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Editorial

Is consensus in anti-aging medical intervention an elusive expectation or a realistic goal?

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Abstract

One of the biggest scandals of the recent history of medicine is the conflict of views between the gerontological establishment and the American Academy of Anti-Aging Medicine (A4M). The style used in that discussion was really rough and unusual. On the one hand, according to some representatives of the American Medical Associations (AMA), the use of human growth hormone (hGH) for anti-aging medical interventions is illegal, criminal, and requires persecution. On the other hand, A4M is of the opinion that all this is "…filled with incorrect, misplaced references and studies, and multiple basic scientific errors, in an apparent attempt to damage the anti-aging medical profession…". It is evident that in the frame of a short article is impossible to treat all the relevant aspects of this complicated story. Nevertheless, this Editorial attempts to point out the main results obtained so far, together with the most important issues of theoretical feasibility of the hGH replacement therapy (hGHRT). The comprehensive explanation of the aging process called "membrane hypothesis of aging" (MHA) offers

a solid basis for the interpretation of the observed beneficial effects of the hGH through its practically ubiquitous membrane receptors, and the species specificity of this peptide hormone. The specific activation of these receptors stimulates the membrane transport functions, rehydrates the intracellular colloids, allowing to speed up the protein synthesis and turnover, and activates a great number of cellular functions, all observed so far. The facts known about the adult growth hormone deficiency (AGHD) syndrome, and the beneficial effects of hGHRT in all aspects of this pathology suggest that aging may generally be considered as an AGHD syndrome. If this concept is accepted by most of the gerontologists, we can resolve practically all problems involved in the above outlined controversies. All this requires an independent, open-minded approach to the problem, and pushes us to a better understanding of the results of theoretical aging research. This approach may open a new, realistic way to the development of efficient anti-aging medical interventions.

Keywords: Human growth hormone (hGH); Anti-aging medical interventions; Theoretical basis of the hGH replacement therapy; The membrane hypothesis of aging (MHA); Adult growth hormone deficiency (AGHD) syndrome

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1. Introductory remarks

As the founder in 1981, and Editor-in-Chief of this journal, and as humanitarian and international medical ambassador, I am compelled to speak the truth regarding fundamental differences of opinion among the spectrum of scientists involved in the

anti-aging medical interventions. As an experimental gerontologist with 40 years of expertise in the basic research on aging, and as the author of the MHA, which is so far the only comprehensive, multidisciplinary description of the cell maturation and aging process, allowing the development of efficient anti-aging medical interventions at least in animal models, would like to express my opinion here on the controversary issues of the use of the hGH in the anti-aging medical intervention, and also to propose a "peaceful" solution of the actual conflict of views at the theoretical level.

In my role as a basic and clinical scientist, I have had an opportunity to witness more than four decades of advances and declines in the arena of preventive medical care. I submit that there has been little else as dramatic, important, beneficial, and significant as the anti-aging medical movement. It is shameful that skeptics have made repeated, calculated attempts to discredit the science and substance of anti-aging medicine. Despite these failed campaigns, anti-aging medicine has flourished in its sixteen-year long history, garnering the support of more than 100,000 physicians and scientists worldwide who practice or research life enhancing, life extending interventions. I am deeply convinced that the aforementioned credentials place me in a unique position to comment objectively and rationally on the realities of hGH and other HRTs, in the anti-aging clinical setting.

Quite to my astonishment and shock, I have been amazed to observe in many occasions, the complete disregard by certain individuals bearing some of the most prestigious affiliations in the gerontological establishment, for truth, academic integrity, and scientific professionalism. Instead, they have waged a wanton effort to sabotage and retard a global movement of clinicians, practicing physicians on the front lines who have embraced that aging is not inevitable and is, indeed, preventable.

