with hGH deficiency, the law does not restrict the physician's judgment in this respect." While concurring that *JAMA* is correct in alerting the world to the unscrupulous sale of HGH, Dr. Mintz added that (as also noted by Dr. Harris, above) the law restricts possession and sale to approved uses, which is different from any other drug on the market. The law, said Dr. Mintz, was originally passed because of the steroid problem, not the HGH problem—and, in fact, the GAO's report in 1990 could not identify any specific abuse of HGH. According to Dr. Mintz, "HGH, when properly used in deficient adults, alleviates symptoms that lead to increased premature cardiac morbidity and death, improves body composition, and improves overall well being. Many physicians in all types of settings—internal medicine, GPs, endocrinologists, and age management specialists among others—understand the benefit HGH can provide patients who are deficient. It would be unwise, contrary to patients' overall health and well-being, and even unethical for physicians to withhold treatment from patients when a drug is approved for a condition."

In an attempt to reassure physicians associated with Cenegenics about their legal status, Adams said, "We will be sending out a letter from our attorneys to those who've gone through training, in a week or two." Callers, however, were clearly concerned about the situation. "This makes me really nervous," said one. "Are we protected?" "Just to give you a little bit of assurance," replied Adams, "we had an exchange with one of the authors, Dr. Neil Reisman, today. Alan (Dr. Mintz) e-mailed him, 'Your article sure caused a stir.' Dr. Reisman got back to him within the hour: 'I am not and never was referring to Cenegenics, I know you are using these substances appropriately.' This article is going after these Internet marketers who are promoting use of growth hormone inappropriately," emphasized Adams. "It (HGH) is not a big percentage of our practice, and is only used in a small portion of applicable conditions. But I'm not the physician, I'm just the president of the company who is waiting for the opinion of the attorneys." According to Adams, "Dr. Mintz said this morning, 'this type of article will get rid of the clouds so you can see the sun.' And you know as well as I do, you can't just prescribe HGH; you have to go through a two-hour evaluation."

Dr. Mintz added, "I want to emphasize that this is really a good thing,

and I'm not just 'spinning'. There's no one more visible in the field of age management medicine than Cenegenics, and we've never shied away from the media. We respect the government, they're trying to do the right thing in policing this. We take the position that sound medicine is the way to stay away from trouble. This is going to serve us well and get us away from an atmosphere of suspicion and false claims." Still, just as the A4M lawsuit was said to have a chilling effect, so is, apparently, the *JAMA* article. When one caller asked, "Is it legal to advertise HGH as part of an anti-aging program? Can you say as an anti-aging physician that you offer HGH and testosterone?" Adams answered, "I would not." And when another requested that Adams ask Cenegenics' lawyers "whether you can use analogous terms, and say you're testing for somatopause?" Adams replied simply, "I would stay away from it."

In 2004, Ron Rothenberg, M.D., Clinical Professor, Family and Preventive Medicine, UC San Diego School of Medicine, and a member of the medical advisory board of LifeExtension Foundation, published a paper in A4M's Anti-Aging Therapeutics titled "Is Growth Hormone Replacement for Normal Aging Safe?" His conclusion was that, "given the state of scientific medical knowledge today, GH is safe." He continued:

> GHRT is associated with less morbidity and mortality, less cardiovascular disease, less inflammation, improvements in body composition, improvements in exercise capacity, and a better quality of life. In the words of Peter Sonksen: "GH is essential for normal adult life, and without it life expectancy is shortened, energy and vitality are reduced, and the quality of this life is impaired. The medical case for GH replacement is now proven beyond any reasonable medical and scientific doubt.

The *e-Journal* contacted Dr. Rothenberg for an opinion on the October 26 *JAMA* article. In reply, he copied us on the following letter that he sent to the editors of *JAMA* on October 30 (presented here without the footnotes contained in the original):

> In my opinion the discussion is confusing and at times inaccurate. The article lumps together web sites selling GH illegally without medical supervision, over the counter products which may or may not contain growth hormone and appropriately medically supervised treatment for Adult Growth Hormone Deficiency (AGHD).
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> There has been extensive documentation in the peer reviewed medical literature on the benefits and low risk profile of GHRT for AGHD.
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> There is an exponential decline in GH release after age 21 with a 50% decline every 7 years. As Savine Points out "Life without GH is poor in quantity and quality". At age 60 most adults have total 24 hour secretion rates indistinguishable from those of hypopitutitary patients with organic lesions in the pituitary gland. If mean IGF-1 of 300 is mean normal for 20-30 year old almost all over 40 have IGF-1 deficit." Hence when we treat AGHD we are treating a deficiency disease.

GHRT has been shown to improve quality of life, muscle strength and mobility, cognitive function, cardiovascular disease, osteoporosis, immune function, body composition, obesity and sarcopenia, fibromyalgia, Crohn's disease and other illness and quality of life issues.

