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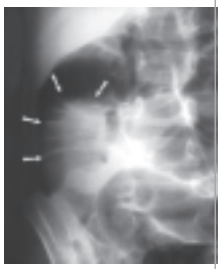

Cover Picture:
Air contrast enema shows a soft tissue mass representing the intussusception (arrows) outlined by air in the ascending colon.
(Refer to page 645-648)

Editorial

Growth Hormone: Beyond Therapeutic Prescription – A Magic Fountain of Youth?

C Rajasoorya

Growth Hormone (GH) was first isolated in 1956. GH was obtained from human cadaver pituitaries since the 1950s and was initially used for the treatment of short stature in children. It was presumed safe until Creutzfeldt-Jacob disease was associated with contaminated GH in the 1980s; at about the same time that recombinant-DNA GH was introduced. With the introduction of synthetic GH, the avenue for newer and more experimental studies in adults with GH deficiency (GHD) was opened. The widespread availability of GH, the continuing difficulty in defining what GHD is, the claims of effectiveness of different preparations, and the proliferation of web-sites offering GH as a magic fountain of youth have added to the confusion and controversy surrounding the use of GH. Notwithstanding these, such information will have a major implication on the safety to the individual consumer, particularly in the non-prescribed context.

GH is produced by the anterior pituitary gland in a pulsatile manner in response to the stimulatory influence of GH Releasing Hormone (GHRH) and the inhibitory influence of Somatostatin from the hypothalamus. The bulk of the effects of GH is mediated by Insulin-like Growth Factor I (IGF-I) which is released predominantly by the liver and to some extent by other tissues. Almost all IGF-I, in the circulation is bound to one of several IGF binding proteins (IGFBP), the most abundant of which is IGFBP-3. GH mediates its physiologic effects via its dual actions of growth promotion as well as metabolic effects. The metabolic effects include its influence on carbohydrate, fat, protein and bone metabolism. GH secretion continues through life; it increases with sexual maturation after which it declines by approximately 14% each year. This age-related decline in GH secretion is paralleled by a decline in IGF-I levels. The similarities of the phenotype of adult GHD with ageing has led to speculation that administration of GH can help reverse ageing – hence the basis for GH being proposed as the fountain of youth. This concept flourished after publication by Rudman *et al*[1] in 1990 who suggested that the decrease in lean body mass, the increase in adipose-tissue, and the thinning of the skin that occur in older men are caused in part by reduced activity of the growth hormone - IGF-I axis, and that this can be restored in part by the administration of human growth hormone. The Rudman study concluded that the effects of six months of human growth hormone on lean body mass and adipose tissue mass were equivalent in magnitude to the changes incurred during 10 to 20 years of ageing. Despite the study authors' own caution and that raised by an accompanying editorial[2] the concept of "reversal of ageing with GH" was expounded by the media and commercial websites liberally since.

Non-idiopathic GHD can result from pituitary/peri-pituitary disease, surgery or radiation therapy. Adult GHD is now a well recognised clinical syndrome[3] manifesting itself with a cluster of cardiovascular risk factors,

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impaired quality of life, increased prevalence of disability-pensions, and reduced bone mineral content and bone-density with increased fracture prevalence. Individuals with GHD tend to have weight-height disproportion, decreased muscle mass and strength and a thin dry skin. They have increased amount of abdominal fat, hypertension, impaired fibrinolysis, glucose intolerance, insulin resistance and premature atherosclerosis - all postulated as reasons for the observed increased cardiovascular mortality in hypo-pituitary patients in epidemiological studies. Randomised, placebo-controlled short-term studies have indicated that GH replacement therapy can reverse several of these biological changes, although none have yet been performed to show reversal of cardiovascular mortality with replacement[4].

GH levels vary at different times of the day. IGF-I is age- and laboratory- dependent and rises during puberty with gradual fall off thereafter. A normal IGF-1 does not exclude GHD. There is no one uniformly agreed test, which diagnoses GHD with certainty[4]. In practice, the diagnosis of GHD is based on careful clinical assessment including auxological data, augmented by a number of tests. The likelihood of GHD rises with an increasing number of pituitary hormone deficits ranging from 30% if only GHD occurs inisolation to almost 100% if three or more pituitary hormone deficiencies exist. Most endocrinologists use provocative testing for confirmation of GHD, although in the right clinical context (e.g. previous pituitary disease) this may not be always necessary. Dynamic testing is done with the insulin tolerance test (the gold standard which has been the most validated), or where contraindicated stimulation with one or more of glucagon, clonidine, arginine or GHRH have been used.