Rather than investing their time, energies, and financial resources into positive endeavors such as research efforts aimed at elucidating tangible near-term applications for human aging intervention, the gerontological elite has instead sought to obfuscate the facts of the anti-aging medical movement. I submit that the reason for this is nothing less than an abject fear by the gerontological elite to avert their loss of control, power, prestige, and position in the multi-billion dollar industry of gerontological medicine. The gerontological elite has waged a multi-million dollar protracted campaign to influence media and exert deliberate control of public information relating to the degenerative diseases of aging and anti-aging medicine. Evidence suggests that selective funding of journalists aimed to deliberately misrepresent the anti-aging

medical movement with the goal of tainting its public perception. For example, as early as in 1997, with the “Madame Eterno” advertisement, produced by the Vilsack Productions for the National Institute of Aging (Press Releases of NIA, 1998) which was funded in its entirety by public funds that were appropriated by the US NIA, the gerontological elite has sought to discredit the safety and efficacy of hGH and HRT therapeutics. Since then, defamatory statements penned by an employee of the US government posing as a reporter have been published in a leading US women's magazine; articles maligning anti-aging physicians have appeared in scientific journals; and national sports and men's magazines have been riddled with biased reporting that distort the scientific conferences taking place in the anti-aging medical field. This lapse of journalistic integrity is a shame, a pity, and a disgrace.

In further libelous conduct, the gerontological elite has trumpeted meaningless public relations stunts, such as awards mocking the anti-aging movement and its physician leaders. These frivolous efforts, led by non-physicians with no clinical experience in addressing the degenerative diseases of aging, clearly were mounted for personal gain and speak volumes as to the extremes of intellectual dishonesty permeating the gerontological establishment.

The facts surrounding the judicious applications of hGH and other hormone replacement therapeutics countermand the position of gerontological establishment that no therapies or interventions currently exist to prevent, reverse, or slow down the aging process, including the progression of the degenerative diseases of aging. While such therapeutics do not affect fundamental aging, they do beneficially impact health, by extending the healthy human life-span. It is entirely conceivable that the resolution of quality of life (QoL) issues may lead to increase in quantity of life. Indeed, it is by initiating a semantics debate that the gerontological elite seeks to discredit the anti-aging movement. Anti-aging medicine is a euphemism for the application of advanced biomedical technologies focused on the early detection, prevention, and treatment of aging-related diseases, including the degenerative diseases of aging. Consequently, “anti-aging” is synonymous with phrases such as “age management”, “integrative aging”, “healthy aging”, “successful aging”, “happy aging”, etc. Through a deliberate campaign aimed at replacing “anti-aging medicine” with a “healthy aging movement”, those who control the purse strings on funding in aging research aim to absorb what they cannot contain. From the perspective of the anti-aging physician, methods that enhance the QoL are synchronous to, and sometimes identical to, interventions that

increase the quantity of life. I submit that it is time to cease frivolous debates over semantics. With its goals to promote research and application to discover safe and effective advancements to extend the healthy human life-span, anti-aging medicine has accelerated the pace of innovations in health promotion and disease prevention. For the gerontological establishment to recant their disapproval of "anti-aging medicine", which they have put forth though a number of US-government-funded media campaigns since 1997, would equate to their admitting they are wrong, and the position that aging is inevitable is wrong.

As of this writing, the US National Library of Medicine's database of peer-reviewed studies houses over 1500 abstracts key-worded as "anti-aging". These studies document a diverse array of therapeutics that currently exist and are being applied in the clinical setting today, as well as interventions that are in the laboratory stage, to slow, prevent, and perhaps even reverse the degenerative diseases of aging and the degenerative biological processes which lead to premature disease, disability, dependence, and death.

2. Some of the most important facts

As evidence of significant recent advancements in hormone therapeutics to address QoL issues, I cite the following peer-reviewed studies catalogued at the US National Library of Medicine:

2.1. KIGS/KIMS outcomes research, Stockholm, Sweden (Hernberg-Ståhl et al., 2001)

"The morbidity associated with GH deficiency in adults is now well established. Furthermore, many controlled clinical trials have demonstrated the efficacy of GH replacement therapy. Data concerning visits to the doctor, number of days in hospital, and amount of sick leave were obtained from patients included in KIMS (Pharmacia International Metabolic Database), a large pharmaco-epidemiological survey of hypopituitary adults with AGHD. For the total group (n = 304), visits to the doctor, number of days in hospital, and amount of sick leave decreased significantly ($p < 0.05$) after 12 months of GH therapy. Patients also needed less assistance with daily activities. QoL improved after 12 months of GH treatment ($p < 0.001$), and both the amount of physical activity and the patients' satisfaction with their level of physical activity improved after 12 months ($p < 0.001$). In conclusion, GH replacement therapy, in

previously untreated adults with GHD, produces significant decreases in the use of healthcare resources, which are correlated with improvements in QoL."

