In his update on the syndrome of adult GH deficiency in this issue of the *JCEM*, Melmed (1) draws attention to the growing number of people being diagnosed with “idiopathic GH deficiency in adults.” He also states that “the propensity by some practitioners for inappropriate IAGHD (idiopathic adult-onset GH deficiency) diagnosis as a prelude to administering unsafe nonapproved GH supplementation for athletes or for the frail elderly underscores the need for a stringent diagnostic approach”—thus implying that the increase in idiopathic adult-onset GH deficiency diagnosis, typified by that seen in the HIPPOCS postmarketing surveillance database that he quotes (2), is because fellow practitioners are overdiagnosing the condition in order to legitimize undesirable practice.

These are strong words. Although few doctors would prescribe GH (recombinant human GH [rhGH]) as a performance-enhancing drug for an athlete, few of us would not prescribe a trial of therapy in someone we believed to be suffering from GH deficiency and appearing to have ill health as a consequence. Let us not forget that in the early days of the use of rhGH in adults, there was considerable skepticism and some frank hostility to this from some established endocrinologists. It is difficult to distinguish the GH deficiency in older people from the GH deficiency secondary to pituitary or hypothalamic damage. There is a clear rationale for prescribing a trial of rhGH for prevention and/or treatment of frailty in suitable patients (3–5).

Let us put this in context: athletes and their coaches were the first to discover the powerful anabolic actions of GH in adults (6, 7). GH was given a glowing write-up by the California “doping guru” Daniel Duchaine in *The Underground Steroid Handbook* (6); in 1982, he wrote: “We find that GH is the most expensive, most fashionable, and least understood of the new athletic drugs. It has firmly established itself in power-lifting and within a few years will be a commonly used drug in all strength athletics.” Thus, human GH was established as a drug of abuse in sport some 7 years before the results of the first 2 randomized controlled trials confirming its powerful anabolic actions in humans were published in the bona fide medical literature (8, 9). A year earlier, the sprinter Ben Johnson won a gold medal at the Olympic Games in Seoul, only to lose it 3 days later when his urine test confirmed that he had been taking the anabolic steroid stanozol; he subsequently admitted under oath that at the time he was also taking GH. These performance-enhancing effects of GH have now been confirmed using randomized controlled trials—first in abstinent, previously steroid-dependent athletes by Graham et al (10); and, together with sex steroids in young athletes, by Meinhardt et al (11), 29 years after Duchaine’s first publication.

I use these anecdotes to illustrate that it is not always the scientists who make the discoveries; sometimes, like the athletes, it is the people who are most likely to benefit and who are always hungry for an effective new therapy. If they find such a substance, try it, and find that it works, then the word spreads and later we, as clinician scientists, come along and discover it “officially.” Athletic competition is so strong and the rewards are so great that new ways of improving performance are constantly being sought. The intelligent athletes and their coaches are constantly using the “trial of one” paradigm (12) to test new training regimes, diets, supplements, and substances. Athletes know their best performance for a given event to a

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**Abbreviation:** rhGH, recombinant human GH.
very high degree of accuracy. It is not difficult for them to test out a range of potential performance-enhancing substances or techniques. Careful observations by athlete and coach make this a very powerful paradigm for evaluating new methods that is much more sensitive (and a great deal quicker and cheaper) than a standard randomized, double-blind, placebo-controlled trial.

A similar process has been occurring in the aging population since Rudman’s hypothesis about aging and GH production in 1981 (13) and his seminal 1990 paper on the effects of GH therapy in men aged over 60 years (14). In this paper, Rudman et al (14) tested the hypothesis that some of the body composition changes associated with normal aging may in fact be due to GH deficiency and can be reversed by GH replacement. The authors showed that some of these somatic changes were indeed reversible by thrice-weekly doses of GH. Although the doses used were more “therapeutic” than “physiological,” the message was clear—there is a potential new approach to combating some of the negative somatic changes associated with aging.

Since then we have developed a world of knowledge about GH and we now understand how GH has a major role in adults: among its many actions is regulating the balance between lean and fat tissues. This role of GH as a “partitioning agent” has long been known in animal husbandry where it is used (along with anabolic steroids and “partitioning agent” has long been known in animal husbandry since Rudman’s hypothesis about aging and GH production in 1981 (13) and his seminal 1990 paper on the effects of GH therapy in men aged over 60 years (14). In this paper, Rudman et al (14) tested the hypothesis that some of the body composition changes associated with normal aging may in fact be due to GH deficiency and can be reversed by GH replacement. The authors showed that some of these somatic changes were indeed reversible by thrice-weekly doses of GH. Although the doses used were more “therapeutic” than “physiological,” the message was clear—there is a potential new approach to combating some of the negative somatic changes associated with aging.

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It is hardly surprising therefore that older people who are beginning to notice the adverse effects of losing lean body tissues look for ways of mitigating these “physiological” effects of aging. A healthy diet, an annual subscription to the local gym, a jog around the local park, and a brisk walk with the dog are all established as beneficial and effective methods, but they have well-recognized limitations. The development of frailty makes exercising more difficult, and indeed it may be dangerous were it to lead to a fall and a broken limb. People find exercise boring and sometimes painful, and however good the initial intention, drop-out rates from exercise programs are very high (22). There is also evidence that excessive exercise may indeed be harmful in older people through stimulation of proinflammatory cytokines (23).

Since 1990, there has been a strong (under) ground movement for the use of GH as a so-called “antiaging” medication, which has not had the support of the medical establishment, particularly in the United States, where in 1993 the use of GH (along with anabolic steroids) was restricted by law to only those indications approved by “...the Secretary of Health and Human Services (24)”.