Besides the standard subcutaneous forms of GH available on prescription, numerous agents (pills, elixirs, sprays or cream) are currently available in the market as GH supplements and GH-secretagogues. These are marketed as "dietary supplements". These agents do not come under the jurisdiction of national regulatory bodies and scientifically conducted studies are scarce. Some questions arise as to claims of their effectiveness. GH is a large polypeptide hormone that requires its exact three-dimensional structure and its manufacturing process by recombinant technology requires precise, elaborate, expensive, patented and monitored methods. Also, GH being a large molecule cannot be absorbed into the body across skin or mucous membranes. Thus, if not injected and taken orally it is digested or broken down into simpler substances. GH-secretagogues (which stimulate the pituitary gland to produce GH, unlike regular GH which acts on the liver) remain an interesting and intriguing area of continual research. Over the years several short chain orally absorbable compounds have been investigated. There still remain a lack of convincing placebo controlled and randomised studies to show its consistent effectiveness.

The first two randomised placebo controlled studies of GH replacement in those with GHD were published in 1989. With 13 years of use, we now better understand that GH replacement requires titrated individualisation of therapy, using IGF-I levels to avoid over replacement and GH-related side effects. There is also evidence surfacing on a sub-population of GH deficient individuals who suffer from significant morbidity; it has been suggested that where finite resources exist in a health care system, resources should be concentrated for these sub-population[5,6].

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A very recently published randomised double blind placebo controlled double blind study concluded that GH therapy was associated with frequent adverse effects including arthropathy, carpal tunnel syndrome, diabetes and glucose intolerance despite having beneficial effects on body mass and fat mass[7]. The safety on the use of GH has always been questioned partly based on the data of increased risk of neoplasm in acromegalic patients observed in some epidemiological studies[8]. Experience from long term surveillance studies in paediatric patients have not demonstrated increased risk of malignancy[9].

GH excess states are well reflected in patients with acromegaly and the associated co-morbidities including arthropathy, hypertension, diabetes mellitus and some epidemiological associations with malignancies. The morbidity and mortality problems associated with acromegaly and the level of GH elevation[8] have been a source of concern on the effects of excess GH replacement. While the dosing in standard GH therapy do not commonly reach the levels commonly seen in acromegaly, the fear exists of the insidious predisposition-to early acromegaly when treated for long term with GH[2]. Some recent large epidemiological data have suggested a strong correlation between IGF-I levels and breast malignancy in women and prostate malignancy in men, but other studies have not shown a similar effects[10].

What then are the current indications for GH therapy? Based on overwhelming evidence of efficacy and safety, the American Association of Clinical Endocrinologists[11] had recommended that GH replacement as established in proven GH deficiency, Turner's syndrome, growth delay in children with chronic renal insufficiency. They also recommend that GH be considered investigational in idiopathic short stature, constitutional delay of growth and development, intrauterine growth retardation, skeletal dysplasia, osteogenesis imperfecta and in certain genetic syndromes and GH replacement be considered experimental in the treatment of "Somatopause", infertility, chronic catabolic states e.g. respiratory failure, those on high dose steroids, inflammatory bowel disease, burns injury. GH has been tried in critically ill patients in randomised controlled trials and it showed a higher mortality in GH treated patients. FDA has approved GH use in cachexic patients with AIDS.

The discovery of Florida in the USA by Ponce de Leon was the outcome of a search for the fountain of youth. He was attacked by natives and died after escaping to Cuba – the irony exists that experiments while leading to new knowledge can lead to unexpected outcomes. Lessons from the Women's Health Initiative Study[12] with regard to hormone replacement in post menopausal women published recently have highlighted the need for carefully controlled large scale, multicentre, controlled studies to tell us on the benefits and risks of an intervention. While there seems to be increasing scientific evidence on the benefit of GH therapy in those who have a documented deficiency, there remains lots of unanswered questions and controversy in the distinction of normal age-related decline in GH secretion from deficiency, the definition and criterion for GHD, the optimal dosing and frequency of GH administration and the long term benefits and side effects of chronic GH administration. Thus the use of GH or GH-secretagogues as a route to the fountain of youth or reversal of ageing cannot be recommended based on current scientific data. GH remains expensive and until further evidence emerges will currently, at least, remain an experimental therapy for the non-GH deficient. SMJ

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ERRATUM

For the article "Peripheral Nerve Blocks for Lower Limb Surgery – A Choice Anaesthetic Technique for Patients with a Recent Myocardial Infarction?" in the November 2002 issue of the SMJ, the acknowledgement should read "The authors would like to thank Drs A Teo, A Ho and Ms A How and staff of the Department of Anaesthesia, Alexandra Hospital for their invaluable assistance." We apologise for the error.

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