2.2. Queen Elizabeth Hospital, University of Birmingham, United Kingdom (Toogood, 2005)

"Studies have characterized the effects of AGHD and the benefits of GH replacement therapy. Areas of greatest impairment and benefit are QoL, skeletal health and cardiovascular risk factors including the serum lipid profile and body composition. By optimizing GHRT at various stages of adult life, it is hoped that it will prevent the development of osteoporosis and reduce the mortality and morbidity associated with hypopituitarism. However, the primary indication for GH therapy in adults in England and Wales is QoL. The benefits of GH treatment are sustained over several years, and long-term surveillance of patients continues."

2.3. MRC General Practice Research Framework, United Kingdom (Welton et al., 2008)

In a randomized, placebo-controlled trial of HRT involving 3721 women, performed in over 500 general practices in UK, Australia and New Zealand the results were: "After one year small but significant improvements were observed in three of nine components of the women's health questionnaire for those taking combined HRT compared with those taking placebo: vasomotor symptoms ($p < 0.001$), sexual functioning ($p < 0.001$), and sleep problems ($p < 0.001$). Significantly fewer women in the combined HRT group reported hot flushes ($p < 0.001$), night sweats ($p < 0.001$), aching joints and muscles ($p = 0.001$), insomnia ($p < 0.001$), and vaginal dryness ($p < 0.001$), than in the placebo group. …". The cited authors concluded that combined HRT started many years after the menopause can improve health-related QoL.

2.4. Memorial Regional Hospital, Florida USA (Canderelli et al., 2007)

"HRT can assist women with postmenopausal symptoms. In addition, research shows that HRT can help some postmenopausal women with selected comorbid conditions such as osteoporosis, type II diabetes, certain cardiovascular pathologies, and colorectal cancer. Certainly HRT can improve QoL and possibly longevity for selected women."

2.5. Universitäts-Frauenklinik Inselspital, Switzerland (Birkhäuser and Reinecke, 2008)

In a survey of 600 physicians in 6 countries, "…overall, 98% agreed that the menopause significantly affects QoL and 97% considered that the majority/all of their patients experienced positive benefits from HRT. Most physicians (90%) believed the benefits of HRT outweigh the risks in suitable patients, and 92% would prescribe HRT for themselves/spouse/family. With regard to the recent negative media coverage on HRT, 78% of physicians felt this was unjustified."

3. Some of the most important practical and theoretical arguments

3.1. Relevant clinical observations

Given my interests in the biological role of hGH in view of the MHA of which I am the author, I am dismayed by the gross and deliberate distortion of a number of scientific facts regarding AGHD and GHRT. The most flagrant distortion of fact was perpetrated by Blackman and his group (Blackman et al., 2002; Christmas et al., 2002), which claimed that GHRT causes a number of permanent adverse effects. It is clinically untrue that GHRT causes diabetes (it may result in a transient elevation of blood sugar, which is not equivalent to the diabetic state); arthritis (it may cause temporary water retention, which leads to swollen joints, but is not equivalent to arthritis); and cancer (such reports are unsubstantiated by peer-reviewed studies of GHRT). None of the purported side effects are documented in patients on a physician-supervised regimen of GHRT. Indeed, dosing of growth hormone for treatment of AGHD is well below pediatric doses, and certainly within physiologic or sub-physiologic levels, which is a founding tenet of anti-aging rejuvenative hormone therapies.

As a result of the false portrayal of some fundamental principles of endocrinological medicine, the US legal system was misled to enact a number of unjust and poorly designed laws and regulations that have been erroneously applied against anti-aging physicians with chilling effect, resulting in the restrictions of freedoms of physicians to administer life enhancing, and potentially life saving, therapeutics such as hGH and HRT therapies.