In the United States, GH is only allowed to be prescribed for Food and Drug Administration (FDA)-approved conditions. The so-called “off-label” (at the discretion of the prescribing doctor) use is no longer permitted and indeed became a crime, punishable by imprisonment and/or a fine (although at least 1 physician prosecuted by the FDA was eventually acquitted by a jury) (25). I am not aware of another democratic country in the world where such harsh penalties are used to discourage medical practitioners from prescribing a drug that they might feel is the appropriate and beneficial treatment for a given patient.

In the 23 years since Rudman’s 1990 publication (14), there has accumulated a great deal more evidence that confirms and extends his original hypothesis. This includes a number of early short-term studies confirming powerful anabolic actions of GH, but many of these encountered too many adverse events. We now know that older people are very sensitive to GH, and these early studies, by using too high of a dosage, engendered these side effects.

In the last 10 years, 4 randomized controlled trials lasting from 14 to 26 weeks have shown convincingly that healthy normal older people can achieve tangible benefits from treatment with rhGH (26–29) and that the beneficial effects can be enhanced by coadministration of sex steroids. This has been achieved using lower doses of rhGH and with minimal containable side effects. These studies, in addition to showing the favorable effects of rhGH on body composition, also showed that rhGH improved strength, mobility, and maximum oxygen uptake, particularly when it was combined with a sex steroid. The additive effects of T and GH in men have been shown to be dose-dependent (26). We have recently published a detailed review of the individual and combined effects of GH and T in older men (30).

So far as practical benefit from treating older people with GH, there have been several encouraging studies. Van der Lely et al (31) gave a 6-week course of rhGH as part of a placebo-controlled, randomized controlled trial to older people presenting with hip fracture. Despite this very short treatment period, it produced a significantly higher proportion of rhGH-treated patients returning to their premorbid state in the most vulnerable group aged >75 years. Weissberger et al (29), in a placebo-controlled, randomized controlled trial, showed that 14-week preoperative treatment with GH in patients awaiting hip replacement resulted in a mean increase of 1.8 kg lean body

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mass that balanced the unavoidable postoperative loss. At the end of the study, there was a 7% increase in strength in the rhGH-treated group vs a 25% fall in the placebo group. This translated into a 26.9-m improvement in a 4-minute walking distance compared with a 19.5-m reduction in the placebo group. Although side effects required dose reduction in 5 patients, none withdrew from the study. In another randomized controlled trial looking at recovery from hip fractures in older people, MK677 (an oral GH secretagogue) given over 24 weeks postoperatively led to an improvement in stair climbing and gait speed compared with the placebo group (32).

Although there is still a need for more long-term safety data on rhGH administration to normal adults, we do have considerable long-term data on the safety of GH replacement in adults with GH deficiency from the postmarketing surveillance and population-based studies. These have confirmed the overall safety of rhGH treatment and shown that there appears to be no evidence of serious adverse events or the development of cancer (33, 34).

On one hand, diagnosing GH deficiency in older people may be easy when the cause is immediately apparent (eg, pituitary tumor, surgery, etc). On the other hand, because it is well-recognized that GH secretion falls as we age and that by the time we’ve reached our late 60s and 70s our daily production of GH has fallen to levels overlapping from older people with pituitary tumors or postsurgery (35), many “normal” people in this older age group are therefore likely to be GH deficient. Thus, making a diagnosis of GH deficiency in older people may be more of a semantic issue than a medical issue. From a therapeutic point of view, not all of these people may benefit from or require treatment, but deciding who deserves a trial of treatment is a clinical decision best made by a fellow physician rather than a regulatory authority. The existing legal and financial rules on reimbursement in many countries limit the off-label use of GH, and because rhGH is still a very expensive drug, it makes it tempting for physicians to “shoehorn” the patient before them, whom they think might benefit from a trial of treatment with rhGH, into a diagnosis of idiopathic GH deficiency—the between-the-lines message of Melmed’s update (1).

Unlike Melmed, I believe that some of these patients will benefit from GH replacement. Of course, we would all want more long-term data on safety and efficacy of rhGH in older people, but those who are beginning to suffer the downward spiral of progressive weakness are looking for help now and cannot wait another 10 years for these results. Who are the people most likely to benefit from treatment with rhGH? There is not space to deal with this adequately here, and this is a decision that can be made as effectively by a well-informed family doctor as an endocrinologist. For me, it includes those who are beginning to show that frailty is becoming a problem. A careful history from an older patient eliciting weakness and unsteadiness, maybe leading to a fall in someone who maybe is thin and beginning to look frail is such a person.

Clearly, anyone who is prescribing GH must do so legally and must alert their patient that GH is not licensed for this indication, that their treatment is off-label, and that it must be considered experimental. The prescribing doctor needs to take on the role of the athlete’s coach. Obtain detailed anthropomorphic, functional, psychological, and biochemical baseline information and then initiate a “trial of one,” starting with a low-dose and monitoring IGF-I as the dose of rhGH is gradually increased. It is appropriate to aim to keep the IGF-I in the upper half of the local age-adjusted range (or if this is not available, below the mean of the IGF-I in younger people). It is important to explain to the patient that treatment may initially lead to some ankle edema, growing pains, and feelings of puffiness that usually settle spontaneously or with a dose reduction. Daily bedtime injections are ideal, but if injections are an issue (uncommon), thrice weekly injections do work. Monitor measured variables, looking for benefit objectively. Increase in muscle size occurs relatively early into therapy, but the translation of this into improved performance takes longer (36). Although some benefits should be apparent within 6 months, it should be explained to the patients that they can expect benefits to accrue over a longer period, particularly for the skeleton.

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