The side effect profile often quoted from the Blackman and Harman studies do not apply to clinical treatment where low doses are used initially and doses are slowly, ramped up and decreased if side effects occur. Significant side effects are rarely seen in clinical practice. Also when the same total dose is divided daily over a week period instead of administering it 3 days a week of the minor side effects are produced. At any rate if side effects do occur they would disappear with cessation of treatment.

Some selected rodent studies are quoted which appear to demonstrate negative effects of GHRT. On the other hand, Khansi et al demonstrated that when mice are aged to senesce, survival and immune function was dramatically improved with GHRT. This is a very different situation from GH resistant mice where calorie restriction may confer longer lifespans.

In Besson et al's study GH deficiency is highly significantly ($p < .0001$) associated with decreased longevity in human siblings. Healthy Aging and longevity are related to GH/IGF-1 levels.

The association of cancer and GHRT has been extensively reviewed in the medical literature. This theoretical risk has been shown to be nonexistent. The preponderance of studies have shown that there is no evidence of increased risk of malignancy, recurrent or de novo.

In terms of diagnosis, stimulation tests have been a standard but clinical judgment still is a primary concept in medicine. It is important to note that many of the studies quoted that demonstrate benefits of GHRT do not have patient groups that have "failed" GH stimulation tests. Low IGF-1 is associated with failed stimulation tests as well. and urine testing may of additional value. If a patient shows sub-optimal IGF-1 and has the clinical phenotype of AGHD and is old enough to consider treatment, it is reasonable and helpful to the patient to treat this deficiency disease.

According to advice from legal counsel the intent of the legislation controlling GH is to avoid doping in sports. Nothing in the legislation dictates a physician's requirements on how to diagnose AGHD.

Our goal as physicians is of course to first do no harm and then to do what we can to improve quality of life; to maximize our patients' health and happiness. Treating AGHD is a step in this direction.

Dr. Richard Walker of the Society for Applied Research in Aging (SARA), who was chairing that society's organizational meeting in Tampa during the weekend of October 28, had invited Dr. Olshansky to speak. He said that the group enjoyed an open and frank discussion on many aspects of the GHRT controversy. "I think what's happened is that certain people have reacted emotionally to the *JAMA* article, resulting in their comments being irrelevant to the main issue," Dr. Walker told us. "For example, I believe that Dr. Klatz and other representatives of A4M have responded to this article by saying that the authors are trying to 'take away the rights of [anti-aging]

doctors'—those are silly comments that make no reasonable rebuttal or relevant counterclaims. They're just being belligerent and argumentative." Dr. Walker went on to say, "While the article may be construed by some as being discriminatory against doctors who practice anti-aging, the material presented in it is factual, albeit somewhat stilted. By that I mean it accurately presents regulatory guidelines for clinical use of HGH as published in the Code of Federal Regulations and correctly reports risks and side effects resulting from high dose HGH use. However, it fails to point out that the dosages used in GHRT are significantly lower and rarely produce untoward effects. In any event, the real issue is that the law clearly prohibits off label use of HGH except as specifically defined in certain types of childhood disorders. So in my mind, the real issue is for doctors who intend to use GHRT in treating their patients, to do so in compliance with the law."

"I think there are legitimate applications for HGH in opposing the maladaptive changes that affect the human body with advancing age," continued Dr. Walker. While the legal assumptions of the *JAMA* article are valid, Dr. Walker emphasized, "that doesn't mean a physician can't use HGH; he or she simply must comply with the law in doing so. The implications of the *JAMA* article are that elderly patients being given GHRT don't meet the criteria for HGH deficiency. That may or may not be true. However, since most doctors do not use a provocative test in establishing their diagnosis, there is no way of knowing. The reason they don't use it is because standard methods employ multiple blood samples drawn from indwelling cannulae for periods often approaching two hours. Since this type of test is not appropriate for routine clinical examinations, the answer is to devise a provocative test that has practical application. If one could create a test that was simple so as to be used with other criteria for diagnosing growth hormone deficiency, then doctors could legitimately prescribe and use HGH—not off label, but on label. It would promote compliance with the law and allow the doctor to practice according to his or her belief of what is best for the patient." Dr. Walker feels there is an appropriate way to solve this problem and says he is currently working on the procedure; it will be announced in the near future, so as to better help anti-aging practitioners comply with the law should they choose to use GHRT in their practice.

"There is a practical solution to the dilemma facing anti-aging physicians who want to use HGH as part of their treatment programs," concluded Dr. Walker. "They simply must show that the patients receiving GHRT meet the diagnostic criteria for HGH deficiency. I would really like to be a part of correcting the distortions of fact that are being bantered about; there's a lot of overblown rhetoric that is not productive, and only creates animosity. This seemingly insurmountable problem has a quite simple solution," he said.

The e-Journal *contacted the FDA for an official comment on the JAMA article, but at press time we were told by the Center for Drug Evaluations and Research that no comment was yet available, though it was "possible the FDA will issue a*

statement in the near future."