In the United States, a federal statute criminalizes whoever knowingly distributes, or possesses with 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, and pursuant to the order of a physician [21 U.S.C. § 333(e)]. The US Food and Drug Administration (FDA) has taken the

language of the federal hGH statute to mean that all prescribing of hGH must be “on label” (i.e., for an “authorized use”). Although the treatment of AGHD is an authorized use of hGH and it is therefore, clear that a legitimate prescription for hGH replacement therapy is lawful, controversy continues. There is not yet a consensus among the medical community as to what constitutes a “deficiency” of GH in an adult. The “no off-label” interpretation held by FDA means that prescribing hGH an authorized use such as legitimate AGHD would be lawful, but prescribing for anything other than authorized uses, even to treat serious diseases where research indicates that hGH would be beneficial, would not. While a literal reading of the statute may support this interpretation, it is improbable that the Congress ever intended to suppress the development and application of medical uses of hGH to treat disease.

The FDA's interpretation of the law places greater limitations on hGH prescribing than exist for controlled substances such as morphine and opiates, which may be prescribed for any legitimate medical purpose. Nothing in the legislative history proves that Congress ever intended that. In fact, this interpretation of the law seems completely at odds with the intent of Congress to treat anabolic steroids more harshly than HGH, not the other way around. In short, the US federal statute enables a witch-hunt of physicians who judiciously administer hGH therapy to patients with demonstrated deficiencies (via independent laboratory testing) which have led to clinically observed degeneration.

A Commentary published by Perls et al. (2005), claims that the US federal statute prohibits the use of hGH treatment for anti-aging purposes. In actuality, the law that restricts its use was voted in 1988, a time where neither the phrase nor the movement of “anti-aging medicine” existed. The federal statute was designed to prevent the illegitimate selling of GH by sports trainers and its illegitimate use by athletes to increase their performance after the “Ben Johnson doping scandal”. The use of GH for treatment of AGHD is fully legal throughout the world. Contrary to the claims by Perls et al. (2005), hGH has been reported to increase in GH-deficient adults muscle strength (Welle et al., 1996), functional capacities such as breathing capacity in patients with chronic bronchitis for example (Pape et al., 1991), and resting metabolic rate (Snel et al., 1995). Substantial adverse effects with hGH only appear at overdoses such as is the case for any other medical treatment (Wüster et al., 1998). An increased cancer risk with GH has never been proven in humans. The cancer recurrence and mortality has been found to be reduced or survival time increased in cancer patients on GH ([Swerdlow et al., 2000] and [Tacke et al., 2000]). GH-deficient patients present a

doubling of the cancer incidence and a nearly four times higher cancer mortality; long-term GH-replacement (60 months) reduced the risk of cancer of these patients by half (Svensson et al., 2004). Adverse effects of GH on life-span have been observed only in special mice species that react completely different than other species. In studies on normal aging mice species, GH-treatment extended the life-span ([Khansari and Gustad, 1991] and [Sonntag et al., 2005]). The persistence of GH-deficiency in hypopituitary adults substantially increases the overall and cardiovascular mortality ([Rosén and Bengtsson, 1990] and [Bates et al., 1996]), while GH-replacement reduces the increased mortality of GH-deficient adults to normal (Bengtsson et al., 1999).

Additionally, the gerontological establishment has repeatedly attempted to confuse the public as to pharmacological hGH therapy, by taking issue with the over-the-counter use of hGH releasers, secretagogues, and amino acid precursors. Numerous young athletes worldwide take such hGH nutritionals for the specific purpose of increasing their natural hGH levels. In over 50 years of such use, no data exists to document any elevated cancer onset in this population group. Thus, if physiologic replacement dosing of hGH (either pharmacologically or nutritionally) were tumorigenic, there would be a cancer epidemic among children and adults. There most certainly is no data to support such a position. Also, the generally well-known fact that cancer frequency is low in the younger ages (when the GH levels are high), and it increases with the advancing age (when the GH levels decrease), must be considered very carefully in this respect.

I am of the opinion that the sharp conflict in case of hGH is not justified, and it is not even necessary, because (a) sufficient empirical observations demonstrate that the use of hGH replacement is really able to produce beneficial effects in the elderly, as presented above, and (b) there exists a solid theoretical basis for the interpretation of the observed beneficial effects of the hGH and feasibility of the hGH replacement therapy, namely the MHA ([Zs.-Nagy, 1978], [Zs.-Nagy, 1979], [Zs.-Nagy, 1992], [Zs.-Nagy, 1994], [Zs.-Nagy, 1995], [Zs.-Nagy, 1997], [Zs.-Nagy, 2004] and [Zs.-Nagy, 2007]), which will be briefly explained below.

3.2. The true nature of the aging process: the essential content of the MHA

Obviously, it is necessary to explain in somewhat more details the basis and content of the MHA for the readers, who are not familiar with the concepts of the experimental gerontology. Below an attempt will be made to outline the most important issues.

If theoretically approaching the problem of aging in biological individuals, we have to answer the following two basic questions: (i) Why and how the ontogenetic development has to end with a progressive, destructive, intrinsic and universal functional deterioration (Strehler, 1959), which is commonly called aging? (ii) Why the time axis of the ontogenetic development (life-span) including aging, is so much different in various animal species?

The present author has explored these problems in a monograph, listing also the obvious contradictions of the existing aging theories (Zs.-Nagy, 1994), and summarized a general cell biological explanation of aging called MHA. An other review (Zs.-Nagy, 1997), outlined the relationship of MHA to the most important results of the molecular genetic research. The present Editorial is aimed only at emphasizing the most important conceptual items and conclusions of the above-mentioned theoretical approach, being relevant for the application and future research regarding the application of hGH replacement, as an anti-aging medical intervention.

The MHA attributes a primary role in differentiation and aging process to the plasma membrane, in which inevitable alterations occur during the life. The alterations are due to free radical induced molecular damage, and also to the “residual heat” formed during each depolarization of the resting potential ([Zs.-Nagy, 1978], [Zs.-Nagy, 1979] and [Zs.-Nagy, 1994]). These membrane alterations dictate the accumulation of dry mass (i.e., a decrease of the intracellular water content) in the intracellular space. This is a necessary process for the development and maturation, but becomes a rate-limiting factor above a certain physical density of the cell colloids, because the in situ enzyme activities in the cells are all strongly dependent on the density of their micro-environment. MHA is valid first of all for the postmitotic cells, like neurons, muscle cells, etc.; it gained a strong support from the recent developments of molecular genetics. Namely, the great majority of the products of oncogenes or anti-oncogenes (e.g., gas, ras, kit, fgr, yes, yet, fsv, ros, met, erb, neu, trk, fms, oncogenes, senescence-associated gene, schwannomin gene, prohibitin gene, mortalin gene, p53 and p21 gene, statin gene, gerontogenes, etc.) have a more or less close plasma membrane localization (Zs.-Nagy, 1997). These facts confirm the central role of the plasma membrane in the realization of mitotic regulation, cell differentiation and senescence. From this approach one can expect a deeper understanding of the function of the cell plasma membrane, its governing role in the aging process, and the possibilities of an eventual intervention to prolong the useful life-span.

The MHA offers a solid basis for the interpretation of the observed beneficial effects of the hGH through its practically ubiquitous membrane receptors, and because of the species-specificity of this peptide hormone, this stimulation may result in quite large differences in the actual life-span of various species. The specific activation of these receptors stimulates the membrane transport functions, rehydrates the intracellular colloids, allowing to speed up the protein synthesis and turnover, and activates a great number of cellular functions, all observed so far in the treatment of the AGHD syndrome.

4. The proposed consensus

There is no doubt that the AGHD syndrome shows a close similarity with most of the age-dependent functional losses. It has also been shown that the hGHRT is beneficial in all aspects of the AGHD pathology, therefore, we have all the reasons to consider aging as an AGHD syndrome. If this concept is accepted by the gerontologists, we can resolve practically all problems involved in the above outlined controversies. I emphasize that all this requires an independent, open-minded approach to the problem, and pushes us to a better understanding of the results of theoretical aging research.

It is my hope that the readers will join me in condemning those who violate the principles of science and clinical responsibility, and their obligations to both peers and the public at-large. By doing so, I submit the framework is set to reconcile fundamental differences of opinion and achieve the realistic goal of a consensus in medical anti-aging intervention.

Conflicts of interest statement

None.

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